BEYOND THE AUTOPSY: POSTMORTEM FAMILIAL VARIANT TESTING

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Postmortem genetic testing

- "molecular autopsy"
  - *Channelopathies and clotting disorders*
- More affordable, more widely available and quicker
  - *Research institutions and commercial entities*
  - *Testing results take 3-4 weeks on average*
- Identification of a pathogenic gene in individuals who die suddenly may provide a more accurate cause of death
- First degree relatives of the decedent may be at risk for having the pathogenic gene
- Testing is available, sometimes at no cost, for familial variant testing

Postmortem genetic testing

- Blood should be collected and stored in a purple EDTA tube
  - *Some labs accept blood submitted in a grey top tube; however, not all the testing can be performed on those samples*
  - *Non-frozen is preferred*
- Save 2-3 extra purple top tubes in individuals who have a sudden unexpected cardiac death, as well as those with a possible cardiomyopathy
- Bloodstain card testing can be done; however, it is not the preferred sample
- Should be submitted as soon as possible after collection

Postmortem genetic testing

- Commercial labs: full-gene-sequencing and deletion/duplication analysis using next-generation sequencing technology
  - *Pre-defined panels*
    - Cardiomyopathy, arrhythmia, skeletal muscle disease, aortopathy, connective tissue disorders, congenital heart disease, familial hypercholesterolemia and pulmonary hypertension
  - *Pathogenic or likely pathogenic variants are confirmed*
- Research institutions: Whole exome testing or targeted full-gene-sequencing may be performed
- Variants are classified according to American College of Medical Genetics (ACMG) guidelines

Variant classification

- Results compared to multiple databases and assessed with medical literature
  - *Population, disease specific and sequence databases*
- ACMG recommends a 5-tier system
  - *Pathogenic: Sequence change directly contributes to the development of disease*
  - *Likely pathogenic: Sequence change is very likely to contribute to the development of disease; however, the scientific evidence is currently insufficient to prove it conclusively*
  - *Uncertain significance: Insufficient evidence currently exists to support a more definitive classification*
  - *Likely benign: Sequence change is not expected to have a major effect on disease; however, the scientific evidence is currently insufficient to prove it conclusively*
  - *Benign: The sequence change identified does not cause disease*

Richards, et al. Standards and Guidelines for the Interpretation of Sequence Variants. Genet Med. 2015 May;17(5):405-24

Commercial cardiomyopathy panel

- Currently tests for up to 150 genes
  - *ABCC9 ACTC1 ACTN2 AGL ANK2 BAG3 CACNA1C CACNB2 CALM1 CALM2 CALM3 CASQ2 CAV3 CRYAB CSRP3 DES DMD DOLK DSC2 DSG2 DSP EMD EYA4 FHL1 FKRP FKTN FLNC GAA GLA GPD1L HCN4 JUP KCNA5 KCNE1 KCNE2 KCNH2 KCNJ2 KCNQ1 LAMP2 LMNA MYBPC3 MYH7 MYL2 MYL3 MYL4 NKX2-5 PKP2 PLN PRKAG2 RAF1 RBM20 RYR2 SCN5A SGCD SLC22A5 TAZ TCAP TGFB3 TMEM43 TNNC1 TNNI3 TNNT2 TPM1 TRDN TTN TTR VCL AKAP9 ANKRD1 CACNA2D1 CALR3 CHRM2 CTF1 CTNNA3 DTNA FHL2 GATA4 GATA6 GATAD1 GJA5 ILK JPH2 KCND3 KCNE3 KCNE5 KCNJ5 KCNJ8 KCNK3 LAMA4 LDB3 LRRC10 MED12 MYH6 MYLK2 MYOM1 MYOZ2 MYPN NEBL NEXN NPPA PDLIM3 PLEKHM2 PRDM16 RANGRF SCN10A SCN1B SCN2B SCN3B SCN4B SLMAP SNTA1 TMPO TRPM4 TXNRD2 A2ML1 BRAF CBL HRAS KRAS MAP2K1 MAP2K2 NF1 NRAS PTPN11 RASA1 RIT1 RRAS SHOC2 SOS1 SOS2 SPRED1 ACADVL ALMS1 CPT2 DNAJC19 ELAC2 MTO1 SDHA TMEM70 DEPDC5 KCNA1 KCNQ2 KCNQ3 KCNT1 PCDH19 PRRT2 SCN1A SCN8A SCN9A SLC2A1*

Commercial arrhythmia panel

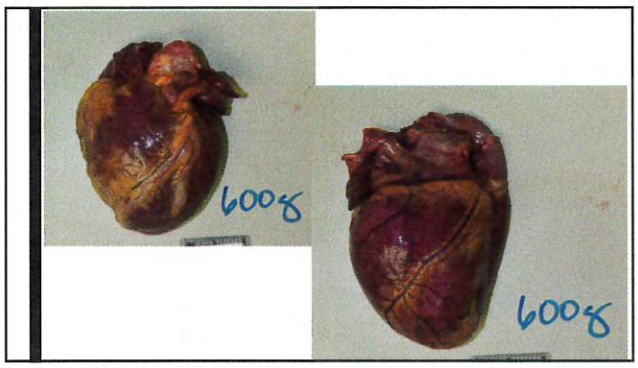
- Currently tests for up to 75 genes
  - *ABCC9 ACTN2 ANK2 CACNA1C CACNB2 CALM1 CALM2 CALM3 CASQ2 CAV3 DES DSC2 DSG2 DSP EMD FLNC GPD1L HCN4 JUP KCNA5 KCNE1 KCNE2 KCNH2 KCNJ2 KCNQ1 LMNA MYL4 NKX2-5 PKP2 PLN PRKAG2 RBM20 RYR2 SCN5A TMEM43 TNNI3 TNNT2 TRDN TTN AKAP9 ANKRD1 CACNA2D1 CTNNA3 GATA6 GJA5 KCND3 KCNE3 KCNE5 KCNJ5 KCNJ8 KCNK3 LDB3 NPPA PDLIM3 RANGRF SCN10A SCN1B SCN2B SCN3B SCN4B SLMAP SNTA1 TGFB3 TRPM4 DEPDC5 KCNA1 KCNQ2 KCNQ3 KCNT1 PCDH19 PRRT2 SCN1A SCN8A SCN9A SLC2A1*

Familial variant testing

- Can be performed on blood relatives of a decedent who was found to have a pathogenic or likely pathogenic variant on a gene or panel test
  - *Cascade screening*
  - *Available for children, parents, siblings, cousins, aunts/uncles*
  - *Looking for the abnormal pathogenic gene, regardless of the disorder it is associated with (not the whole panel initially ordered)*
  - *Family members do not need to be symptomatic*
- Saliva is the preferred sample; however, it can also be performed on blood in a purple top tube
  - *Kits can be sent directly to the individuals, so location is not a problem*
- May alleviate the need for lifelong medical tests and follow up if testing is negative

Case presentation

- 34 year old overweight black male had witnessed cardiac arrest after complaints of difficulty breathing
- Pronounced dead at the scene
- Spouse reports being diagnosed with an unspecified cardiomyopathy in another state a couple of weeks prior; prescribed a beta blocker
- Autopsy:
  - *600 gm football shaped heart with asymmetric left ventricular and septal hypertrophy with fibrosis*
  - *Myocyte disarray involving all sections*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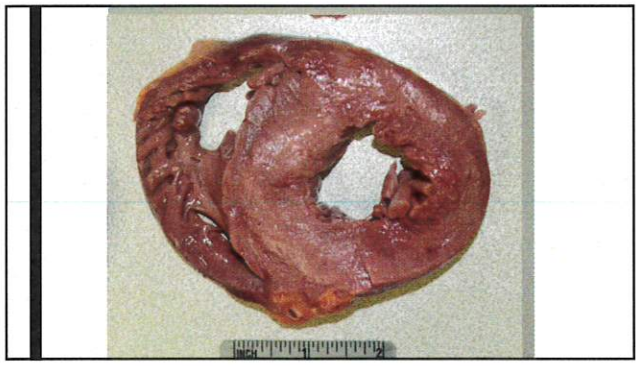
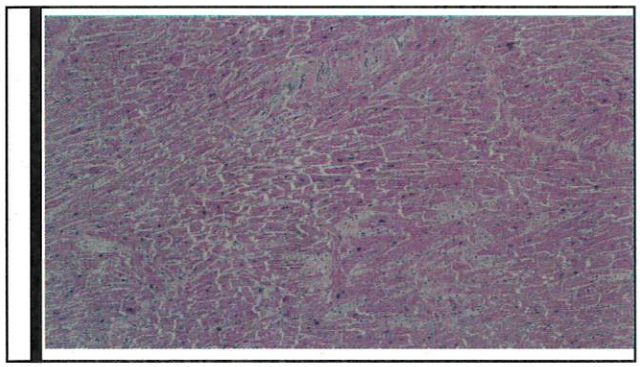
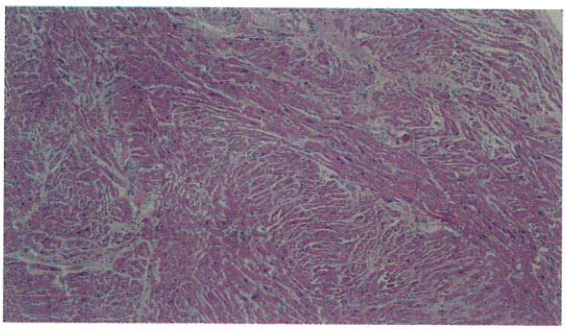
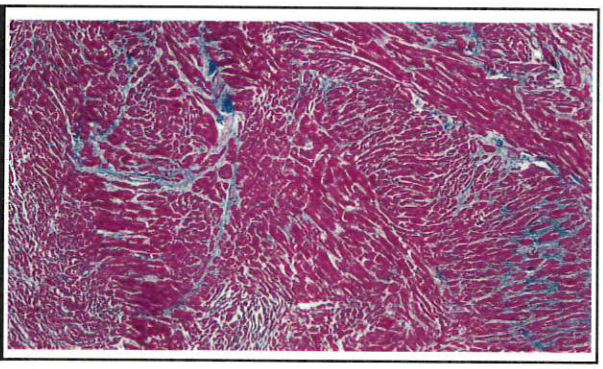








Hypertrophic cardiomyopathy

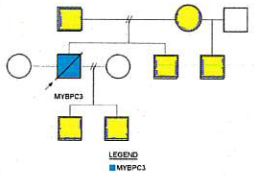
- Most common cause of sudden cardiac death in young athletes
- Variable anatomic appearance
  - *Negligible to severe myocyte hypertrophy*
  - *Minimal to excessive myocardial fibrosis*
  - *Absent to severe left ventricular outflow tract obstruction*
  - *Any of the ventricular walls may be affected*
- Variable presentation
  - *May be asymptomatic or result in sudden cardiac death at any age*
- Echocardiogram is the gold standard screening test
- No known cure; however treatments and screening tests are available
  - *Important for first degree relatives*

Hypertrophic cardiomyopathy

- First chromosomal locus identified involved MYH7 gene (encoded beta-myosin heavy chain)
- Several hundreds of mutations amongst almost 30 genes now known to exist
  - *Encode sarcomeres, calcium handling, mitochondrial proteins*
- Most common genetically transmitted form of HCM involves 9 genes encoding myofilaments critical to the cardiac sarcomere
  - *MYBPC3: One of the most common (myosin binding protein C)*
  - *MYH7 (beta-myosin heavy chain)*
  - *MYL2 (regulatory) and MYL3 (essential) myosin light chains*
  - *TNNT2 (cardiac troponin T)*
  - *TPM1 (alpha-tropomyosin)*
  - *TNNI3 (cardiac troponin I)*
  - *TNNC1 (cardiac troponin C)*
  - *ACTC (actin)*

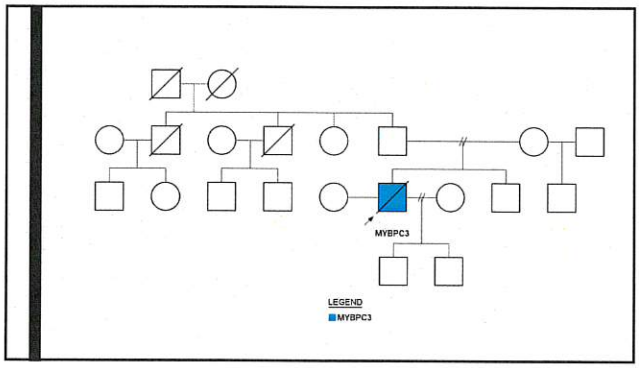
Case presentation: Genetic testing

- With consent of the family, blood sent for genetic testing for cardiomyopathy panel
  - *Pathogenic variant in MYBPC3 known to be associated with HCM identified*
- Informed the spouse of the findings and obtained more information on the family
  - *The current spouse is the second wife; no kids together*
  - *First wife has 2 kids with the decedent*
  - *Mother and father still alive; two brothers alive*
  - *Testing offered to all and all accepted*
    - Saliva is preferred sample for this testing



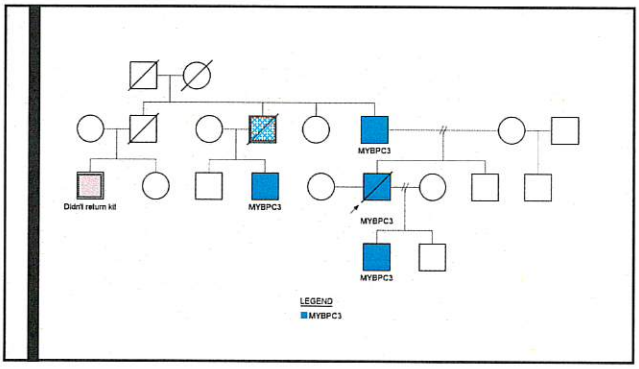
Genetic testing

- Father of decedent informed us that two of his brothers (decedent's uncles) died suddenly at young ages
  - *One had an autopsy in another state*
  - *Both brothers have living adult children*
  - *Due to the sudden cardiac death in the decedent's uncles, the decedent's cousins were located and testing was offered*
    - 11 family members total; 10 submitted samples for testing



Genetic testing results

- The decedent's father, one of his children and one cousin tested positive for the MYBPC3 mutation (sample never received for one cousin)
  - *3/10 samples positive for mutation*
- Referred for genetic counseling (offered through genetic testing lab) and referred to cardiologist with autopsy report and genetic results
  - *Father had MRI and was found to have significant left ventricular hypertrophy*
    - Internal defibrillator placed
  - *Child had full cardiac workup and has no hypertrophy at this time*
    - Will undergo cardiac testing every 2 years
  - *Cousin had echocardiogram and then referred for MRI (results not currently known)*



Postmortem genetic counseling

- Families **must** be referred for counseling services
  - *May be offered through testing lab*
  - *National Society of Genetic Counselors*
    - www.nsgc.org
    - Find a genetic counselor resource
    - Provides additional resources and information for patients and their families
- Help explain results and potential risk of transmission
- Provide emotional support
  - *Can be very difficult to receive positive results*

Postmortem genetic testing

- 14 cases submitted to date (2 year period)
  - *Gross and/or microscopic findings suggestive of cardiomyopathy, aortopathy or other sudden cardiac death*
  - *4 cases with pathogenic variants identified (28.6%)*
    - MYBPC3 (Hypertrophic cardiomyopathy)
    - TTR gene (Transthyretin amyloidosis)
    - SCN5A (arrhythmias (Brugada, long QT) and cardiomyopathy)
    - CPT2 and GAA (AR carnitine palmitoyltransferase deficiency and Pompe disease)
  - *6 cases with variant of unknown significance (VUS) identified (42.9%)*
    - 2 allowed familial variant testing
      - *Initially only 2 VUS tests offered free of charge*
      - *Contacted company and they are allowing additional tests when needed*
  - *3 cases negative (dilated cardiomyopathy (1), thoracic aortic dissection (2)) (21.4%)*
  - *1 case still pending*

Postmortem genetic testing

- Of two cases with pathogenic variants identified, 13 family members tested
  - *4 were positive for the pathogenic variant (30.7%); 1 not returned*
- Testing kits sent out for 6 other family members this month for other 2 cases
- Two cases with VUS that allowed testing
  - *3 testing kits sent out to date*
- Discussion with lab to allow testing of family members for cases with autopsy diagnosis of disease associated with the VUS mutation identified
  - *Case by case basis*

Summary

- Postmortem genetic testing may identify inheritable conditions in a decedent's family
  - *Should be standard of care for decedents identified with cardiomyopathy and/or sudden cardiac death of unknown etiology*
  - *Important not only for cause of death determination; **potential to prevent sudden cardiac death in other family members***
- Familial variant testing can be performed on first degree relatives of any age, regardless of the presence or absence of symptoms
  - *The costs and stresses of lifelong medical tests and follow up could be avoided for family members who test negative*
  - *Only tests for the pathogenic gene identified*
- Treatments and preventative measures are available for many conditions
- Family members must be referred for genetic counseling

An Assessment of Cardiomegaly and Opioid-Related Death

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Outline

- Research questions
- Opioid action, classic autopsy findings, and needles in arms: a tense trio
- Methods
- Present data collected at the Jefferson County OCME
- Discussion of findings

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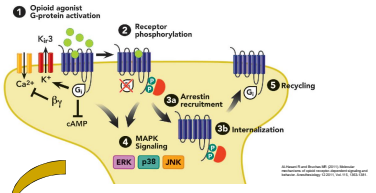
Opioid receptors: Signaling



Neuronal calcium influx, neurotransmitter release

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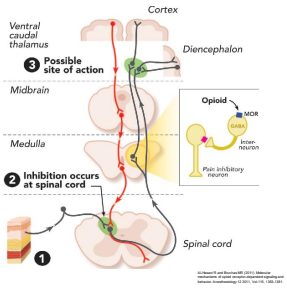
Opioid signaling: Sites of action



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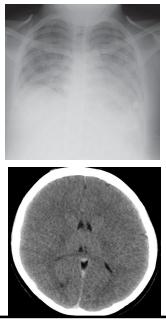
Classic autopsy findings in opioid-related deaths



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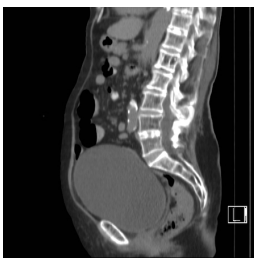
Completing the classic triad…

- Opioid-mediated diminished outflow from CNS/spinal cord diminishes micturition reflex → diminished urinary outflow → distended bladder



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JCOCME Experience: Decedents don't always "read the book."

- Many decedents who died an opioid-related death do not show classic autopsy findings just described.
- Next-of-kin, friends, or others present around time of death often do not report the decedent displaying signs of a respiratory-driven death, such as snoring or coughing.
- Some decedents who used heroin are found with a needle in their arm, suggesting a relatively rapid death, such as a cardiac event.

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...But opioid receptor signaling can be cardioprotective

- However, there is evidence that activation of the delta-opioid receptor induces cardiac myocyte hibernation, thereby protecting them from cell damage or death in the event of ischemic events.
- This protection may be even greater when kappa-opioid receptors are simultaneously activated.

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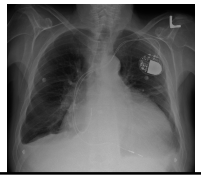
Research questions

- Given the tension among the classic triad, our office's experience, and the putative role of opioid signaling in cardioprotection, do decedents dying opioid-related deaths exhibit cardiomyopathy (e.g. cardiomegaly?)



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Methods

- Queried OCME FileMaker database for deaths
  - Data range: January 1, 2016 – December 31, 2018
  - Deaths due to opioid toxicity vs. control
  - Exclusions:
    - Drugs detected at time of death
    - Deaths due to chronic substance use
    - Age < 20 years
    - BMI < 10 kg/m^2
- Data concerning demographics, BMI, heart weight, body length, body weight were compiled and analyzed using Microsoft Excel

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Results: Demographics

Comparison of Mean Baseline Characteristics			Pr > F
	Opioid (n=537)	Control (n=662)	
Age	39.04	46.03	<0.0001
BMI	27.97	27.89	0.8797
Height (in)	68.82	68.85	0.8878
Weight (lb)	189.20	189.06	0.9708

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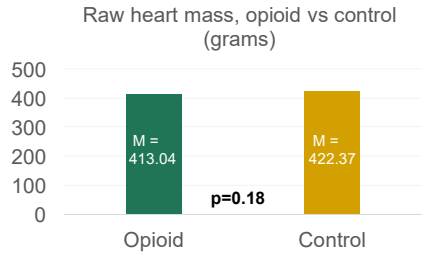
Results: Opioid-related death vs. control heart size 1



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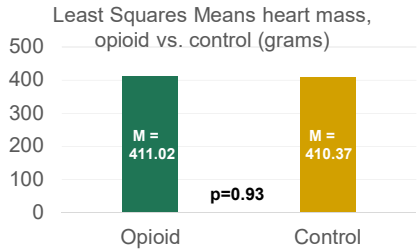
Results: Opioid-related death vs. control heart size 2 -- LSM



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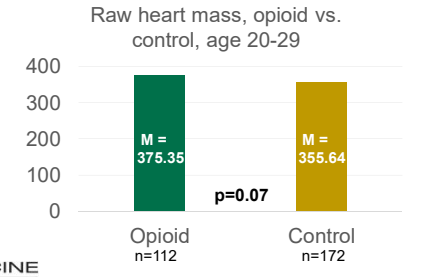

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Conclusions

- Opioid-related deaths have spiked in the past two decades, but the exact pathophysiology underlying the cause of death in many opioid-related deaths remains unclear.
- Some decedents dying of opioid-related deaths do have more massive hearts than previously-published references – as do many controls.
- .There may be underlying cardiac susceptibility in young adults dying of opioid overdose, but its possible significance may be difficult to assess in older populations with comorbid diseases of aging.

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Discussion

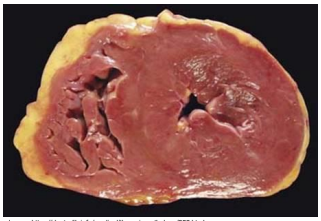

Image: https://doctorlib.info/medical/thoracic-pathology/256.html

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Thank you!

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References

Slide references:

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2. Lewis T. The Normal Size of the Heart Muscle Weight.Association for the Publication of the Journal of Internal Medicine 1951.
3. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. Morbidity and Mortality Weekly Report. 2016;65:1445–1452.

SAMs references:

1. Headrick JP, See Hoe LE, Du Toit EF, et. al. Opioid receptors and cardioprotection- 'opioidergic conditioning' of the heart. *British Journal of Pharmacology* 2015; 172(8): 2026.
2. Pelletier D, Andrew T. Common findings and predictive measures of opioid overdoses. *Academic Forensic Pathology* 2017; 7(1):91.

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CME Question 1

Which of the following represents the classic autopsy findings of an opioid-related death?

a. Cardiomegaly, cerebral edema, distended bladder

b. Pulmonary edema, cerebral edema, distended bladder

c. Pulmonary wedge infarct, cardiomegaly, cerebral edema

d. Abdominal aortic aneurysm, pulmonary edema, distended bladder

e. Cardiomegaly, pulmonary edema, cerebral edema

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CME Question 2

Activation at which of the following opioid receptors induces a cellular hibernation-like state, promoting anti-ischemic effects, thereby partially explaining the cardioprotective mechanism of opioids?

a. Delta

b. Kappa

c. Mu

d. Nociceptin/orphanin FQ

e. Zeta

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CME Question references

1. Pelletier D, Andrew T. Common findings and predictive measures of opioid overdoses. *Academic Forensic Pathology* 2017; 7(1):91.
2. Headrick JP, See Hoe LE, Du Toit EF, et. al. Opioid receptors and cardioprotection- 'opioidergic conditioning' of the heart. *British Journal of Pharmacology* 2015; 172(8): 2026.

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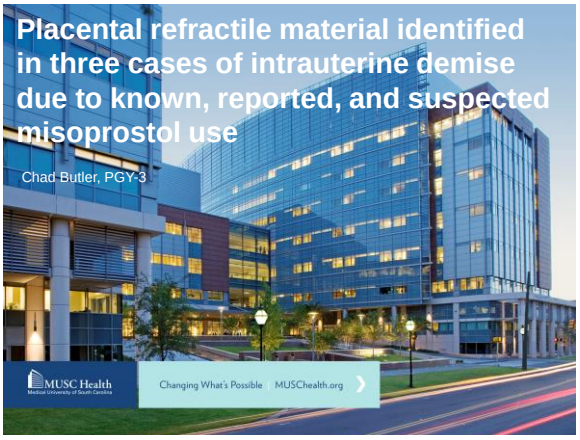
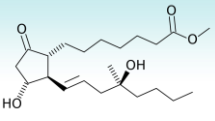


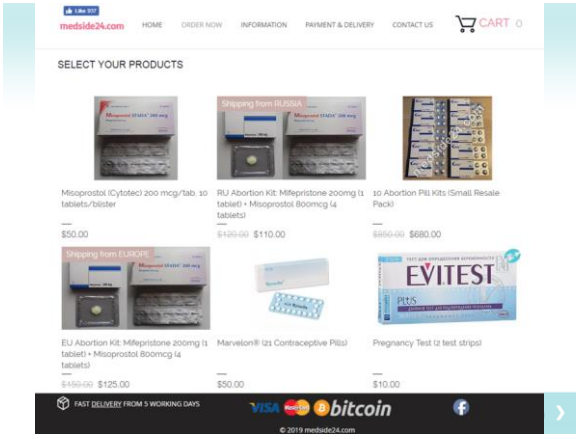
Objectives

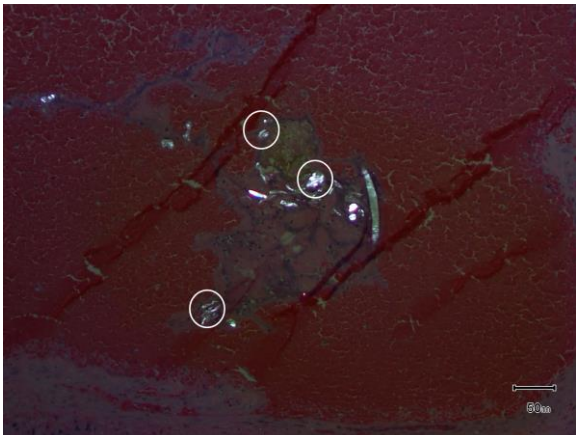
- Define misoprostol
- Discuss home abortions
- Present index cases
- Present data on refractile material and purple deposits identified in placentas with history of vaginal misoprostol use

Misoprostol (Cytotec)



- Synthetic prostaglandin E1 (PGE1)
- Uses:
  - Treat ulcers, induce labor, control postpartum bleeding, medical abortion
    - Dose dependent
      - Induction: 25 mcg/dose (vaginal low-dose)
      - Medical abortion, miscarriage, IUFD: 800 mcg (vaginal high-dose)
- Routs of administration: Oral, sublingual, buccal, rectal, **vaginal**
- Oral administration less effective due to first pass metabolism by liver
  - Vaginal administration bypasses first-pass effect of liver, greater local effect





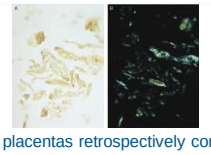
Am J Surg Pathol. 2007 Dec;31(12):1880-6.

Misoprostol associated refractile material in fetal and placental tissues after medical termination of pregnancy.

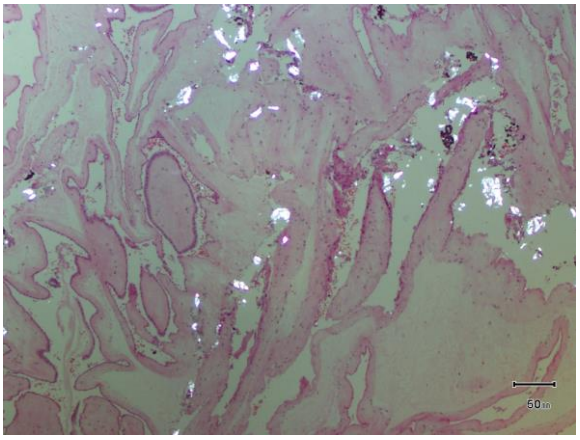
He Y[1], Ngatina S, Kingdom J, Shannon P

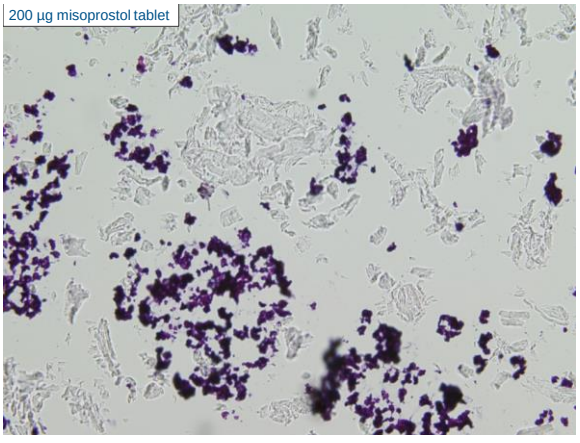
Author information

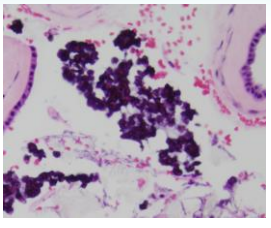
1 Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada.

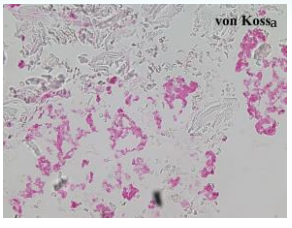


- 20 2nd trimester placentas retrospectively compared
  - 10 terminations with misoprostol and 10 without misoprostol induction
- 5/10 terminations with misoprostol showed refractile material - -microcrystalline cellulose (pharmaceutical tablet filler) deposits on maternal surfaces of placental membranes
- 0/10 placentas with no known misoprostol administration showed microcrystalline deposits


50 µm


200 µg misoprostol tablet




von Kossa

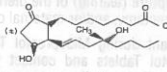
Cros

Mukhopadh

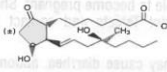
DESCRIPTION

Misoprostol oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and

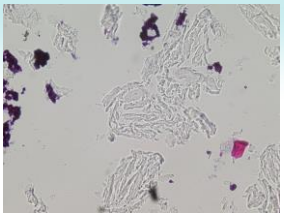


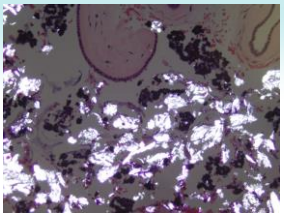
$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Misoprostol is a water-soluble, viscous liquid.

Inactive ingredients of tablets are hydrogenated castor oil, microcrystalline cellulose, and crospovidone.



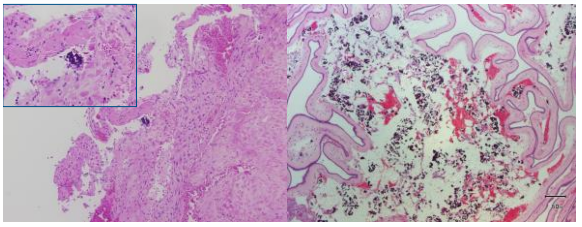


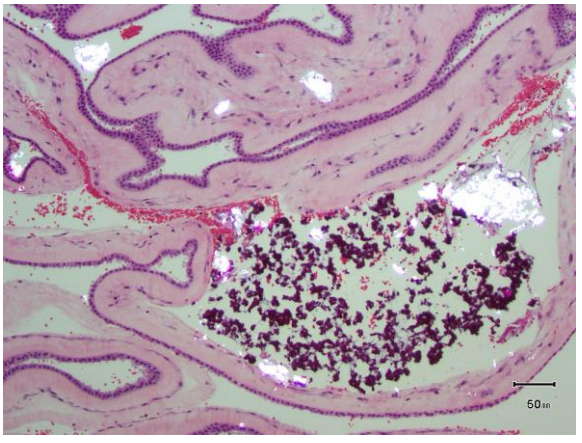
- MCC and crospovidone: inactive fillers in pharmaceutical tablets
- Deposit following placental delivery through vaginal canal
- MCC polarizable with matchstick or thatch roof morphology
- Crospovidone dark purple, clustered, non-polarizable, with coral or grape-like morphology

Retrospective Study

- **Materials and Methods**:
  - 101 placentas from surgical pathology service retrospectively reviewed
    - No vaginal dose, low-dose, and high-dose
      - Low dose = <100 mcg; High dose = >600 mcg
    - No intravaginal tablets other than misoprostol
  - Location and quantity of presumed microcrystalline cellulose (MCC) deposits, presumed crospovidone (CP), and cotton fibers documented
- **Results:**
  - MCC/CP present in:
    - 19/26 (73%) high-dose administration
    - 0/16 (0%) low-dose administration
    - 0/59 (0%) no dose administration
  - No false positives (sp = 100% for vaginal tablet use)
  - Most common locations: maternal surface of extraplacental membranes > within parenchyma of placental disc > surface of chorionic plate > surface of umbilical cord

Focal vs Diffuse





Conclusions

- MCC/CP only identified in high-dose vaginal administration, most commonly on maternal surface of extraplacental membranes
- No additional cost, just need placenta and polarizer
  - Need placenta
  - Requires vaginal tablet use
- Sensitivity ~75% in high-dose vaginal administration
  - Predictive values likely lower in community
- Specific for vaginal tablet use, not diagnostic of misoprostol use
  - Any tablet could contain these fillers
  - Misoprostol purchased from unregulated manufacturers; not known what fillers are in these tablets
  - Confirmatory methods identifying active misoprostol ingredients on slides containing these fillers would be useful, but are not currently available

Special thanks to:
Dr. Angelina Phillips (forensic pathologist)
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Dr. Ryan Cuff (maternal-fetal medicine)
Tyrish Page (research assistant)

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FORENSIC ASPECTS, CHALLENGES, AND LEGAL CONSEQUENCES OF THE MÜNCHAUSEN BY PROXY SYNDROME

Report of 6 Cases from the Institute of Forensic Medicine Aarhus Denmark and 1 from the Brody School of Medicine, University of East Carolina.

Iana Lesnikova MD, Ph.D
MGF Gilliland MD
Jytte Banner MD. Ph.D
Annie Vesterby MD

AARHUS UNIVERSITET

VIDANT™ Medical Center

Introduction

- In 1977 Sir Roy Meadow introduced the term “Münchausen syndrome by proxy”
- Child caregivers had either induced or fabricated disease in a child, resulting in considerable medical attention and treatment for the child
- Rare form of child abuse
- Incidence unknown
- Affected feign disease, illness, or psychological trauma to draw attention, sympathy, or reassurance to themselves

Introduction

- Majority of cases, the abuser is the mother or another female guardian or caregiver

- Usually, fathers deny the possibility of abuse, even in the face of overwhelming evidence

- An elusive, potentially lethal, and frequently misunderstood and overlooked form of child abuse or medical neglect

- Post-mortem diagnosis of Münchausen by proxy is very difficult (probably not possible) without clear investigational evidence and medical records

Introduction

- Mortality of Münchausen by proxy is estimated to range from 8% to 12%
- Psychiatric long-term morbidity is reported close to 50%
- Median age of children was 39.8±32.1 months and abuse lasted for 14.9±14 months

Ref: Rosenberg DA; Munchausen Syndrome by Proxy: medical diagnostic criteria. Child Abuse Negl. 2003;27(4):421-30.

Aims for Current Presentation

As a number of cases suspicious for the Münchausen by Proxy Syndrome have never been diagnosed, the incidence of Münchausen by Proxy Syndrome is low, and almost every case is unique and idiosyncratic, we believe that this presentation can contribute to recognizing and diagnosing the Münchausen by Proxy Syndrome

Case 1

4-year-old girl over three year period had a total of 27 out-patient consultations and admissions in the Ear-Nose-Throat Department due to pain, bleeding from the left ear and perforations of the left tympanic membrane.

She underwent surgery on her left ear 11 times including 4 tympanomastoidectomy procedures with myringotomy tube placement.

Morganella morganii species cultured from the left ear.

Case 1

A nurse occasionally observed that the mother was standing over the girl with her right hand over her daughter's left ear

The girl said spontaneously to a nurse, "Mom hurts my ear," while she put her hand on her left ear.

The mother walked over to the TV and said "No, I'm about to put the video on"

Case 2

4 children (10-year-old girl, 5-year-old boy, 3 -year-old boy, and 1-year-old girl).

Child A, Girl: The eldest daughter had been hospitalized three times in pediatric department after drinking lamp oil, chlorine, and gasoline.

Child B, Boy: Admitted at the age of 3-months for pneumonia after swallowed water during a bath

Child C, Boy: Admitted twice for a possible epileptic seizure and fever and unconsciousness and gasoline smell.

Case 2

Child D, Girl: longest and most complex illness

Within her first year she had been admitted 15 times

The vast majority of times she was admitted due to fever, upper respiratory symptoms and dyspnea. She was treated with antibiotics

X-ray examinations performed several times showed bilateral patchy infiltrates

A few episodes were associated with swimming, two others with smell of petrol and with smell of “deodorant”

Case 3

- **Two children, 14 months (deceased) and 8 month old with seizures.**
- **Boy A**: The oldest boy had ”seizures” with onset at age 6-months; he died at home during a ”seizure” at the age of 14-months, while the mother was alone with him
- In both children all of the ”seizures” occurred when the mother had been alone with the child, mostly in the bathroom
- Some ”seizures” occurred in the hospital, always while staff was not present
- ”Seizures” were not observed while the mother was away from the children

Case 3

- **Boy B**: began having ”seizures” at the age of 3-months
  - ”Seizures” continued during a number of hospitalizations and extensive anticonvulsant treatment
  - Strong suspicion that there was ”...something wrong with the child and his mother...” and covert video monitoring was established

Case 3

- Video

Case 4

Girl was examined at Institute of Forensic Medicine in Aarhus for suspected sexual assault perpetrated by the girl's father five times: at the age of 5-, 6-, 8-, 10-, and 11-years, respectively

The girl was accompanied by her mother on each visit

The mother described in detail the sexual assault including intercourse allegedly perpetrated by the girl's father during weekend stays

On each of the 5 examinations, genital examination revealed redness and possible scarring of the hymen

Case 5

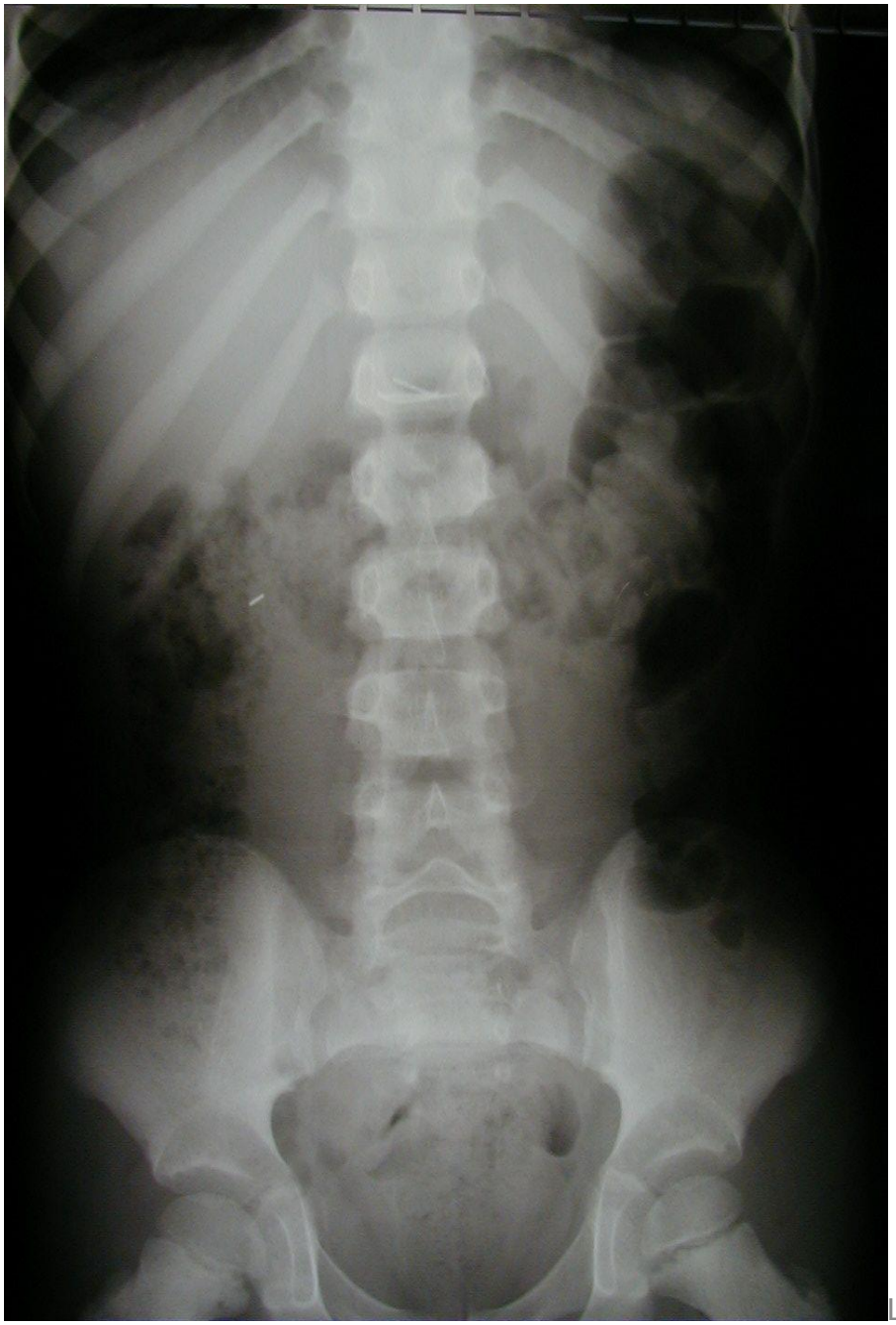
5-year-old boy with intellectual and developmental disability had many contacts with health professionals, both practitioners call physicians, emergency rooms, children's departments, and various other departments

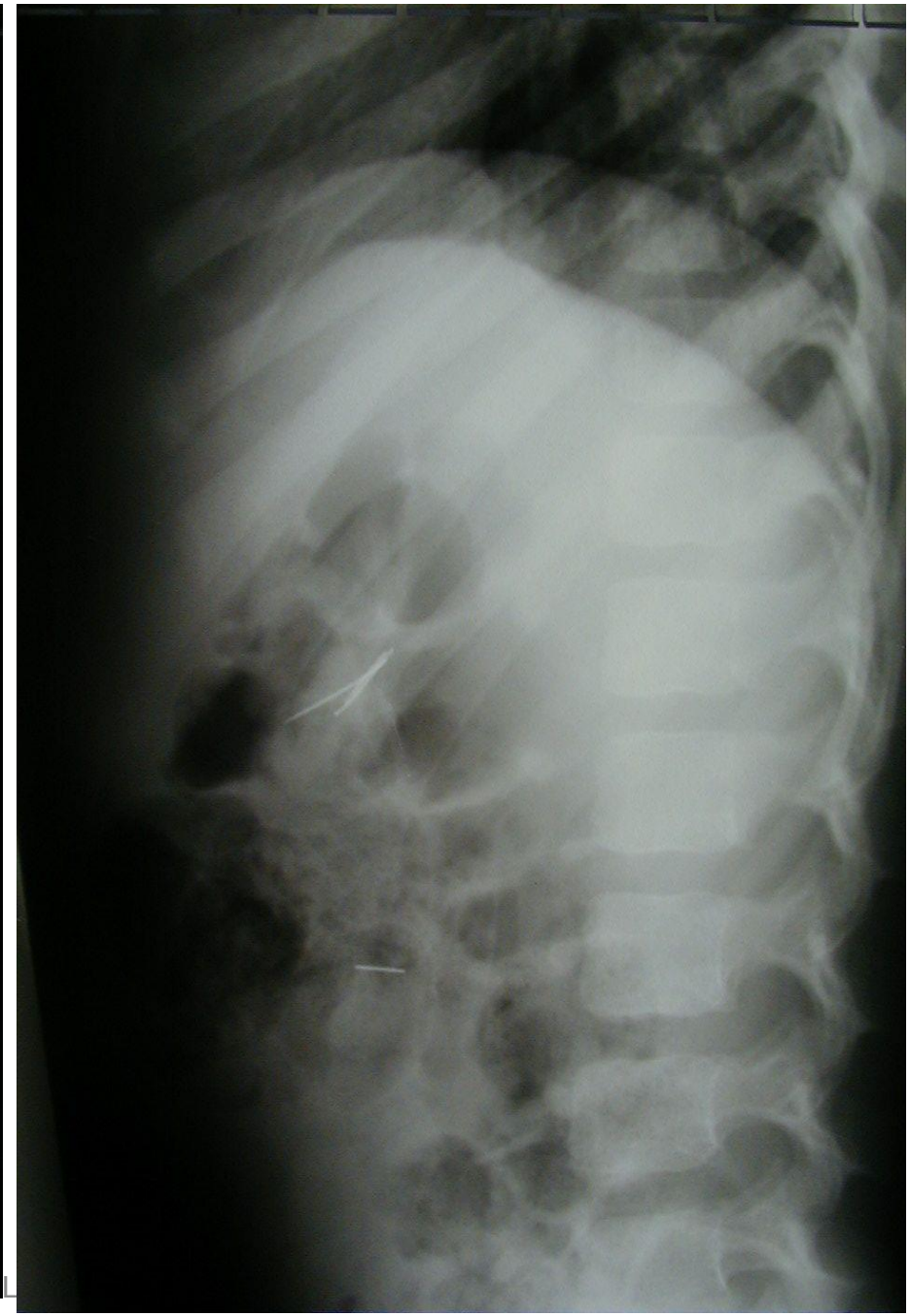
First Admission: Short needle found; according to the mother, the needle was swallowed during play while at school

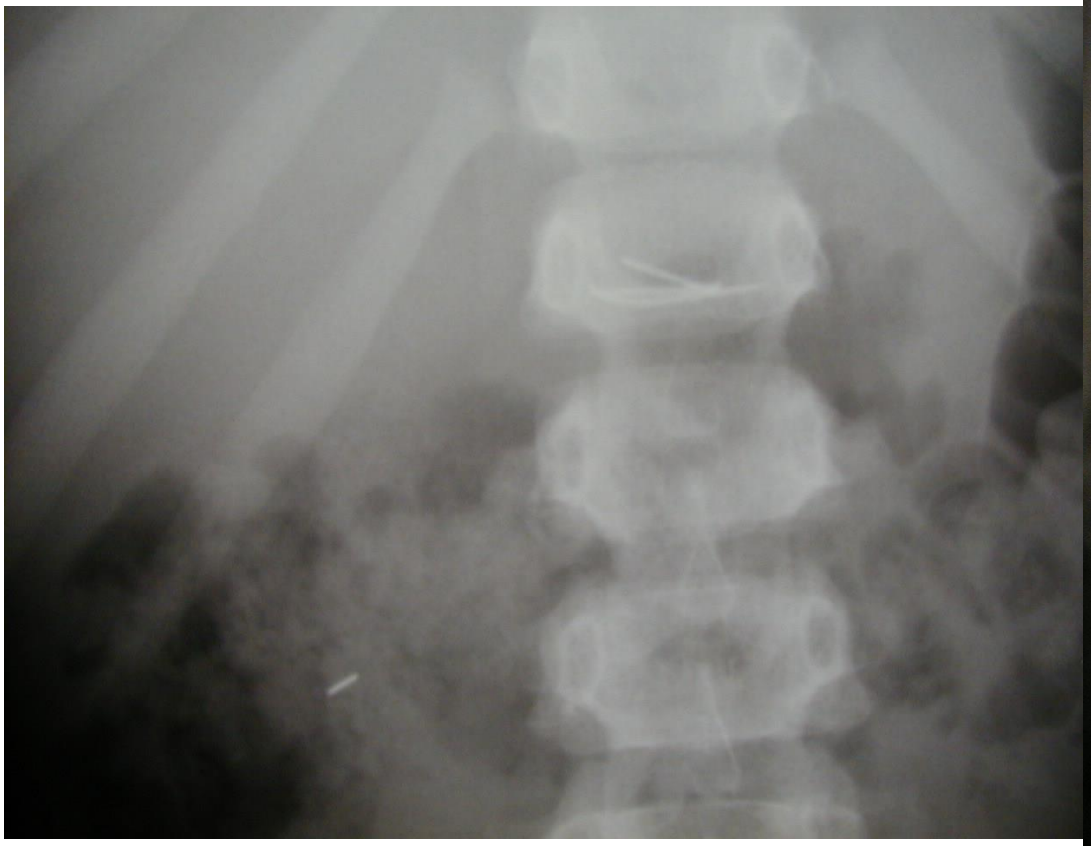
Second Admission: Reportedly “ingested” four needles; X-ray showed three close to each other, probably in the stomach, and the fourth separate

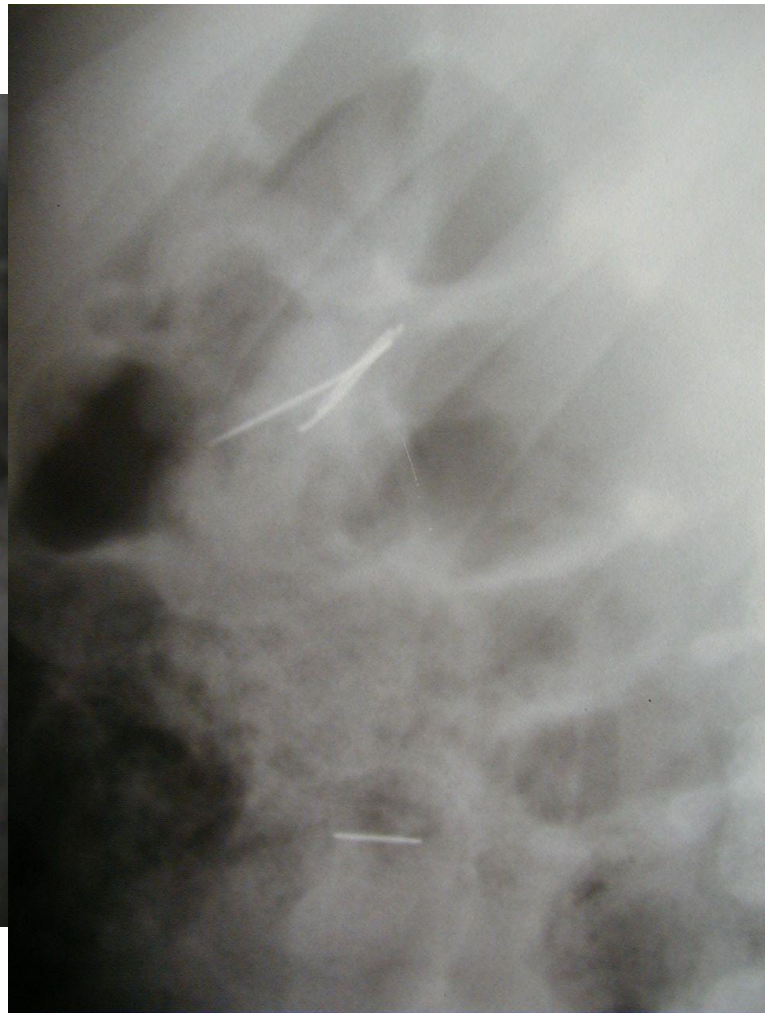
Last Admission: Reportedly “ingested” a single needle; the needle was found in the throat and was removed

Upon questioning, the mother eventually admitted placing needles in child’s throat









Case 6

Family with 4 children: 6-, 4-, 3-,1-years-old

Girl A:

Hospitalized of a total of 334 days in different Pediatric, Surgical and Psychiatric Units for constipation, fever and sepsis and malnutrition. Colostomy placement

Girl B:

Numerous admissions for fever and sepsis; no infectious focus found; blood culture identified intestinal bacteria

Massive constipation

Ileostomy, after surgery; continued with fever and sepsis

Surgery removed most of the colon; no definite abnormality was found in resected colon

Case 6

A syringe with possible intestinal contents was found in the home by police

After removal of children from family:

Children were observed to thrive and developmental conditions improved significantly

None of children have had significant infections subsequently

Intestinal stomas were reversed

Case 7

3-month-old girl and and unrelated child had multiple episodes of arrest requiring cardiopulmonary resuscitation while in daycare.

The other child had no episodes when at home or with other caregivers.

This clinical forensic consultation was considered the result of intentional actions after review by TEDI Bear Children's Advocacy Center, pediatricians, and forensic pathologist and was reported to the Department of Social Service Child Protective Services.

Discussion

- Similarities
- Differences
- Long-standing abuse
- Features described by Sir Roy Meadow in 1977 are present in these cases

Discussion

- Persistent feeling that “something is wrong”, but long time before action is taken
- Other causes cannot be completely excluded
- Strong feelings are often involved
- Sparse or no evidence
- Many controversial opinions

Take Home Messages

- Münchausen by proxy is difficult to diagnose
- Even if suspected, difficult to prove
- Almost impossible to diagnose post-mortem without significant investigative evidence
- Controversial opinions and unclear evidence
- Serious legal consequences for caregivers
- Interdisciplinary team effort is necessary

Brodifacoum Poisoning with Synthetic Marijuana

By Jarred Michalski, MD and Daniel Schultz, MD

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Disclosure

- None of the authors have any commercial or financial interest in the following presentation.

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Disclaimer

- Many of the images included in this presentation are graphic in nature.

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History

- A 45-year-old male with a past medical history of Schizophrenia and Marijuana use living with his father complains of hemoptysis in the evening.
- The decedent denies fathers request for him to go to the hospital and falls asleep on the couch.
- The father wakes up in the morning to find son covered in blood on the couch and unresponsive.
- EMS arrives and he is pronounced DOS.

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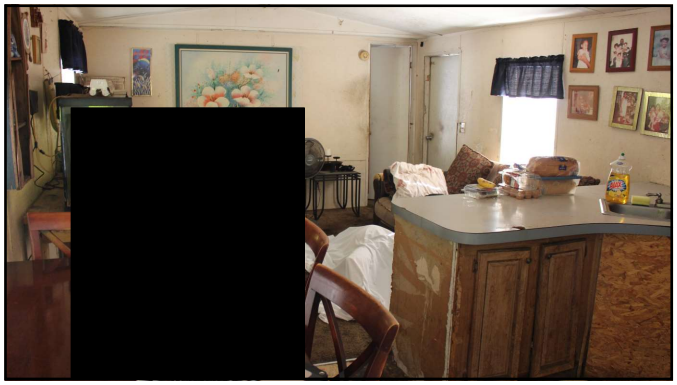

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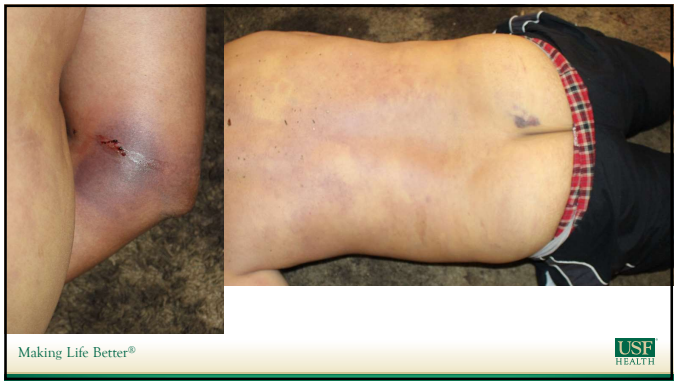
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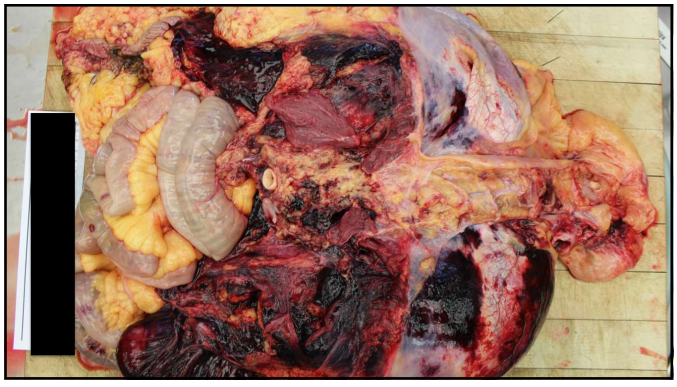

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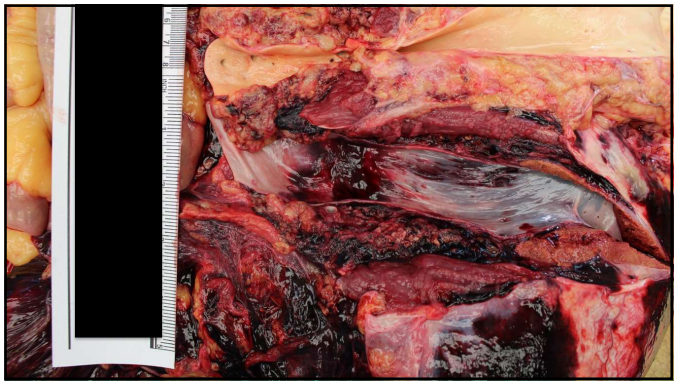

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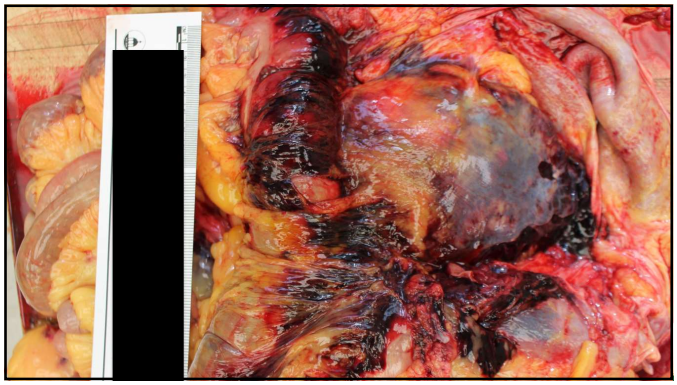

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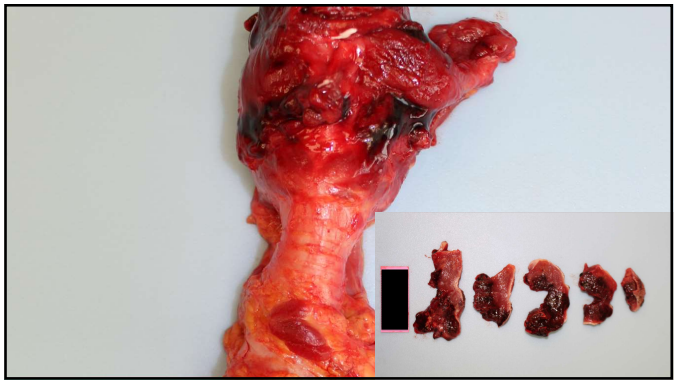

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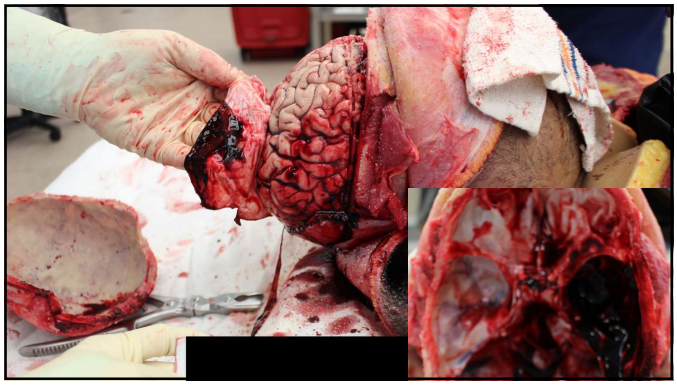

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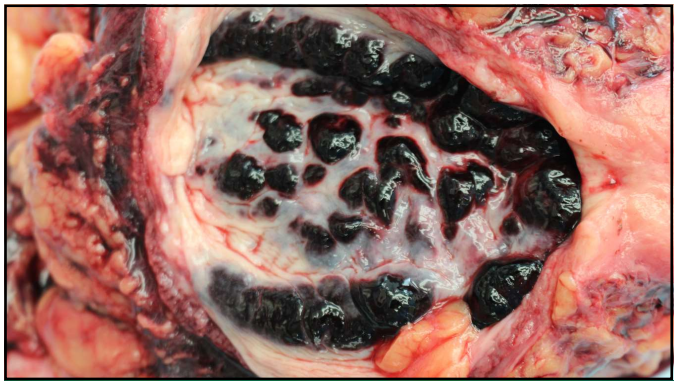

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Differential Diagnoses

- Bleeding Diathesis
  - Acquired
    - Warfarin, Vitamin K Deficiency, Liver Failure, Disseminated Intravascular Coagulation
  - Inherited
    - Hemophilia, von Willebrand disease, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, and Glanzmann's thrombasthenia

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- *Final Diagnosis:*
  - Brodifacoum poisoning
    - Hemorrhagic diathesis
  - Schizophrenia
  - 5F-ADB(synthetic cannabinoid) detected
  - THC metabolite detected
- *Cause of Death:*
  - **Hemorrhagic Diathesis** *due to* **Brodifacoum Poisoning**
- *Manner of Death:*
  - **Undetermined**

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Brodifacoum

- Created in 1975 to combat warfarin resistant rats
- Inhibits Vitamin K epoxide reductase
  - Blocks regeneration of Vitamin K1
  - Results in life-threatening anticoagulation
  - 100 times more potent than warfarin
- Half-life of 24 days

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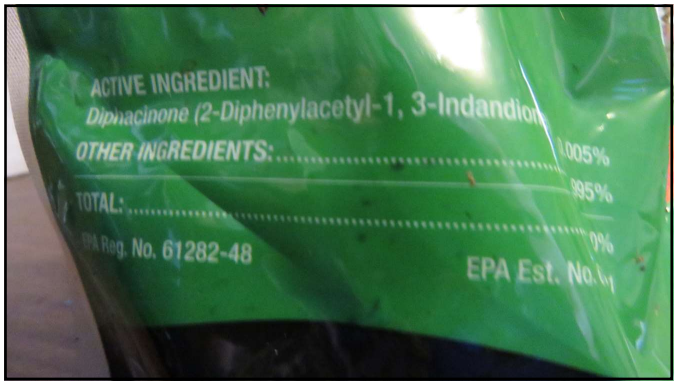

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Types of Rodenticides

Table 2. Summary of common rodenticides			
Rodenticide	Type	Chemical Class	Days of feeding needed
Warfarin	Anticoagulant	Hydroxycoumarin	multiple
Chlorophacinone	Anticoagulant	Indandione	multiple
Diphacinone	Anticoagulant	Indandione	multiple
Bromadiolone	Anticoagulant	Hydroxycoumarin	single
Difethialone	Anticoagulant	Hydroxycoumarin	single
Brodifacoum	Anticoagulant	Hydroxycoumarin	single
Bromethalin	Non-anticoagulant	other	single
Cholecalciferol	Non-anticoagulant	Vitamin D3	multiple
Zinc phosphide	Non-anticoagulant	other	single
Strychnine	Non-anticoagulant	other	single

Making Life Better® Source: http://npic.orst.edu/factsheets/rodenticides.html#references USF HEALTH

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References

- *1) Reregistration Eligibility Decision (RED) Rodenticide cluster*; EPA 738-R-98-007; U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Office of Pesticide Progams, U.S. Government Printing Office: Washington, DC, 1998
- 2) https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+3916
- 3) McPherson, R. A., & Pincus, M. R. (2017). *Henrys clinical diagnosis and management by laboratory methods*. St. Louis, MO: Elsevier.

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Image Resources

- https://www.psychemedics.com/blog/2017/08/psychemedics-corporation-launches-synthetic-cannabinoids-hair-test/
- https://www.ebay.com.au/itm/TALON-PELLETS-1kg-Rat-Mouse-Mice-Bait-Poison-Killer-Rodenticide-Brodifacoum-/161810798756
- http://npic.orst.edu/factsheets/rodenticides.html#references

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A Poison Most Peculiar: Suicide by Sodium Azide

Julia Berry, MD and Elizabeth Ventura, MD

Department of Pathology
Baylor University Medical Center
&
Southwestern Institute of Forensic Sciences

Disclosures

- None

Background

- 28 y/o male with history of suicidal ideation and attempts
- Sent text messages to wife one night stating, in part, “I just want to say goodbye,” and “I’m sorry I was a bad husband.”
- He then called his wife and said the same thing

Background

- His breathing escalated to panting really hard, and then his wife couldn't hear anything else from him
- She called a friend to check on him
- When the friend was unable to gain entry into the home, police were called who forced entry

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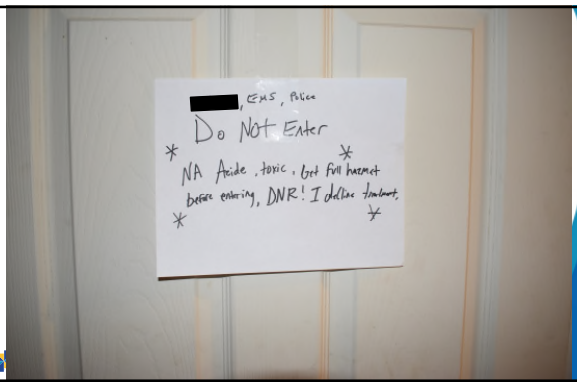
Scene

BaylorScott&White HEALTH




Nikon


HIMEDIA
GRM1038-100G
Danger

Scene

- When police officers entered the room, there was a haze, fog, &/or misty type cloud in the room
- Five officers exhibited symptoms of exposure:
  - Headache that got worse and worse, chest pain, extremely scratchy throat
  - Headache and throat discomfort
  - Headache and sore throat
  - Headache and feeling that throat was tightening up
  - Lightheaded after turning over decedent
- Four of the officers evaluated at the hospital and then released

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Autopsy

Baylor Scott & White HEALTH

External Examination

- Cyanosis of:
  - Nose
  - Gingivae
  - Fingertips
- Evidence of injury:
  - 1-5/8 x 3/8 inch red, dried abrasion over left eyebrow
  - ¼ inch linear red abrasion on lower right leg

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Internal Examination

- Petechiae on posterior one-third of the tongue, larynx, and trachea
- Laryngeal and esophageal cyanosis
- Approx. 250 mL of partially digested food and clear liquid in the stomach
- Congested gastric mucosa, lungs, and liver

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FBI Laboratory Testing

Specimen	Result	Note(s)
Item 1 blood	Azide was not detected.	1, 2
Item 2 blood	Azide was not detected.	1, 2
Item 3 gastric contents	Azide was identified.	1
Item 4 lung tissue	Azide was identified.	1, 3

Notes:

1 Analysis was performed by acidification followed by headspace gas chromatography with mass spectrometry (HS-GC-MS).
2 The non-detection of azide in Item 1 and Item 2 was confirmed by demonstrating detection of azide in portions of those specimens which had been spiked with azide at a concentration of 5 micrograms per milliliter (µg/ml).
3 For Item 4, analysis was performed on the fluid surrounding the solid tissue.

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FBI Laboratory Testing

The identification of azide in Item 3 and Item 4 indicates exposure to an azide-containing compound, such as sodium azide, lead azide, or tetrabutylammonium azide. Current FBI Laboratory procedures cannot determine the specific compound that was the source of this exposure.

Remarks:

CAUTION: The estimated concentration of azide in Item 3 is high enough that the entire specimen should be treated as an acutely toxic material.

Azide is a highly toxic chemical ion found as part of a number of different synthetic compounds with various uses. Sodium azide is the most commonly encountered of these compounds.

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Autopsy Report

- Cause of death: Toxic effects of sodium azide
- Manner of death: Suicide

Sodium Azide

- White to colorless
- Crystalline powder
- Highly water soluble
- Tasteless
- Odorless
- Forms hydrazoic acid (HN_3) when combined with water

Uses

- Component in many car airbag systems
- Chemical preservative in laboratories and hospitals
- Reagent in synthetic laboratory work
- Component in the manufacture of rubber, latex, and lead acid
- Soil sterilizing agent, fungicide, herbicide, or pesticide
- Used to treat hypertension in the 1950s

Possible Mechanisms of Action

- Human health effects of sodium azide were first reported in 1927, but to date, the mechanism of toxicity remains unknown
- Some possible mechanisms of action:
  - Inhibition of cytochrome oxidase and interference with cellular respiration
  - Enhanced excitatory transmission in the CNS after conversion to nitric oxide
  - Stimulation of carotid body chemoreceptors

Signs and Symptoms of Exposure (Low-Dose)

- Hypotension
- Dizziness
- Headache
- Nausea
- Vomiting
- Diarrhea
- Faintness
- Syncope
- Wheezing
- Coughing

Signs and Symptoms of Exposure (High-Dose)

- Hypotension
- Metabolic acidosis
- Coma
- Seizures
- Cardiac arrhythmia
- Oliguria
- Tachycardia
- Bradycardia
- Systole
- Tachypnea
- Pulmonary edema
- Respiratory failure

Specimen Considerations

- Sodium azide is extremely labile
- Acidity and enzyme activities can induce rapid deterioration postmortem
- Blood and urinary samples likely insufficient to confirm presence
- Need multiple samples of biological fluids and tissues
- In most reported cases, major concentrations observed in the stomach, bile, brain, liver, kidney, lung, and muscle
- Analysis must be performed as soon as possible

Specimen Recommendations

- Get to autopsy quickly
- Freezing is best
- Specimens must be fresh (not embalmed or formalin-fixed)
- Best specimens:
  - Lung
  - Gastric contents

Specimen Recommendations

- Lung:
  - Put chunk of wet tissue in 50 cc cryo-compatible plastic centrifuge tube
  - Don't add any solution
  - Freeze

Specimen Recommendations

- Gastric contents:
  - Considered hazardous material (shipping consideration)
  - Option 1: put in sterile specimen cup
  - Option 2 (ideal):
    - Don't submit entire specimen cup
    - Put in 15 cc cryo-compatible plastic centrifuge tube → 5 mL is more than enough
  - Freeze

Specimen Recommendations

- Bile has given positive results
  - 15 cc in plastic centrifuge tube (cryo-compatible)
  - Freeze
- Only blood? Don't bother
  - Something causing chemical to break down
    - Residual enzyme in blood (esterase)?
    - Reaction with preservative agent?

Autopsy Safety

- Potential for liberation of hydrazoic acid from the stomach
- Unless absolutely necessary, avoid opening the stomach
- If unavoidable, perform autopsy in well-ventilated setting, & ideally:
  - Wearing a supplied air respirator (or)
  - Under a fume hood (or)
  - With air extractor over autopsy table
  - Nitrile gloves Ok

Autopsy Safety

- Avoid pouring gastric contents down drain
- Hydrazoic acid can react with copper and lead metal drain pipes to form explosive azide salt
- Less risk with PVC pipes
- If contents go down the drain, flush sink very thoroughly with water

Specimen Handling

- Avoid metal containers
- Have a blood specimen tested for infectious diseases at the time of autopsy
  - If negative, can use hazardous waste disposal
- Otherwise, have to work with biohazardous waste vendor for disposal
  - Challenging because a combo (potentially) of infectious material and hazardous waste

Scene Considerations

- Sodium azide (NaN_3) forms hydrazoic acid (HN_3) when combined with water (as in our case)
- Can enter the body via cutaneous absorption or inhalation of hydrazoic acid vapor
- No specific antidote exists
- No treatment has demonstrated any efficacy
- Sodium azide poisoning is treated with supportive medical care in a hospital setting
- The most important thing is for victims to seek medical treatment as soon as possible

Case Revisited

Sodium Azide

- Toxic dose: 10 mg/kg or above 700 mg
- Decedent consumed approximately 75 g
- He researched method on the internet
- He purchased sodium azide through Amazon

References

- Blanc-Louvry IL, Laburthe-Tolra P, Massol V, et al. Suicidal sodium azide intoxication: An analytical challenge based on a rare case. *Forensic Sci Int*. 2012;221:e17–e20.
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NMS

BHB Testing in Postmortem Blood to Differentiate Between Solvent Ingestion and DKA

LAURA LABAY, PhD, F-ABFT, DABCC-TC
KENNETH GALLAGHER, MD

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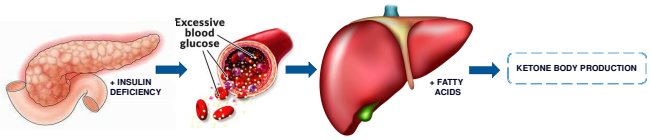
Diabetic Ketoacidosis (DKA)

- Characterized by hyperglycemia, ketoacidosis, ketonuria
- Ketone overproduction causes accumulation in the blood



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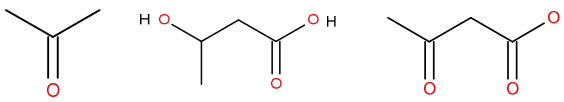
Ketone Bodies



acetone | β-hydroxybutyric acid (BHB) | acetoacetate

3

How else can you get Acetone/IPA positive results?

Ingestion

minor metabolic pathway (reduction)

alcohol dehydrogenase

4

How else can you get Acetone positive results?

Isopropyl Alcohol Metabolism After Acute Intoxication in Humans

D.R. Daniel, B.H. McAnalley, and J.C. Garriott
Southwestern Institute of Forensic Sciences at Dallas, Post Office Box 35728, Dallas, Texas 75235

Journal of Analytical Toxicology, Vol. 5, May/June 1981

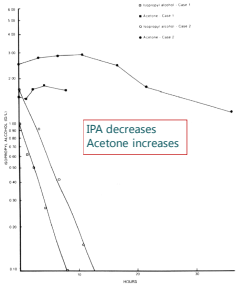


Figure 1. Isopropyl alcohol and acetone concentrations in two cases of acute overdose of isopropyl alcohol. Concentrations are averages of triplicate analyses of each sample.

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TOXICOLOGY – DKA PRESENTATION

Detailed Findings:

Analysis and Comments	Result	Units	Rpt. Limit	Specimen Source
Isopropanol	8.1	mg/dL	5.0	001 - Peripheral Blood
Acetone	34	mg/dL	5.0	001 - Peripheral Blood
Benzoylecgonine	330	ng/mL	50	001 - Peripheral Blood
Delta-9 Carboxy THC	7.1	ng/mL	5.0	001 - Peripheral Blood
Delta-9 THC	1.5	ng/mL	0.50	001 - Peripheral Blood
Isopropanol	Confirmed	mg/dL	5.0	001 - Peripheral Blood
Acetone	Confirmed	mg/dL	5.0	001 - Peripheral Blood
Creatinine (Vitreous Fluid)	2.3	mg/dL	0.050	002 - Vitreous Fluid
Sodium (Vitreous Fluid)	141	mmol/L	80	002 - Vitreous Fluid
Potassium (Vitreous Fluid)	>20	mmol/L	1.0	002 - Vitreous Fluid
Chloride (Vitreous Fluid)	105	mmol/L	70	002 - Vitreous Fluid
Glucose (Vitreous Fluid)	>500	mg/dL	35	002 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	61	mg/dL	3.0	002 - Vitreous Fluid

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TOXICOLOGY - DKA?

Analysis and Comments	Result	Units	Limit	Specimen Source
Acetone	10	mg/dL	5.0	001 - Femoral Blood
Delta-9 Carboxy THC	12	ng/mL	5.0	001 - Femoral Blood
Delta-9 THC	6.1	ng/mL	0.50	001 - Femoral Blood
Acetone	Confirmed	mg/dL	5.0	001 - Femoral Blood
Creatinine (Vitreous Fluid)	0.88	mg/dL	0.050	003 - Vitreous Fluid
Sodium (Vitreous Fluid)	138	mmol/L	80	003 - Vitreous Fluid
Potassium (Vitreous Fluid)	14	mmol/L	1.0	003 - Vitreous Fluid
Chloride (Vitreous Fluid)	114	mmol/L	70	003 - Vitreous Fluid
Glucose (Vitreous Fluid)	None Detected	mg/dL	35	003 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	18	mg/dL	3.0	003 - Vitreous Fluid
Acetone	11	mg/dL	5.0	003 - Vitreous Fluid

Not stable

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Acetone Concentrations – Are they helpful?

HEALTH STATUS	ACETONE (mg/dL)	REFERENCE(S)
Controlled Diabetics	Blood: < 3.0	• Jones AW., et al. J Anal Toxicol. 1993 May-Jun;17(3):182-5.
DKA	Blood: 14.5 – 74.8 (27 patients)	• Sulway MJ, Malins JM. Acetone in diabetic ketoacidosis. Lancet. 1970 Oct 10;2(7676):736-40.
Acetone Ingestions	Serum: 83.6 and 390 (2 cases) Blood: 200 and 250 (2 cases)	• Kallenberg K, et al. MR imaging-based evidence of vasogenic brain edema in a case of acute acetone intoxication. AJNR Am J Neuroradiol. 2008 Apr;29(4):e16. • Kostusiak V, et al. Survival after drinking lethal dose of acetone. Intensive Care Med. 2003 Feb;29(2):339. • Ramu A, et al. Disposition of acetone following acute acetone intoxication. West J Med. 1978 Nov;129(5):429-32. • Zettinig G, et al. [Survival after poisoning due to intake of ten-times lethal dose of acetone]. Dtsch Med Wochenschr. 1997 Nov 28;122(48):1489-92.

8

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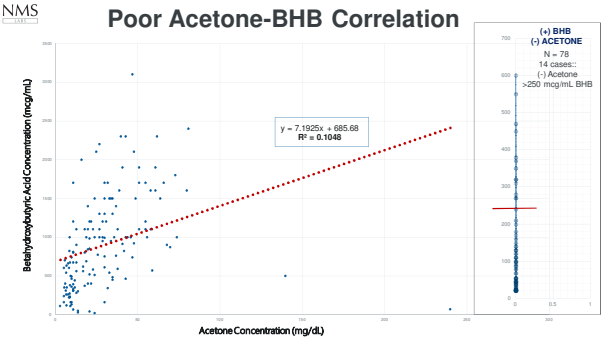
Poor Acetone-BHB Correlation



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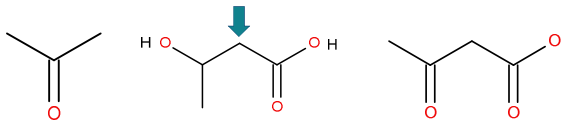
Ketone Bodies

The most stable and specific indicator of ketoacidosis
Can be used to differentiate between ketoacidosis and solvent ingestion



acetone
Least abundant

β-hydroxybutyric acid (BHB)

acetoacetate
Not stable

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BHB Sample Preparation

1) **Sample + ISTD**
   - 100 µL Blood, S/P, Fluid, Urine
   - 3-Hydroxybutyric Acid-D4 (ISTD)
2) **Solvent Crash**
   - 1mL Acetonitrile
   - -20°C for 10 min
   - 3800 rpm, 15 min, 4°C
3) **Dry Down**
   - 45 ± 5°C
4) **Derivatize**
   - BSTFA + 1% TMS
   - Transfer to autosampler vial

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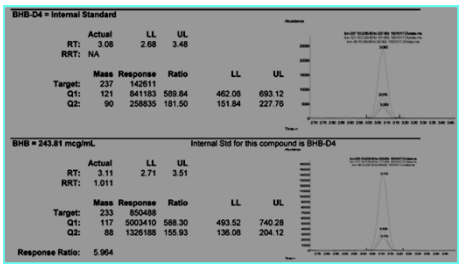
SIM-GC/MS Data

- Agilent 5973 GC/MS
- DB-17 (Agilent) 15M x 0.25 mm
- Helium carrier gas
- Selected Ion Monitoring
- 6 point calibration; area
- 1/x weighting



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NMS LABS

Alaska Department of Health and Social Services
Division of Public Health

Case History

- 46-year old male with history of ethanol abuse
- During hotel stay found incoherent at 12 PM
- Assisted back to room and police notified
- Discovered unresponsive at 12:52 PM
- Death pronounced
- Multiple empty Vodka bottles at scene

Specimens Received:

ID	Tube/Container	Volume/ Mass	Collection Date/Time	Matrix Source
001	Gray Top Tube	5.5 mL	01/14/2019	Femoral Blood
002	Homogenate Container	Not Given	01/14/2019	Femoral Blood
003	Gray Top Tube	4.75 mL	01/14/2019	Heart Blood
004	Gray Top Tube	9.25 mL	01/14/2019	Subclavian Blood
005	Red Top Tube	2.5 mL	01/14/2019	Vitreous Fluid
006	Red Top Tube	9.75 mL	01/14/2019	Postmortem Urine

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NMS LABS

Case – First Round of Toxicology Testing

Isopropanol	43	mg/dL	5.0	002 - Femoral Blood
Acetone	170	mg/dL	5.0	002 - Femoral Blood

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NMS LABS

Case – Second Round of Toxicology Testing

Isopropanol	43	mg/dL	5.0	002 - Femoral Blood
Acetone	170	mg/dL	5.0	002 - Femoral Blood
Creatinine (Vitreous Fluid)	1.2	mg/dL	0.050	005 - Vitreous Fluid
Sodium (Vitreous Fluid)	141	mmol/L	80	005 - Vitreous Fluid
Potassium (Vitreous Fluid)	11	mmol/L	1.0	005 - Vitreous Fluid
Chloride (Vitreous Fluid)	125	mmol/L	70	005 - Vitreous Fluid
Glucose (Vitreous Fluid)	None Detected	mg/dL	35	005 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	27	mg/dL	3.0	005 - Vitreous Fluid

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Case – Third Round of Toxicology Testing

Isopropanol	43	mg/dL	5.0	002 - Femoral Blood
Acetone	170	mg/dL	5.0	002 - Femoral Blood
Creatinine (Vitreous Fluid)	1.2	mg/dL	0.050	005 - Vitreous Fluid
Sodium (Vitreous Fluid)	141	mmol/L	80	005 - Vitreous Fluid
Potassium (Vitreous Fluid)	11	mmol/L	1.0	005 - Vitreous Fluid
Chloride (Vitreous Fluid)	125	mmol/L	70	005 - Vitreous Fluid
Glucose (Vitreous Fluid)	None Detected	mg/dL	35	005 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	27	mg/dL	3.0	005 - Vitreous Fluid

Blood BHB: NONE DETECTED

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Case – COD & MOD Determination

Isopropanol	43	mg/dL	5.0	002 - Femoral Blood
Acetone	170	mg/dL	5.0	002 - Femoral Blood
Creatinine (Vitreous Fluid)	1.2	mg/dL	0.050	005 - Vitreous Fluid
Sodium (Vitreous Fluid)	141	mmol/L	80	005 - Vitreous Fluid
Potassium (Vitreous Fluid)	11	mmol/L	1.0	005 - Vitreous Fluid
Chloride (Vitreous Fluid)	125	mmol/L	70	005 - Vitreous Fluid
Glucose (Vitreous Fluid)	None Detected	mg/dL	35	005 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	27	mg/dL	3.0	005 - Vitreous Fluid

Blood BHB: NONE DETECTED

The cause of death was reported as acute acetone/isopropanol ingestion and the manner of death was accident.

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BHB – biomarker for DKA v. solvent ingestion

-INTERPRETATION TABLE-			
Acetone/IPA	Glucose (>200 mg/dL)	BHB (>250 mg/dL)	Interpretation*
+	+	+	DKA
+	-	+	DKA/EtoH ketoacidosis
+	-	-	Solvent Ingestion

* If someone has ketoacidosis and consumes acetone or IPA → I'm out ☺

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CONCLUSIONS

ACETONE

- Analytical testing only shows presence and quantity, not its source
- Acetone by itself is not a robust biomarker for determination of a pathologically significant ketoacidosis or to show its absence
- A low or negative acetone concentration does not preclude an elevated BHB

VITREOUS GLUCOSE

- While elevated concentrations are indicative of hyperglycemia, instability can mean the reported concentration is not representative of the antemortem concentration

BHB

- A strong indicator of ketoacidosis and can be used to substantiate or negate a diagnosis

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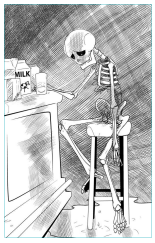

Questions

Laura.Labay@nmslabs.com

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Use of Biofire® FilmArray® in a Medical Examiner's Office, A Case Series

Presenting Author: Megan Lee, M4

Boone/Callaway County Medical Examiner's Office
University of Missouri Health Care

Disclosures

- None
- No affiliation with bioMérieux
- All mention of BioFire® FilmArray® technology is for academic purposes only

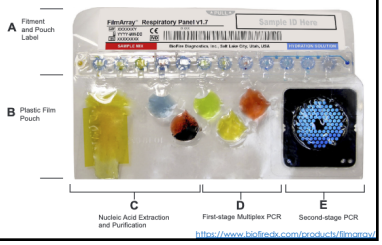
Post-Mortem Pathogen Testing Options

- Histopathology +/-
  - Special stains
  - IHC
  - ISH
- Culture
- Molecular genetics, including PCR

https://www.biofiredx.com/products/the-filmarray-panels/filmarray-gi/

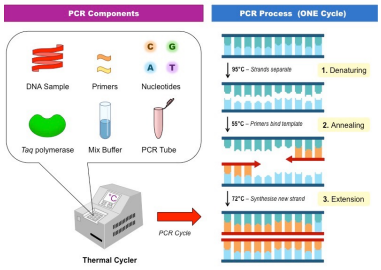
What is the BioFire® FilmArray®?

Automated, User-Friendly, Multiplex PCR



https://www.biofiredx.com/product/filmarray/

Polymerase Chain Reaction Overview



https://jb.biopinion.com.au/standard-level/topic-3-genetics/3-5-genetic-modification-and-biotechnology/3-5-1-polymerase-chain-reaction-pcr-html

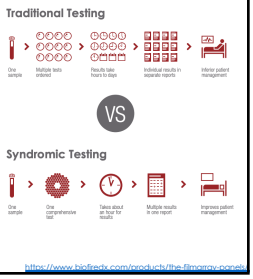
BioFire® FilmArray® Panels

The FilmArray® Respiratory Panels
Sample Type: Nasopharyngeal Swab

The FilmArray® Gastrointestinal (GI) Panel
Sample Type: Stool in Cary Blair FDA-cleared and CE-marked

The FilmArray® Meningitis/Encephalitis (ME) Panel
Sample Type: Cerebrospinal Fluid (CSF) FDA-cleared and CE-marked

The FilmArray® Blood Culture Identification (BCID) Panel
Sample Type: Positive Blood Culture FDA-cleared and CE-marked

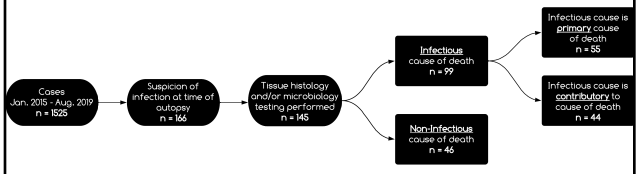


https://www.biofiredx.com/products/the-filmarray-panels/

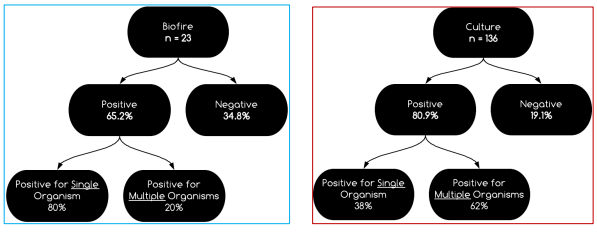
Cost

- Two Options
  - Purchase machine and pouches and run samples in-house
  - Send out to the closest lab with BioFire® FilmArray® capabilities
- Our office is associated with the University of Missouri Health Care System
  - We send out the sample (down the hall) and are charged **$460 per panel**

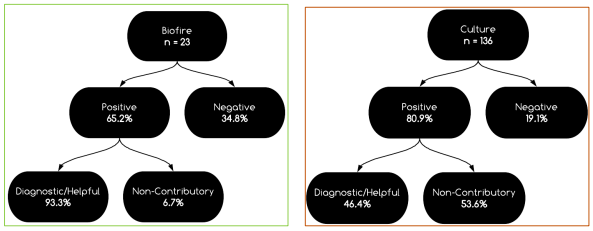
Methods



Results



Results



Case 1: 11-Year-Old Male

- Scene History
  - The decedent reportedly "had the flu" prior to death. Other family members were also ill, but no one had gone to see the doctor. He was found dead in bed by his mom.
- Autopsy Findings
  - Vitreous glucose greater than 500 and ketones present in blood
  - R. ventricular dilation
  - R. and L. lung parenchyma uniformly congested, edematous, and hemorrhagic

Case 1: 11-Year-Old Male

- Histologic Findings
  - R. and L. lungs: Edema and vascular congestion, mild autolysis, bacterial colonies present
- Culture Results
  - Lung: Heavy *Staphylococcus aureus* and scant *Klebsiella* species *oxytoca/Raoultella ornithinolytica*
- BioFire® FilmArray® Results
  - Respiratory: Positive for influenza A/H1-2009

Case 1: 11-Year-Old Male

- Cause of Death
  - Influenza complicating diabetes mellitus resulting in diabetic ketoacidosis

Case 2: 5-Year-Old Female

- Scene History
  - The decedent had been sick the entire week before death; she had a sore throat. She went to urgent care and was sent home. She went to take a nap and was found unresponsive later. 911 was called, and she was dead upon arrival in the ER.
- Autopsy Findings
  - Splenomegaly, enlarged cervical and mesenteric lymph nodes
  - R. and L. lung parenchyma uniformly congested and edematous
  - Moderate edema of the brain

Case 2: 5-Year-Old Female

- Histology Findings
  - R. and L. lungs: Vascular congestion; material consistent with aspirated stomach contents in some airways with no associated inflammatory reaction
  - Lymph node, R. upper neck: Paracortical lymphoid proliferation; IHC negative for EBV
- Culture Results
  - Blood: Positive for *Streptococcus salivarius*, likely a contaminant
- BioFire® FilmArray® Results
  - Respiratory: Positive for rhinovirus/enterovirus

Case 2: 5-Year-Old Female

- Cause of Death
  - Sudden unexplained death in a child with an infectious mononucleosis-like illness
  - Asner et al. describe two patients who died from a sepsis-like illness who had respiratory failure and possible pneumonia with no pathogens identified other than human rhinovirus/enterovirus

Case 3: 2-Year-Old Female

- Pertinent Medical History
  - The decedent had been to the ER, was diagnosed with Influenza A, and was sent home with Tamiflu
  - She had previously been diagnosed with strep throat
- Scene History
  - Mom found her unresponsive and took her back to the ER, where she was pronounced dead
- Autopsy Findings
  - Lung parenchyma uniformly congested, edematous
  - R. lower lobe consolidation

Case 3: 2-Year-Old Female

- Histology Findings
  - R. lung: acute bronchopneumonia consisting of neutrophils around bronchi. Abscesses consisting of focal necrosis containing bacterial colonies (cocci) surrounded by neutrophils
- Culture Results
  - Culture not performed
- BioFire® FilmArray® Results
  - Respiratory: Positive for influenza A/H3

Case 3: 2-Year-Old Female

- Cause of Death
  - Influenza A/H3 infection
  - Complicated by acute pneumonia, including abscess formation

Summary

- Biofire® FilmArray® is an easy to implement, all-in-one rapid PCR device that identifies the presence of disease-causing pathogens in a syndromic fashion
- It can be useful in a variety of cases, especially pediatric cases
- PCR is less likely to have the limitations and inherent confounders of microbiological culture testing
  - Interval time after death
  - Contamination
  - Viability
  - Antibiotic use

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- Jason Stewart – Forensic Technician
- Scott Noble – Forensic Technician
- Dori Burke – Forensic Investigator
- Stacey Huck – Forensic Investigator

A NEW WAY TO LOOK AT DATA: COLLABORATION BETWEEN THE COOK COUNTY MEDICAL EXAMINER'S OFFICE AND THE BUREAU OF TECHNOLOGY

DR. ECKHARDT
DR. ARUNKUMAR
COOK COUNTY BUREAU OF TECHNOLOGY, GRAPHIC INFORMATION SYSTEMS

1

NO CONFLICTS OF INTEREST TO DISCLOSE

2

BACKGROUND
GUN VIOLENCE EPIDEMIC

- 2017:
  - 840 homicides, 744 caused by gun violence = 89%, more than NY + LA (CCMEO)
- Most victims die from multiple GSWs
- Higher velocity = more devastating injuries
  - Many cases of rifle GSWs – multiple injuries/fragments of projectile
- Combo of crushed/shredded tissue & effects of temporary cavity = extent of wound

3

BACKGROUND
OPIOID ADDICTION EPIDEMIC

- 2017:
  - 1,167 deaths due to opioid overdose (CCMEO)
    - 787 heroin related
    - 669 fentanyl related
      - Strong synthetic opioid, 50-100 x morphine
- CCMEO first to identify drug use trends
  - Info relayed to IDPH, ED Drs to aid Tx

4

BACKGROUND
FREEDOM OF INFORMATION ACT

- 1967:
  - public right to access info from federal agencies
  - Exemptions related to national security, trade secrets, PHI, etc.
- 2017:
  - CCMEO 400 FOIA requests (more than any other county dept)
    - Journalists, residents, law enforcement, medical professionals and researchers related to opioids or gun violence
- ALL CCMEO's data public under Illinois law

5

FOIA REQUEST

FOIA Officer

Public Information Officer with help of SQL database administrator

Wait time could be up to 10 days (usually less than a week)

Statistical requests (51 in 2017):
- Researcher/journalists must make specific request for data- funneled into narrow focus

6

LABLYNX

- Electronic case management system
- Introduced August 2014
- Each case entered has geographic, demographic, COD/MOD in system
- Hosted by cloud
- Nightly backup of all data to server on premises

7

CCMEO-/BOT PARTNERSHIP

- Feb 2017:
  - –CCMEO + BOT created dashboards, maps, open data set of all CCMEO deaths since 2014
  - –BOT, dept of Geographic Information Systems (GIS) extracted SQL data from backup
  - –Geocoded data
  - –Populated online map and page County's Open Data Portal
- January 30th, 2018 open to the public
- Maps and dashboard populated by online database updated nightly:
  - –COD/MOD
  - –Demographics
  - –Location of incident
- Separate maps for opioid deaths and gun violence deaths
- Users can create heat maps, locate cluster, export data to analyze

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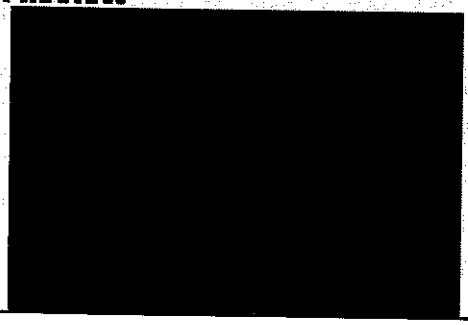
PREVIEW



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COST

- $0
  - Created in-house by GIS and IT Communications creating templates included in existing contracts with software companies
    - Cook County GIS department pulls or receives data directly from Lablynx database nightly. GIS and open data teams fed templates on County maps portal and County Open Data Portal
  - Map portal paid as part of enterprise software license with Esri
  - Data portal included with Socrata contract

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RESULTS

- FOIA requests reduced
  - 51 statistical requests by in 2017 by March 1st
  - 14 statistical requests in 2018 by March 1st
- Increased transparency
- Real-time data for researchers, law enforcement, journalists and public
- Chicago Sun Times used database to report on kratom:
  - https://chicago.suntimes.com/2018/3/5/18329523/kratom-health-supplement-targeted-by-fda-linked-to-9-deaths-in-cook-county

11

COMING IMPROVEMENTS

- More mobile friendly
- Eventual transition to cloud based data repository
  - Physical server outdated
- Improve capturing of opioid related deaths
  - Recent check box added to Lablynx to better identify cases
- Extreme temperature related deaths
  - Possibly with cooling/warming centers
- Motor vehicle collisions

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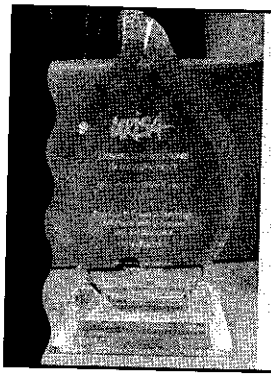

OUTCOMES

- Better distribution of healthcare resources
- Assist DEA/law enforcement when there are opioid death/homicide death clusters
- Real time outbreak tracking
- More transparency of medical examiner data for researchers/journalists/general public

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POSSIBLE CONSEQUENCES

Use of data for real estate

Criminal activity
Rob vacant houses

Family disputes
Family members trying to shield others from the COD

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LIVE PREVIEW (TIME PERMITTING)

- https://maps.cookcountyil.gov/medexammaps/
- Need google chrome to function properly

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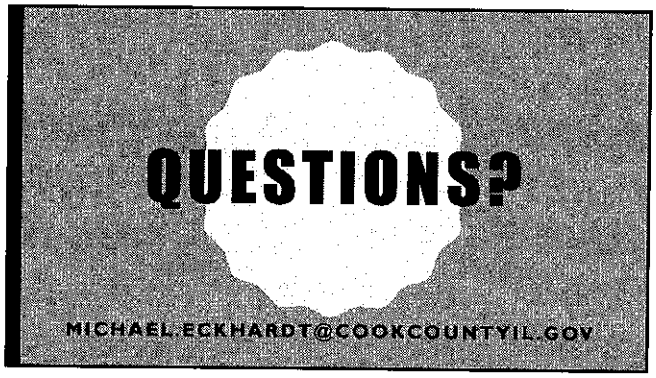

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Improving Contagious Disease Reporting in a Medical Examiner's Office

Christopher Rogers, MS, MD, MBA
Lakshmanan Sathyavagiswaran, MD, FRCPC, FCAP, FACP
Los Angeles County
Department of Medical Examiner-Coroner

Influenza Pandemic of 2009

- In the 2009-10 season, there were 149 deaths from influenza in Los Angeles County.
- The Medical Examiner's Office reported one. The ME handles 30% of deaths in the County.
- Why so few?

Reasons for Limited Reporting

- Physicians may not be aware of reporting requirement.
- ME staff do not recognize signs of possible influenza death.
- ME staff recognize signs of influenza but do not take appropriate specimens.
- Influenza is diagnosed but not reported.

Ways to Increase Reporting

- Prospective increase—find more reportable disease in future cases
- Retrospective increase—find reportable disease that was not identified originally

Physician Education

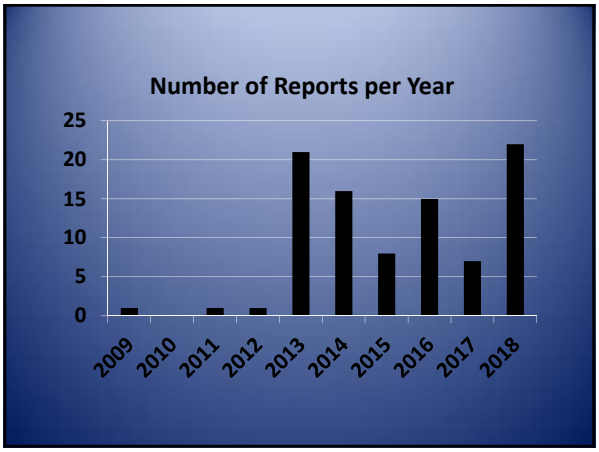
- List of reportable diseases distributed to medical examiners
- Public Health physicians gave a conference on reporting contagious disease
- The Medical Examiner published a notice in the local pathology newsletter about the need to complete cultures in deceased patients

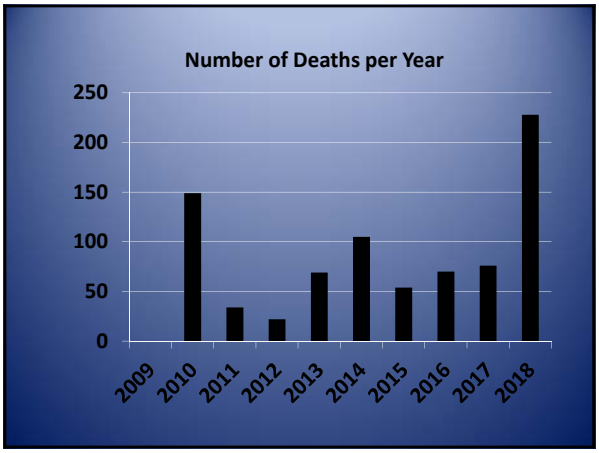
Rapid Reporting

- Information reported to the Medical Examiner is transmitted daily to Public Health.
- Public Health computer searches for terms such as “flu” and “cough”, then flags those cases for manual review.
- If appropriate, public health nurse calls the ME and requests cultures.

Single Point of Contact

- All culture results come to a single individual, who reports any result required.
- In some cases (for example, rubeola), telephone reporting is required.





Retrospectively Identified Case Circumstances

- A 35-year-old woman delivered a normal baby, then expired at home four days later.
- She was found in a secure residence by her boyfriend.
- Decedent resides at the residence with her children.
- It was single story, family style residence.

Circumstances

- The father of the children (boyfriend) does not always stay at the residence.
- The decedent did not use tobacco. She used alcohol socially and also used marijuana.
- There was no history of MI, CVA, or seizures.
- Boyfriend stated that since giving birth, when it was cool outside the decedent would be very warm, and when it was warm she would feel very cold.

Coroner Investigator Scene Investigation

The ambient temperature – unregulated was 87.0 degrees at 1700 hours. The core body (liver) temperature was 90.9 degrees F at 1705 hours, nearly 6 hours after being found. Livor mortis blanched to medium pressure and was consistent with the position found. Rigor mortis was 2+ throughout.

Autopsy Findings

- Well-built and well nourished adult Black female .
- No evidence of trauma found at autopsy.
- The uterus had a post-gravid appearance with an expected enlarged, swollen congested appearance. The uterine cavity was empty and free of foreign material.
- Heart weighed 260 grams and showed no coronary atherosclerosis. Spleen (300 grams) and lungs were congested.
- Toxicology studies showed hydrocodone, ibuprofen and acetaminophen.
- The cause and manner of death were opined as undetermined.

Retrospective Peer Review

- At peer review, additional sections of uterus were taken and special stains were ordered, as cervix showed inflammation.
- Additional histopathology exam showed severe acute inflammation of cervix and myometrium, and endo-cervical necrosis with Gram-positive cocci in chains in vessels and infiltrating tissue.
- There were similar findings on Gram stain of liver, lung, pancreas and heart.
- Medical records were ordered.

Retrospective Medical Record Review

- The decedent delivered a male fetus on 6-14-15 at 1434 hours by manually assisted vaginal delivery. Her admission WBC count was 8800 (74.6% neutrophils).
- The placenta was delivered at 1436 hours.
- Apgar scores were 9 at 1 minute and 9 at 5 minutes. The weight of the baby was 3205 gm, length 49.5 cm.

Retrospective Medical Record review

- The night after delivery her temperature was 103° F and she had chills and abdominal pain. She was treated with acetaminophen and discharged the next day.
- Her WBC count that morning was 18800 (90.8% neutrophils)
- Records reviewed show no cultures were done and no antimicrobial therapy was given. Per the pathology department, no placenta pathology report was available

Consultation

- In view of the autopsy findings and no culture being done at the hospital CDC was consulted through the local Health Department.
- The consultation included:
  - Medical records
  - Autopsy report
  - Formalin-fixed tissue
  - Digital images

  NOTE: Group A Streptococcus (Streptococcus pyogenes) confirmed by immunohistochemical stains at CDC

Case review/Conclusion

Following retrospective case review/CDC -IHC result, cause of death was amended

- Group A streptococcus (Streptococcus pyogenes) sepsis
- due to Postpartum uterine infection

Manner of death : Natural

Concern: Lack of therapy for probable sepsis at the hospital and not sending the placenta for pathological exam.

This was a possible preventable death.

Take Home Messages

- Look at the whole case file when reviewing cases.
- Order medical records as warranted in hospitalized cases.
- Know what cases need to be reported to public health/Medical Board.
- Value of a thorough scene investigation.
- In this case it was very useful including getting a core body temperature (liver temperature).
- Note: Reporting the treating OB/Gyn to the Medical Board was considered but not done due to delay in diagnosis/lack of placental pathology report.

Critical Diagnoses and Duty to Warn in Forensic Pathology: an Evaluation of Ethics and Proposed Reporting Recommendations

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Disclosure

- The authors have documented that they have no financial relationships to disclose or conflicts of interest to resolve.

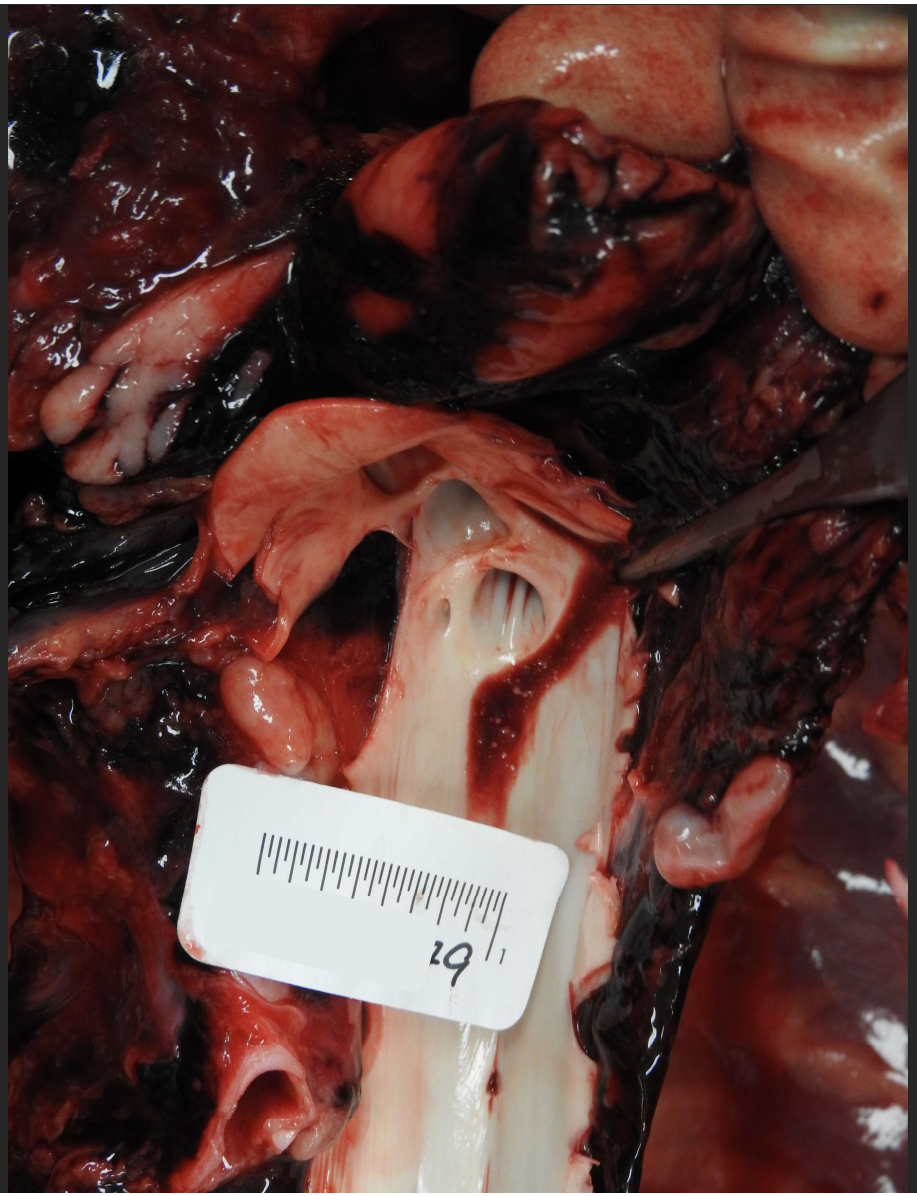
A catalyst case

9-year-old female with no medical history except one-week upper respiratory illness with cough

Became cyanotic and unresponsive

Died following attempted resuscitation

No known or suspected trauma



- Bilateral hemothoraces
- Extensive mediastinal soft tissue hemorrhage
- Dissection of ascending aortic arch
- Delicate tissues

Spontaneous aortic dissection in a 9-year-old

- Cause of death: “aortic dissection due to probable connective tissue disorder, unspecified type”
- No other risk factors for aortic dissection
- Suspected vascular Ehlers Danlos Syndrome
- Mother found to be pregnant
- Prompt contact made with family
- What is the responsibility of our office to notify this child’s family/physician?

American Journal of Forensic Medicine and Pathology 2005

Standards

- **No standard currently exists regarding the notification of unexpected autopsy findings to family or clinicians.**

Background

- What is a critical value?
- Implications in Anatomic Pathology
- Applications in Forensic Pathology

Archives of Pathology and Lab Medicine 2012

The task

- What is a critical value in forensic pathology?
- What is the ethical duty of a forensic pathologist to notify next of kin?
- What is the legal liability if such findings are not reported?

Virtual Mentor American Medical Association Journal of Ethics, 2009 and 2012

Legal Precedent

- *Pate v. Threlkel*
  - Woman diagnosed with **Multiple Endocrine Neoplasia (MEN-1)**
- *Safer v. Estate of Pack*
  - Woman diagnosed with Familial Adenomatous polyposis related colorectal cancer

Proposed guidelines

- Adopt standardized, national set of guidelines for notification of forensic critical values
- Scenarios to consider notification of next of kin or decedent physician
- Establish timeline for notification
- Suggest methods for documentation of communication

Proposed guidelines: Recommended cases

- Marked (>75%) coronary artery disease in a non-obese person less than 30 years of age without concern for stimulant use.

Proposed guidelines: Recommended cases

- Findings suggestive or diagnostic of hypertrophic cardiomyopathy or other heritable cardiomyopathies.

Proposed guidelines: Recommended cases

- Pulmonary thromboembolism/deep vein thrombosis **without** trauma, surgery, instrumentation, or other risk factors.

Proposed guidelines: Recommended cases

- Unexpected heritable conditions such as connective tissue disorders or heritable cancers with risk of sudden death.

Proposed guidelines: Recommended cases

- Carbon monoxide poisoning if unexpected

Proposed guidelines: Who to contact

Identify next-of-kin or other suitable contact, in some cases decedent's primary care physician

Obtain telephone numbers, mailing address, or email address

Proposed guidelines: Timing

- Timing should be driven by the nature of the condition and ability to diagnose the respective pathology
- Consider notification of contact as soon as a diagnosis is made, rather than waiting for finalization of report.

Proposed guidelines: What to communicate

- Comment in summary section of autopsy report or other location in records addressing finding and potential impact on surviving family

Proposed guidelines: what to communicate

- "In the course of examination of (the decedent), findings suggestive of a potentially heritable (disorder) were identified. While this office does not have the capacity for genetic testing or the ability to offer clinical care, we strongly recommend that blood relatives discuss the information with their own physician to determine if preventative measures are necessary. It is also recommended to bring a copy of the examination report to these discussions with your physician. In this case, blood was collected and stored for future private testing as requested. This recommendation was communicated to family on (date)."

What is the investment?

These cases would represent a small overall investment of time

NC OCME estimates 1 dozen cases/year

4.5 million population	31 counties	1600 annual autopsies

Limitations

- Family/physician contacts may not be forthcoming even after extensive investigation
- Condition already diagnosed
- Offices should not be responsible for education or referrals
- Avoid redundancies in reporting

Plans at OCME

Currently developing best practices

Discussions with internal agency legal specialist to balance minimization of liability as well as burden on pathologist.

Draft final best practices to disseminate among all NC Regional Autopsy Centers.

Acknowledgments

- Tracy Yorkdale, NC OCME Autopsy Facility Manager
- Kim Janssen, M.D. NC OCME Associate Chief Medical Examiner
- Michelle Aurelius, M.D. NC OCME Chief Medical Examiner

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Attitudes Towards Forensic Autopsy Standard B3.7 and the Use of Physician Extenders in Select Autopsy Cases

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The authors report no conflicts of interest.

Objectives

Background
- Rationale for NAME Standard B3.7

Scope of Current Problem
- Increasing number of overdose deaths
- Is compliance with standard B3.7 feasible?

Physician Extenders
- Definition and roles: The “PA”

Focus of Current Study
- Attitudes/opinions towards standard B3.7 and the use of PAs in forensic autopsy
- Define and explore factors predicted to influence opinions

Methods

Results

Conclusions

Background

- Studies have repeatedly demonstrated that a full autopsy (complete with internal examination) is the gold-standard method of determining cause and manner of death.

National Association of Medical Examiners (NAME)
forensic autopsy standard B3.7 states that:

"…a forensic pathologist shall perform a forensic autopsy when the death is by apparent intoxication by alcohol, drugs or poison, unless a significant interval has passed, and the medical findings and absence of trauma are well documented."

Background

Vanatta & Petty (1987): Retrospective review of 185 cases:

- External examination may be considered as a reliable alternative to full autopsy in assigning manner of death and cause of death in non-natural cases
  - 99%-100% accuracy rate in this study
- Accuracy in determining cause of death by external examination alone in natural deaths diminishes
  - 29% inaccuracy rate in this study (overdiagnosis of arteriosclerotic CVD)

Background

Nashelsky & Lawrence (2003): Retrospective review of 261cases (natural deaths):

- **Forensic pathologists are generally able to recognize natural deaths without an autopsy**
  - 96.9% accuracy in their study
- **Forensic pathologists tend to overestimate prevalence of cardiovascular death**
  - 93.9% assigned cardiovascular cause of deaths vs. 79.7% truly cardiovascular-related
- **Forensic pathologists may underestimate the prevalence of pulmonary disease**
  - 1.9% assigned pulmonary cause of deaths vs. 18% true pulmonary-related
- **Forensic pathologists may underestimate neoplasia as cause of death**
  - 0.38% assigned cause of death due to neoplasia vs. 2.3% true death due to neoplasia
- **Without a forensic autopsy (with internal examination), forensic pathologists are prone to error when determining cause of death in natural manner cases**
  - 28.4% cases were assigned an incorrect cause of death

Background

Dye et al. (2019): Blinded review of investigative narratives based on 60 cases of suspected drug-related deaths:

- Cause and manner of death may be accurately determined by external exam alone in **75% and 80%** of cases respectively, when scene findings and/or medical history indicate evidence of illicit or prescription drug abuse.
- Demonstrated variable and inconsistent inter-reviewer agreement in assigning cause and manner of death
- Additional years of experience/practice did not correlate with accuracy when determining cause and manner of death

Scope of the problem

- Over 70,200 overdose deaths in 2017 (Centers for Disease Control and Prevention)
  -9.6% increase in age-adjusted overdose rate from 2016 – 2017

- Some question about the feasibility of compliance with NAME standard B3.7
  - Offices located in busy urban centers
  - Offices with lower staffing ratios & finite resources

- Annual NAME Business Meeting in 2018
  - Use of physician extenders (i.e. pathologist assistant) in select forensic autopsy cases?

Physician extenders

- Physician extenders are health care professionals who are not physicians, but participate in patient care on behalf of or in conjunction with supervising physicians.
- Concept introduced in the1960's when a surplus of medically-trained military personnel returning home from the Vietnam War were stationed in underserved areas.
- Most common physician extender roles in the United States include physician assistant and nurse practitioner.
- In pathology, the equivalent physician extender role is a pathologist assistant (PA)
- PAs undergo 2 years of focused practical and academic post-graduate training

Focus of our study

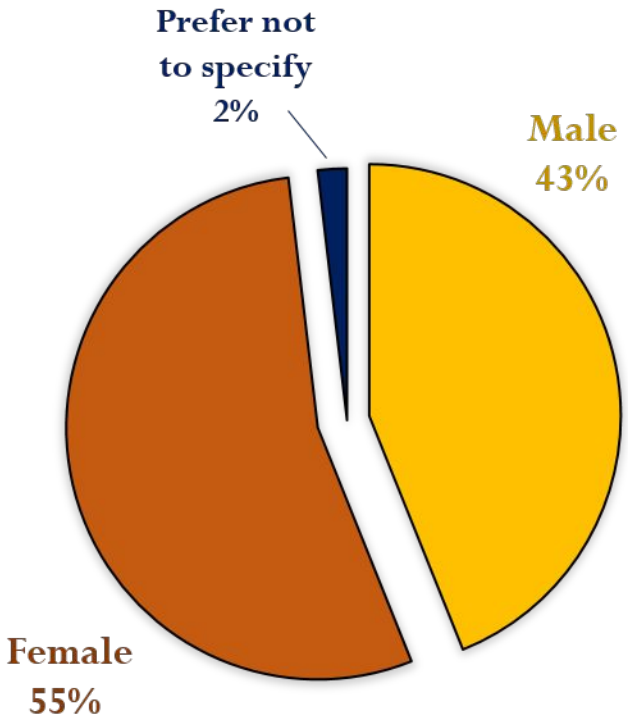
- Consensus on the appropriateness of NAME standard B3.7
- Consensus on the use of supervised accredited PAs in select forensic autopsy cases
- Determine whether variables related to experience, workload and resources impact forensic pathologists' opinions

Methods

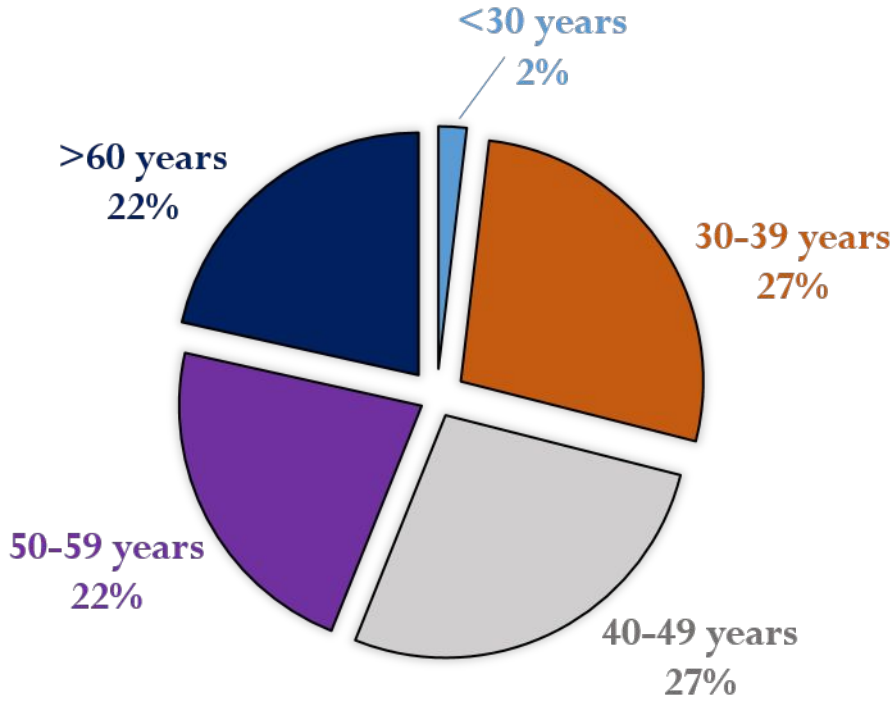
- Voluntary anonymous survey consisting of 17 multiple-choice questions and 3 fictitious death scenarios (used for internal validity).
- The survey was constructed using Google Forms
- Distributed via the NAME-L electronic mailing list
- Left open for response for 3 weeks
- Demographic statistics were obtained from Google Forms; statistical comparisons performed using SPSS software.

Demographics

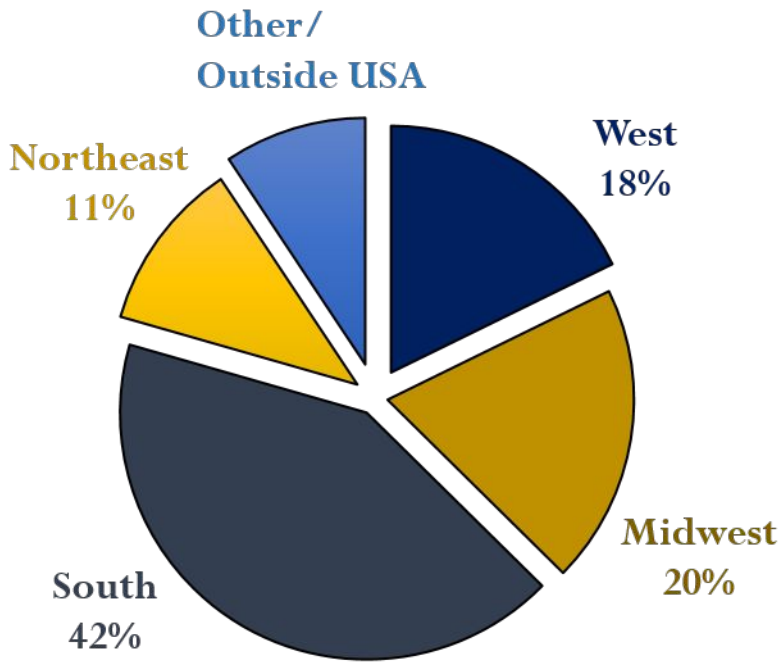
Total Responses: 107



SEX

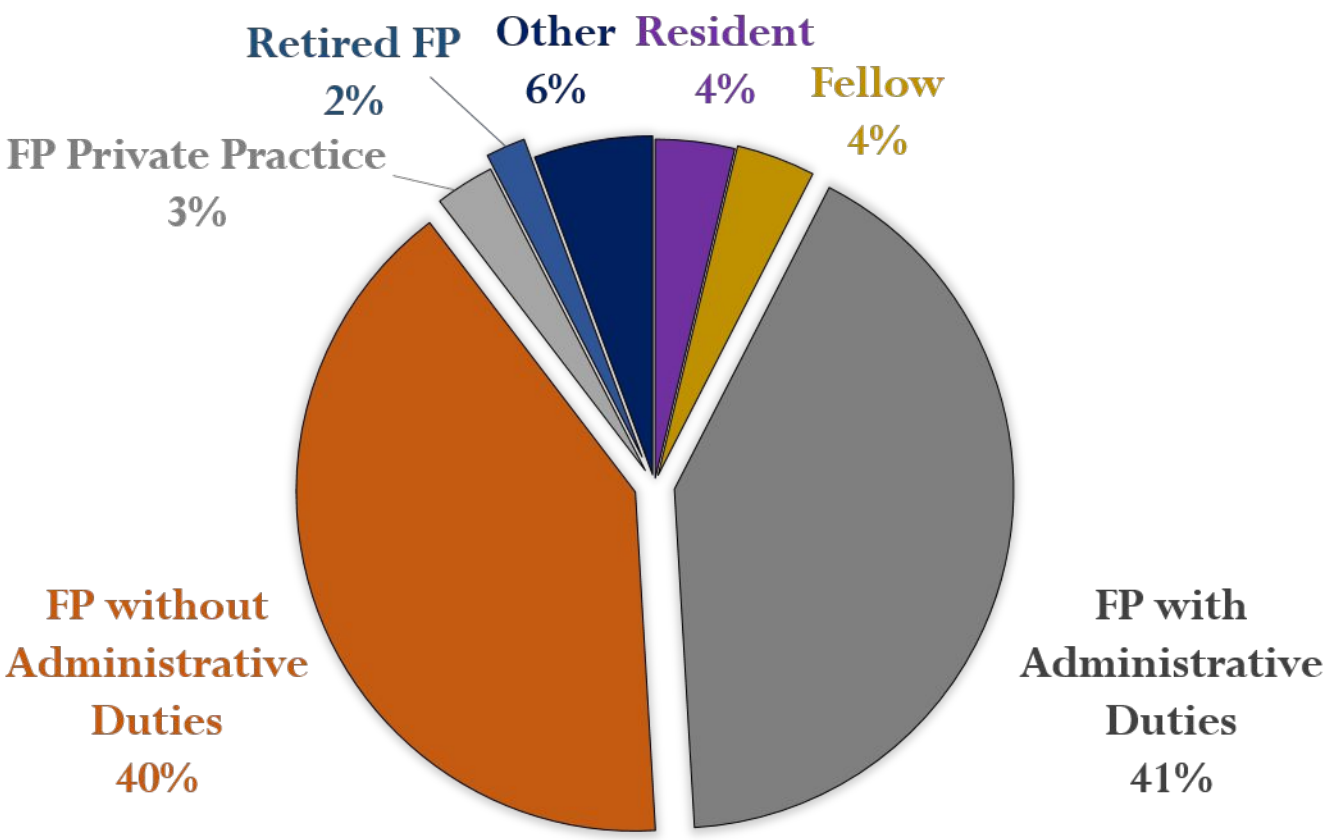


AGE

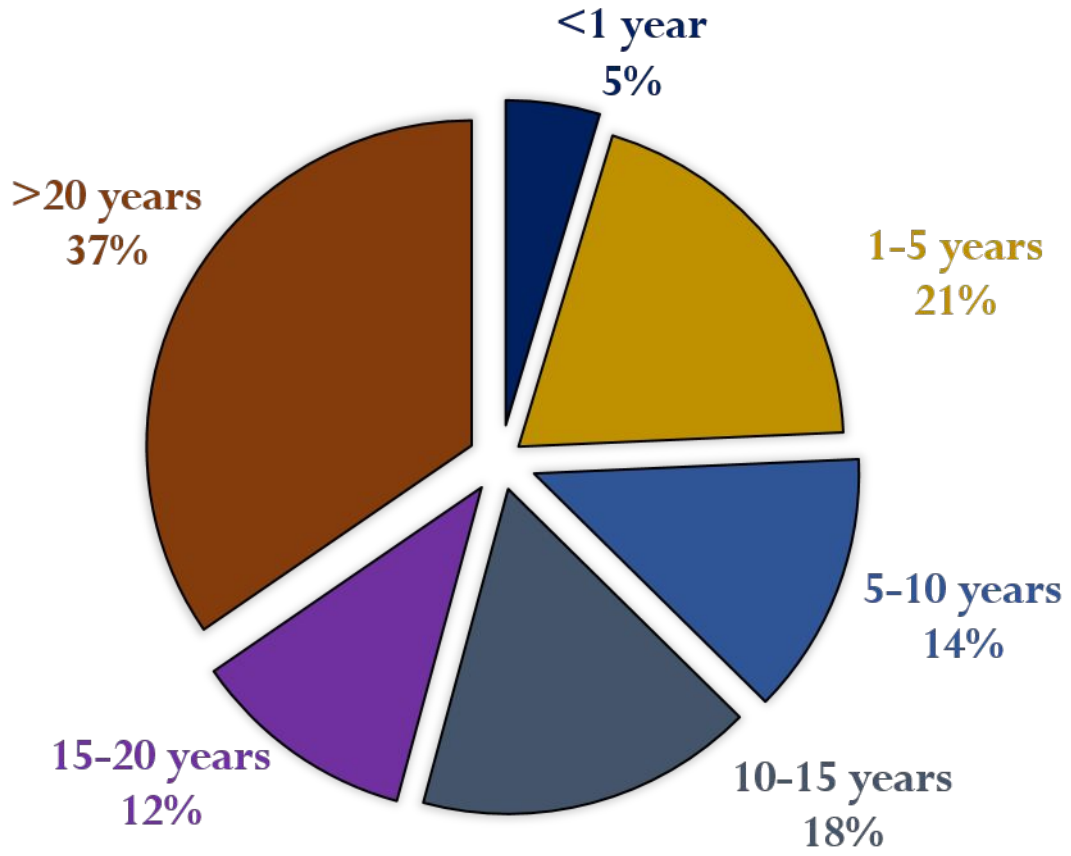


LOCATION

Demographics

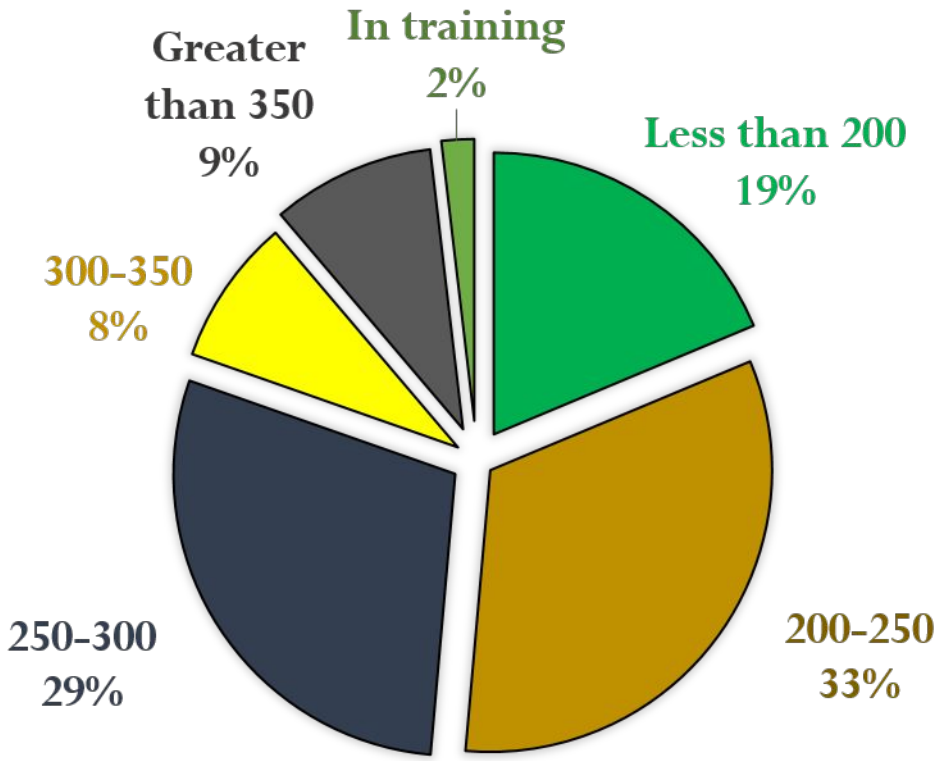


JOB ROLE/LEVEL OF TRAINING

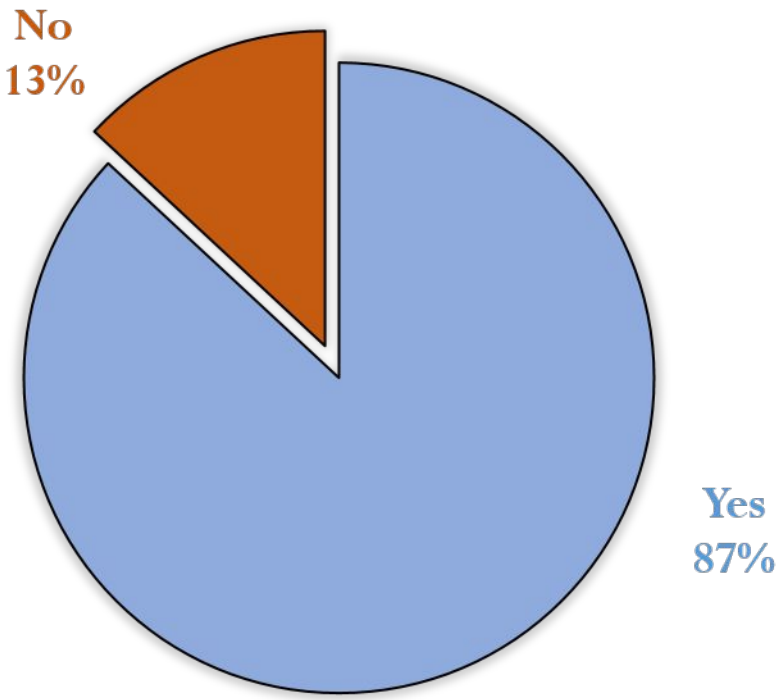


YEARS OF EXPERIENCE

Variables predicted to impact FP's opinions

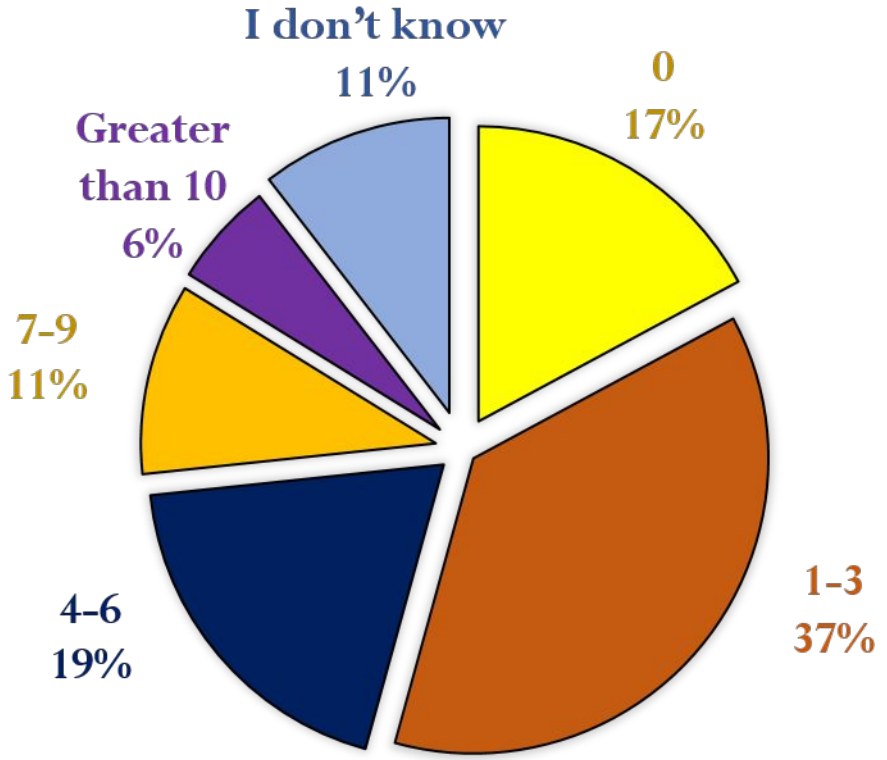


INDIVIDUAL AUTOPSIES

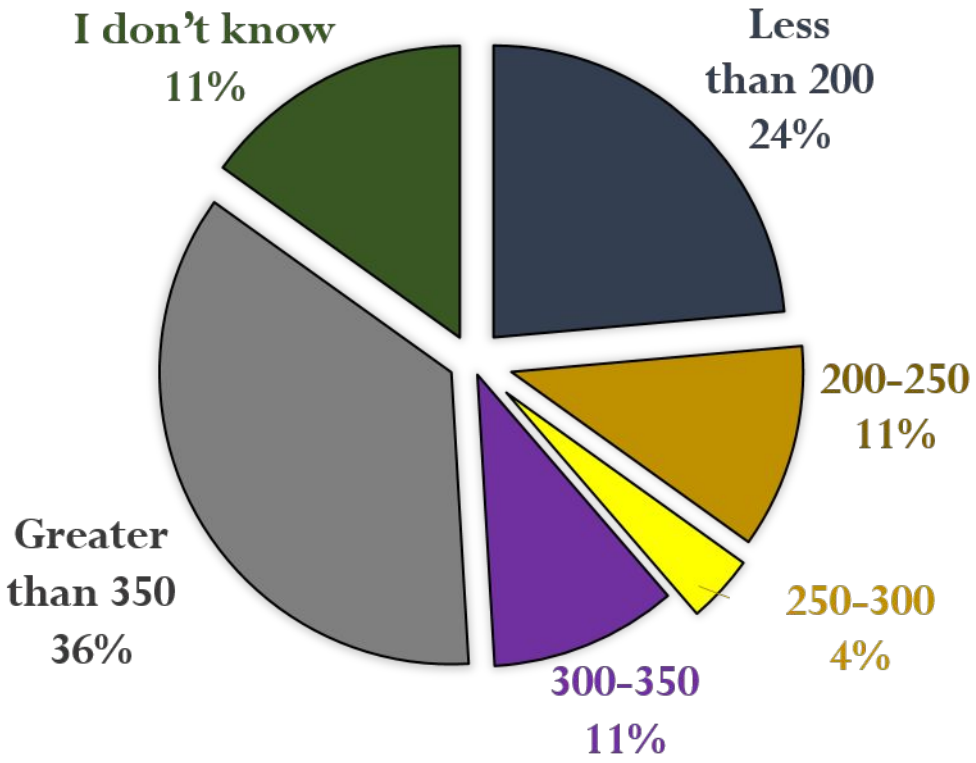


OFFICE EMPLOYS MORGUE TECHNICIANS

Variables predicted to impact FP's opinions

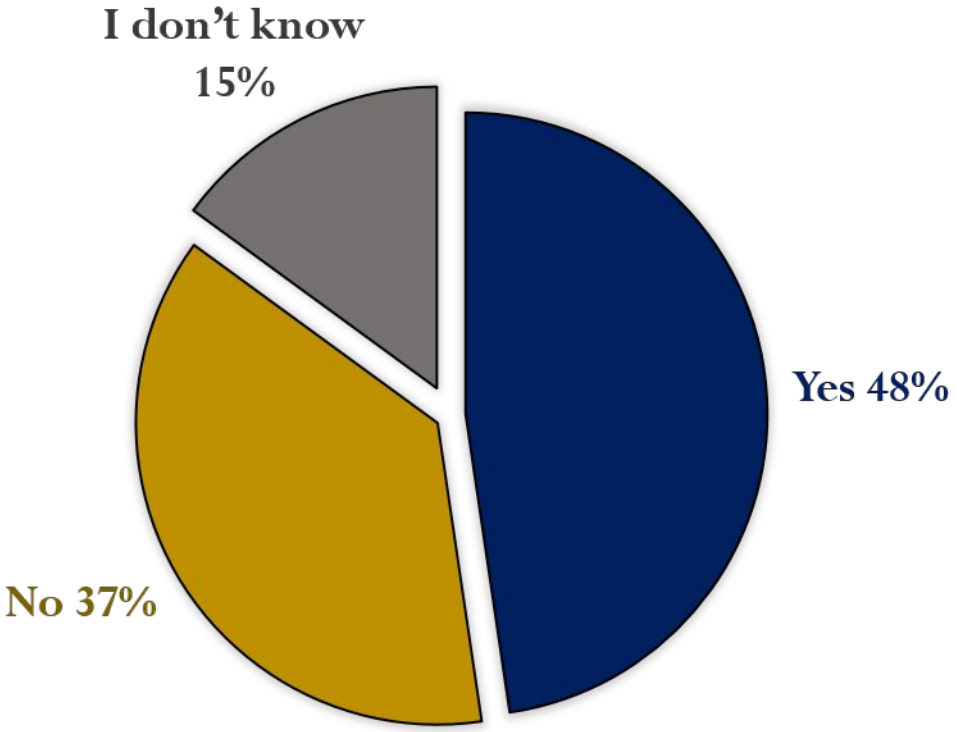


NUMBER OF FPs PERFORMING
>275 AUTOPSIES

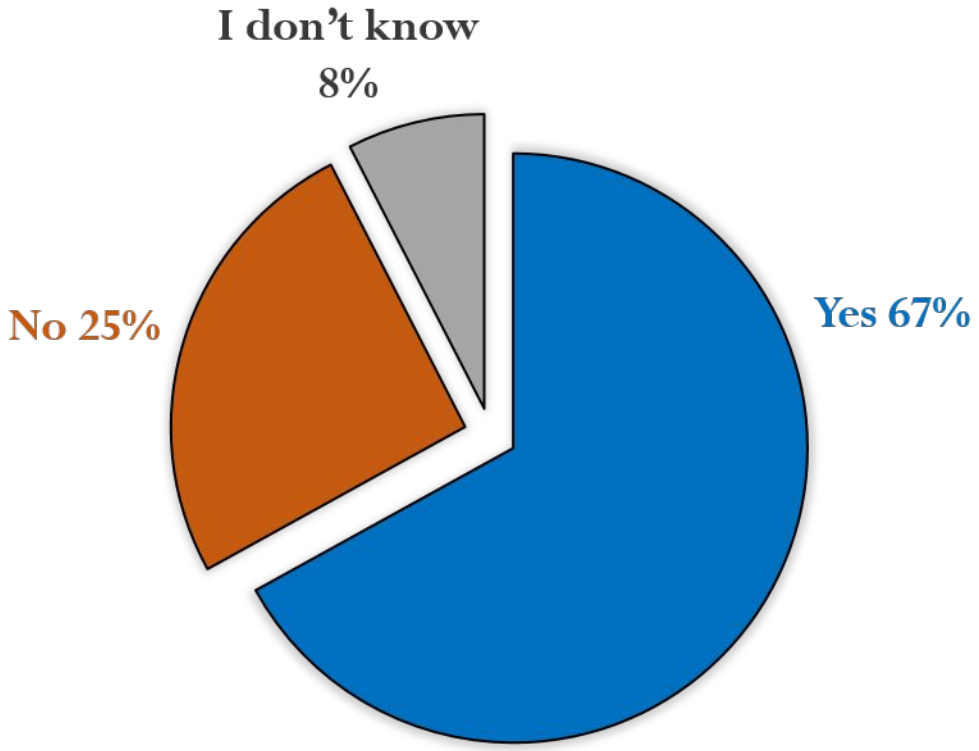


NUMBER OF OVERDOSE CASES
PER OFFICE PER YEAR

Variables predicted to impact FP's opinions

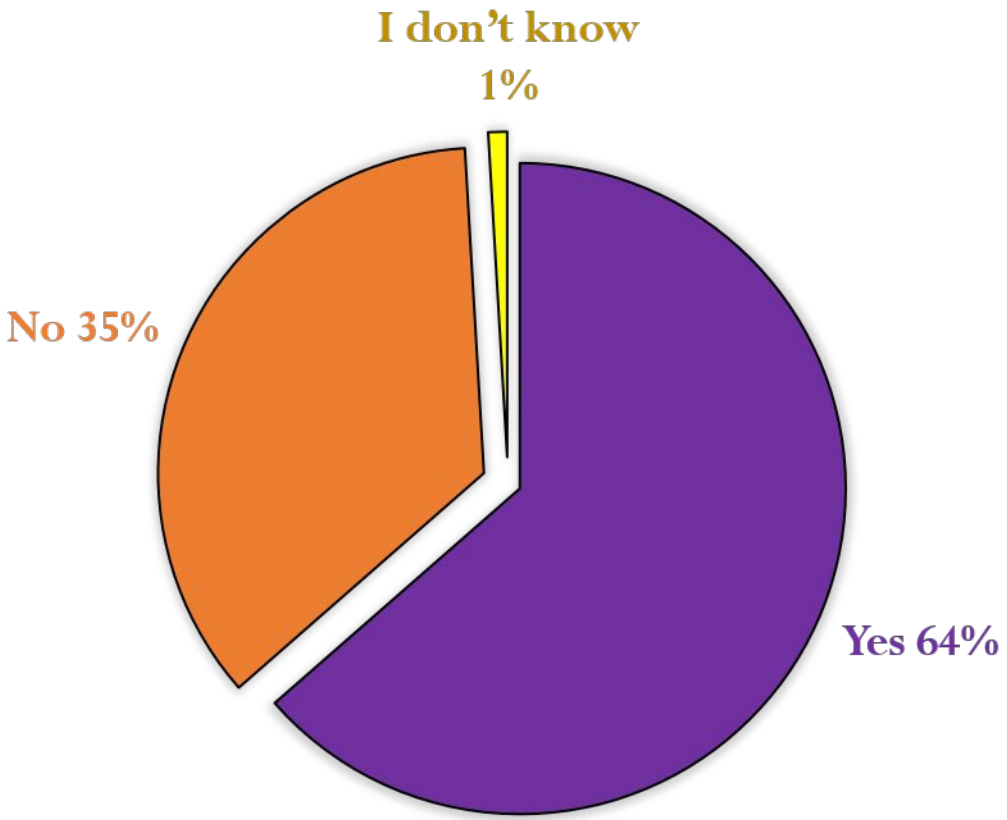


JURISDICTION THAT ROUTINELY PROSECUTES DRUG DEALERS

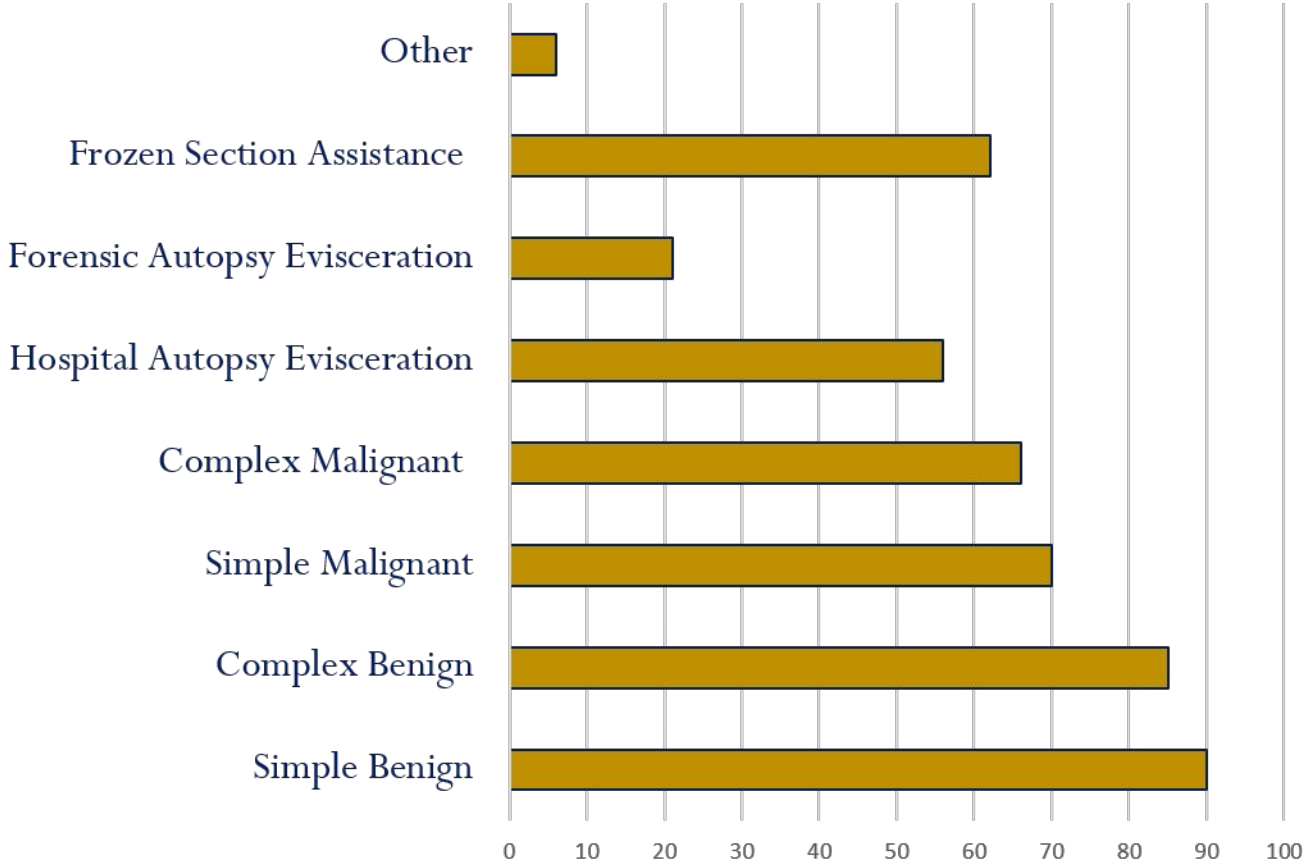


AUTOPSY FINDINGS RADICALLY CHANGED DIAGNOSIS

Variables predicted to impact FP's opinions

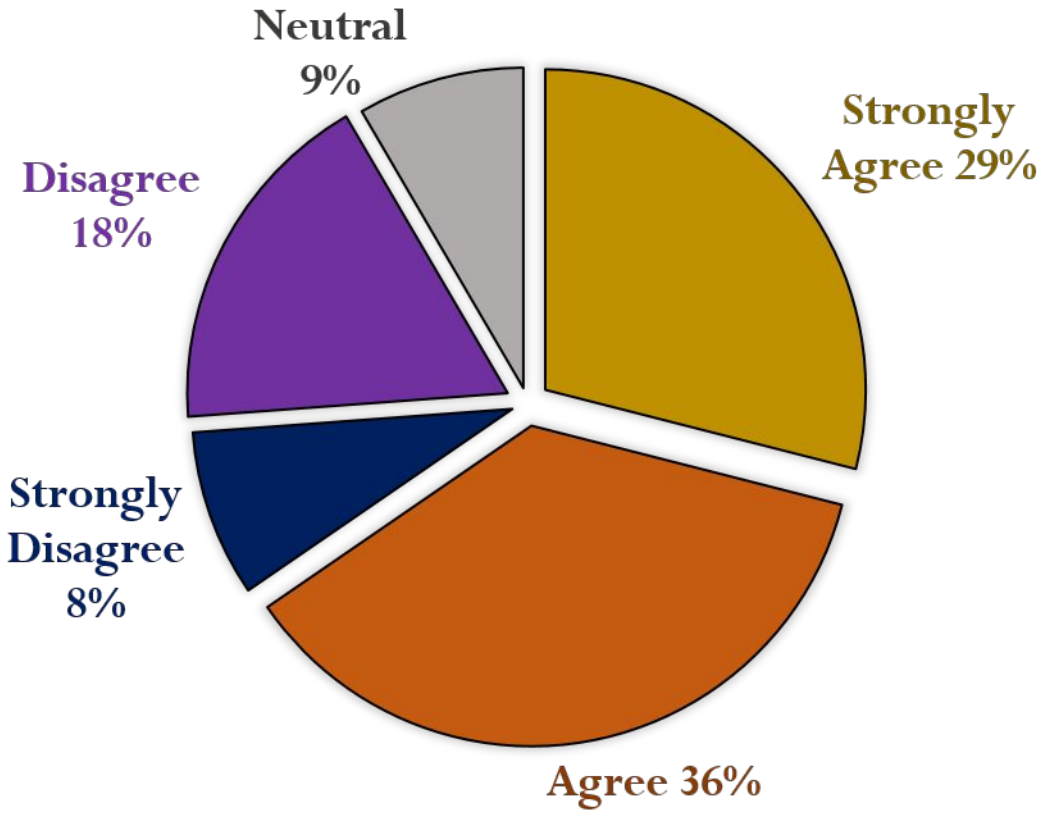


PAST EXPERIENCE WITH PAs

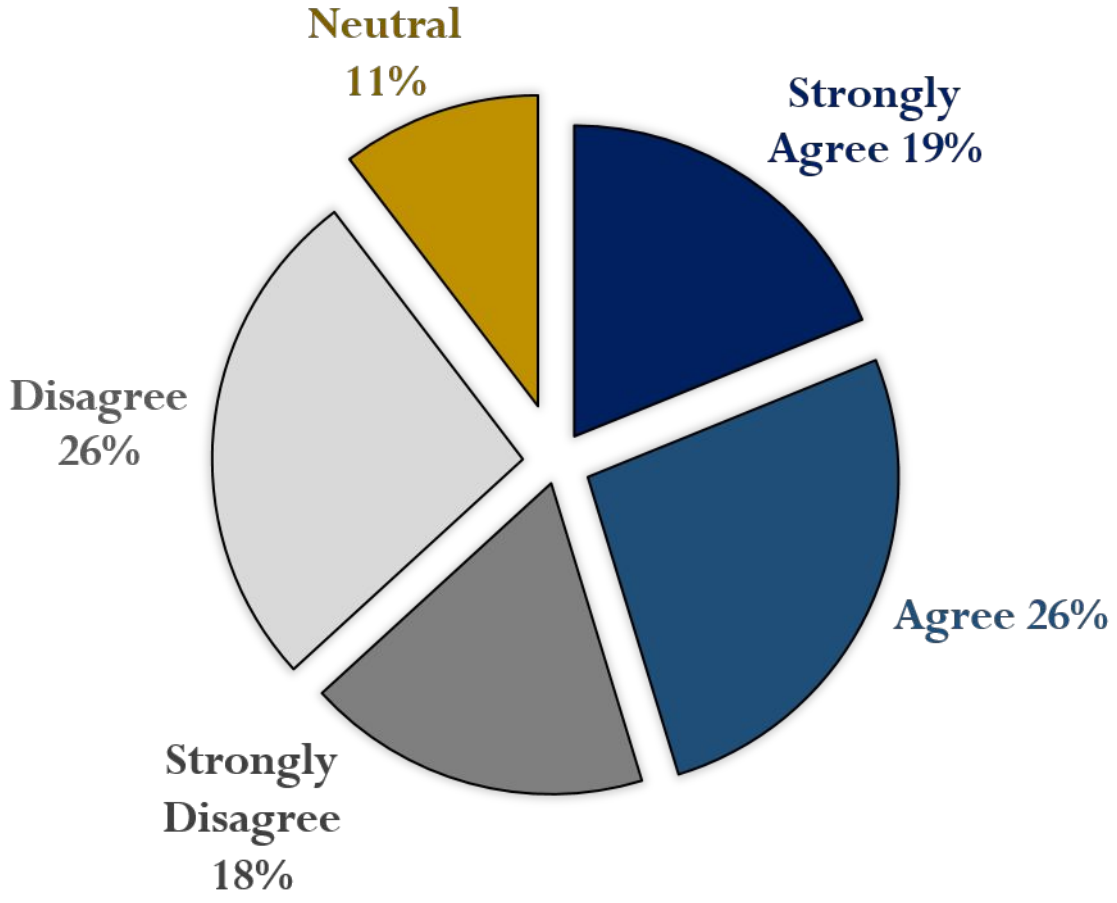


EXAMPLES OF PA RESPONSIBILITIES

outcomes



AGREEMENT WITH NAME STANDARD B3.7



WILLINGNESS TO SUPERVISE AN ACCREDITED PA IN SELECT FORENSIC AUTOPSY CASES

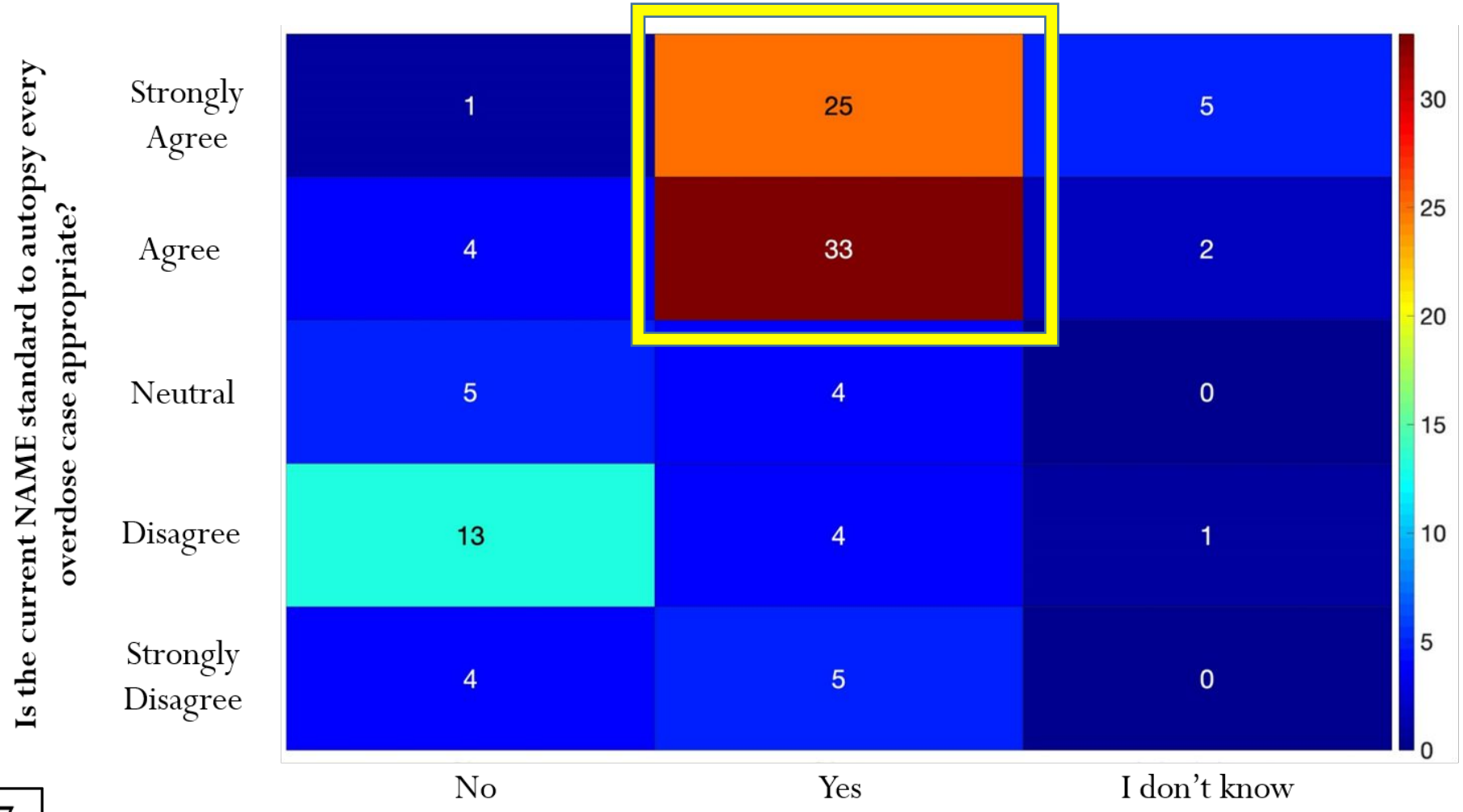
Results

Predictive Variables vs. Agreement with NAME Standard B3.7	df	F	P-value
Years of experience in forensic pathology	1,106	2.01	0.08
Number of forensic autopsies individually performed per year	1,106	0.71	0.62
Number of colleagues (working in same office) who perform >275 forensic autopsies per year	1,86	1.86	0.13
Number of potential overdose cases per office per year	1,105	1.62	0.52
Office employment of morgue technicians	1,106	0.13	0.72
Experience working with PAs	1,106	2.64	0.08
Working in jurisdiction that routinely attempts to prosecute drug dealers in overdose deaths	1,106	1.21	0.30

Results

Predictive Variables vs. Use of PAs in Select Forensic Autopsy Cases	df	F	P-value
Years of experience in forensic pathology	1,105	0.70	0.62
Number of forensic autopsies individually performed per year	1,105	1.62	0.16
Number of colleagues (working in same office) who perform >275 forensic autopsies per year	1,86	0.78	0.54
Number of potential overdose cases per office per year	1,104	0.97	0.44
Office employment of morgue technicians	1,105	0.02	0.88
Experience working with PAs	1,105	0.23	0.80
Working in jurisdiction that routinely attempts to prosecute drug dealers in overdose deaths	1,105	0.78	0.46

Results



$p = 8 \times 10^{-7}$

Death scenarios in which respondents were asked to specify the minimum acceptable examination type they would deem suitable within the scope of their current or past practice

	Full Autopsy	External Exam
SCENARIO 1: A 63 year old man with history of hypertension, hyperlipidemia, diabetes mellitus, and previous myocardial infarction requiring RCA stenting is found deceased in his secured residence when he failed to answer the phone for two days. The medicolegal investigator finds a "dime bag" and unmarked pills on the decedent's nightstand.	63%	37%
SCENARIO 2: A 28 year old woman is found unconscious by her roommate in their secured apartment. The decedent has history of illicit substance use including opioids, however, her roommate reports she has been "trying to stay sober" for the past 6 months. The immediate scene lacks visible drug paraphernalia, however, marijuana and a prescription for benzodiazepines are identified in the decedent's drawer (name on prescription matches that of the decedent). On external exam, the decedent has scarring in her left antecubital fossa. Urine quick tox testing is positive for marijuana, opioids, benzodiazepines and cocaine.	73%	27%
SCENARIO 3: A 31 year old man collapses while jogging with his partner. The decedent was a surgical resident who frequently took stimulant medication (ie. Dexedrine) to stay awake. External examination is unremarkable and urine quick tox screening is not performed.	99%	1%

Results summary

- A majority of respondents agreed with NAME standard B3.7 (65%)
- Consensus on the use of PAs in non-suspicious forensic autopsy is split
  - 45% Agree
  - 44% Disagree
- Tendency to agree with either standard B3.7 and the use of PAs in select forensic autopsy cases was independent of virtually all of the variables we chose to examine in this study.
- Respondents were more likely to agree with NAME standard B3.7 ($p<0.001$) if they had a past experience where autopsy findings radically altered diagnosis in an otherwise suggestive overdose death.
  - There was no significant relationship between agreement with the use of PAs in select forensic autopsy cases and such past experience.
- Internal control (scenario 1) response for full autopsy approximated agreement with B3.7

Conclusions

- Forensic pathologists rely on clinical judgement when determining which cases should receive a full autopsy vs. external examination alone.
- Tendency to agree with the use of PAs in forensic autopsy is independent of all predictive variables measured in this study.
- Forensic pathologists are more likely to agree with standard B3.7 if they have encountered unexpected autopsy findings in an otherwise suggestive overdose death.
- The use of PAs in select forensic autopsy cases may be one solution to ensuring every potential overdose death receives a full autopsy.
- Future research is warranted in order to characterize the role of PAs in forensic autopsy and for the development of practice guidelines.

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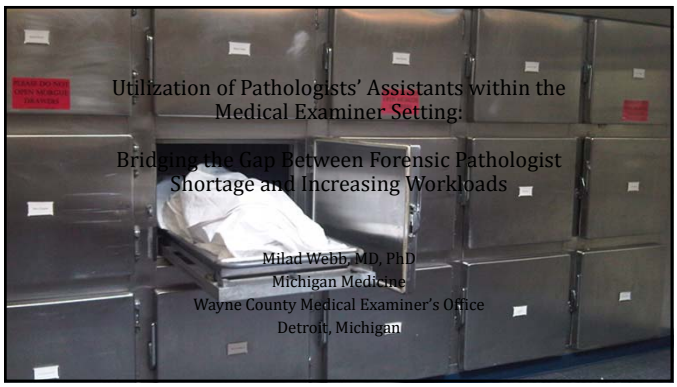
Thank-you



Utilization of Pathologists' Assistants within the Medical Examiner Setting:

Bridging the Gap Between Forensic Pathologist Shortage and Increasing Workloads

Milad Webb, MD, PhD
Michigan Medicine
Wayne County Medical Examiner's Office
Detroit, Michigan

Concerns are incredibly legitimate and require reflection, discussion, and consensus.

- Decrement of professionalism
- Cheapens the profession
- We're cutting our own throats
- Selling society short
- Physician relegated to a manager
- Will result in loss of physician jobs/salaries/benefits
- Will result in indictment of our medical credentials
- Will result in indictment of our legal expertise
- PAs will start testifying as experts
- Autopsies done by frauds

We are in critical shortage

- The autopsy is the bastion upon which Western medicine was built upon
- Forensic pathologists (FP) operate in complete autonomy to support public health and the justice system
- Recruitment into pathology is lowest ever
- Forensic caseloads are increasing
- The service that forensic pathology provides our communities must remain outstanding

Populations are increasing and we are not.

- US population grew an average of 0.8% per year (+2.6 million)
- ~17% increase in physicians
- ~17% decrease in pathologists
- Trickled down into a critical workforce shortage for forensic pathology.

We need more than twice the number of board-certified FPs than we currently have

A 2013 report predicted that the US requires approximately 1100 board certified FPs

Estimates show there are less than 500 board certified FPs working full-time.

Medical students do not choose pathology

- In 2019, the National Resident Matching Program (NRMP) had an all-time high of medical school registrants applying for residency match
- Pathology residency is available at 162 programs, offering 601 positions
  - 569 positions
  - 21 programs failing to fill their available positions
  - Pathology accounted for 1.1% of all matched US seniors

Residents and fellows do not choose forensics

- Of all ACGME Pathology residents pursuing fellowship in 2018
  - 9% (49) were board certified in forensic pathology; 10% increase over the previous years (44, 2014-2017)
  - 41 forensic fellows sat for their board examination in 2019 (~16% decline)
- In two studies on forensic fellowship training programs in 2011 and 2014
  - Only 2/3 of fellows practice full-time; more than 20% do not practice at all
- Only 2/3 of fellows become board certified; only 3/4 practice full-time.
- Of 49 fellows board certified in 2018, only 38 are projected to practice full-time.
- Attrition is expected to far exceed recruitment:
  - retirement, death, and career changes, and burnout.
- Based on reports from 2012, the average age of a FP was 55; and likely now closer to 60.

We are struggling to keep case numbers down.

- There should be approximately 3.7 FP per 1 million population served.
- Optimal caseload for a FP is 250 – 325 cases per year.
- Wayne County Medical Examiner's Office should employ 7 full-time FPs.
  - In reality, we need 8 – 10
- Spoiler alert—we don't have 7 FPs.
- Wayne County has 6.3% increase in caseload per year
- Wayne County is not alone.

Our sacrifices are keeping us afloat

- The elasticity of the remaining workforce has kept it from falling apart.
- The individual cost has been great: stress, fatigue, burnout, lost research opportunities, and perhaps critical errors which have gone, so far, unnoticed.
- It will, unfortunately, take a catastrophic failure to draw enough attention to this issue.

The current situation is tenuous at best

Bottom line is simple:

- 1) Medical Student do not go into pathology
- 2) Only half of BC-FP fellows practice full-time
- 3) The average FP is of retirement age
- 4) Caseload are large—and growing.

It will take decades for these trends to re-align.

WCMEO is a teaching center

- Wayne State University School of Medicine
- Multiple Departments of Pathology
  - University of Michigan
  - Henry Ford Hospital
  - Beaumont Hospital
  - Ascension St. John Hospital
- Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University – Pathologists' Assistant Masters Program

WSU PA program is comprehensive

WAYNE STATE UNIVERSITY PATHOLOGISTS' ASSISTANT

- Established in 1989, the Wayne State University Masters in Pathologists' Assistant is one of thirteen accredited programs
- Upon completion of their 2 years of training, they are expected
  - *"to provide accurate gross examinations and dissections of human anatomic pathology specimens; perform postmortem examinations, train pathology personnel, medical students and pathology residents; instruct in anatomy, physiology, gross pathology, gross dissection, and autopsy techniques; photograph surgical and forensic specimens; and assist in, perform, and conduct research."*

PA Program incorporates an 8-week rotation through the Wayne County MEO

- Training includes:
  - Prosection and external and internal examination including in situ and ex situ examination of organs
  - Proper collection and submission of trace evidence, serology kits, specimens for toxicology and histology
  - Forensic photography
- They attained significant proficiency in completing a low-complexity postmortem examination
  - Many assisting in high-complexity cases

WCMEO Hired Two Pathologists' Assistants

- In 2018, there were extended discussions
  - Not possible to perform 8-12 autopsies per day and manage:
    - Courtroom responsibilities, safety and accreditation, quality improvement / quality assurance, teaching responsibilities, administrative and logistical needs
  - Existential reflections about the long-term effect this might have
- We hired two of our very best PA students, full-time
- Bottom line—Necessity wins.

Kayla Dill

Andrea Jaworski

With time comes experience

- Today, our staff of three forensic PAs assist in a wide range of essential tasks, not limited to:
  - Postmortem examinations (toxicology, histology, serology, cultures) – When Needed
  - Teaching rotating medical students and residents
  - Administrative and logistical tasks
  - Management of SOPs
  - Research projects
- All their responsibilities are performed under appropriate supervision by staff pathologists.

Breanna Kindel

The PA is a significant and underutilized resource

- Improvement in turn-around-times, educational experiences for our students and residents, and improved organization of resources
- Allows FP to address many other vital needs, including prioritizing complex cases
- Has not jeopardized the quality or integrity of our service

We need to safeguard our position in forensic investigation

The board-certified FP remains the ultimate authority on the postmortem examination.

A PA, or any other physician extender, should never function with the autonomy and license afforded to the physician through years of education, certification, and experience.

Only with appropriate supervision can a physician extender provide proper and defensible service.

So, what now?

- Utilization of physician extenders needs to be formally and directly addressed and regulated with clear and concise language
  - Consider forensic certification of PAs
  - Discussion of what will constitute appropriate supervision
- Failure to take this step now may result in forfeiture of this opportunity
- This is how we protect our profession, credentials, and expertise.

Realities of employing a PA

- No effect on caseload
- Employing a PA costs money
- If you employ a PA, they will eventually get a subpoena
  - Testify to the collection of objective facts present in the autopsy report
  - No role in the interpretation of observations or physical evidence, or the formulation of an anatomic diagnosis, cause of death, or manner of death.

Conclusions

- The autopsy is a vitally important tool essential in medicine, public health, and law – and we control it.
- FPs and our national organizations should take this opportunity to ensure that the integrity of the autopsy is not compromised by the inevitable inclusion of physician extenders.

- This is our opportunity to appropriately utilize, standardize, and regulate pathologists' assistants—not fear them.

Special Thanks

- Dr. Carl Schmidt, MD, Chief Medical Examiner
- Dr. Jeff Jentzen, MD, PhD, Chief Medical Examiner
- Dr. Leigh Hlavaty, MD, Deputy Chief Medical Examiner
- Dr. LokMan Sung, MD
- Dr. Omar Rayes, MD
- Dr. Teresa Nguyen, MD

- Ms. Andrea Jaworski
- Ms. Kayla Dill
- Ms. Breanna Kindel

- Investigators
- Staff

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The Great Smoky Mountain Wildfires

KATHERINE COCHRANE MD, WILLIAM OLIVER MD, DARINKA MILEUSNIC-POLCHAN MD, PHD

The Great Smoky Mountains National Park

- Most visited national park with 11.3 million annual visitors[1]
- Main park entrance at the town of Gatlinburg, Tennessee[2]
- Wildfires of 2016 one of the largest natural disasters in Tennessee's history[5]
- The towns of Pigeon Forge and Gatlinburg were affected
- 14,000 people were evacuated[5]
- 14 fatalities

Cause of Death in Severely Compromised Remains

- Thermal burns vs. smoke inhalation
- The level of carbon monoxide in several of these cases argues against smoke inhalation alone
- Rely on scene and investigational information

Smoke inhalation and heart disease

- In natural disasters sudden cardiac death doubles[8]
- Exposure to smoke, fire, and the cardiac stress associated with fleeing represent exactly the kind of stress that would trigger sudden cardiac death

Direct Deaths in Disasters

- **Direct death:** a death directly attributable to the forces of the disaster or by the direct consequences of these forces[9]
  - Structural collapse
  - Flying debris
  - Radiation exposure
  - Fire
  - Flooding

Indirect Deaths in Disasters

- **Indirect death**: when the unsafe or unhealthy conditions present during a disaster contribute to a death[9]
  - Including pre-disaster preparation and post-disaster clean-up
    - Vehicular accidents
    - Electrocution
    - Heart attacks

Indirect Deaths

- Four main factors[9]:
  - Power problems
  - Cardiovascular failure
  - Evacuation
  - Vehicular accidents
- Cardiovascular Failure is most common[8]
- Indirect fatalities increase with age[8]

Summary of Fatalities

- 14 fatalities
- Direct deaths: 10
  - Smoke inhalation: 9
  - Falling debris: 1
- Indirect deaths: 4
  - MVC: 2
  - Heart disease: 2

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Faith or Delusion? Death Investigation of a Bizarre Mass Hanging- A Case Report

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Case report

- A tragic and bizarre case of mass hanging deaths of 11 family members (4 males, 7 females) was reported
- 9 were found hanging from the skylight of their living room.
- 1 from a ventilation outlet in the same living room
- 1, the eldest member was found lying on a mattress on the floor of an adjacent bedroom

S. no	Family Members	labeled	Age in years
1	Mother	A	80
2	Elder son	B	50
3	Younger son	C	42
4	Daughter	D	58
5	Wife of elder son	E	42
6	Wife of younger son	F	38
7	Grand-daughter	G	30
8	Granddaughter	H	24
9	Granddaughter	I	22
10	Grandson	J	12
11	Grandson	K	12

Case report

- Complete hanging: 3 ; Partial hanging: 8
- Plastic stools shared between members
- Strips of neatly cut cloth material strewn
- Blue plastic rope bundle was found on the bed
- House was being renovated for impending wedding of granddaughter

Autopsy findings

Ligature Material	No of cases
Scarf	11
Black telephone wire	10
Knots	multiple and fixed

Autopsy findings	No of cases	Material Used
Blindfolding	5	Cut outs from a fresh white cotton cloth
Masking	7	Adhesive tape
Padding	10	White cotton cloth
Gagging	1	Handkerchief
Cotton plugs in ears	10	

Binding of limbs

Finding	No of cases	Material used	Position of hands
bound hands	**5** (3 M,2 F)	rope, cloth, telephone wire	front:1 back: 4
free hands	**6**	blue plastic rope on right wrist	
bound feet	**6**	cloth, loose figure of 8 fashion (3)	

Autopsy findings

- Knots of bound limbs were complex, multiple and fixed
- Ligature mark: typical of hanging in all the cases
- Asphyxial signs were seen in all cases
- Insignificant minor bruises over upper limbs in 2 cases
- No other fatal injuries appreciated

Crime Scene

- Multiple Registers/Diaries recovered (Entries dated back to 2011)
- Detailed stepwise instructions of a ritual
- Ritual was religious in nature (Hindu)
- For the well being and good fortune of the family.
- Few members assigned specific duties
- Indications of similar practices in the past

Diary notes

- Bizarre hallucination and delusion in the younger son (C).
- Auditory Hallucination: hearing dead father's voices
- 'C' used to assume his father's alter ego
- Instructions about the ritual given by him while assuming his fathers alter ego
- Family believed the dead father was communicating through the younger son

Other investigations

Toxicological report

- Negative in all the cases

Handwriting expert report

- Notes written by wife of younger son (F) and granddaughter (G)

Psychological evaluation of the diary entries

- Psychological evaluation conducted

Opinion:

- Delusion in the younger son
- Shared delusion among family members

Manner of death

Homicidal hanging?

- Disparity in size
- Victim drugged/ drunk
- Injuries/grip bruises/signs of resistance
- All of these were ruled out
- Bound limbs, gagging, masking, blindfolding also seen frequently in suicides

Suicide??

Points in favor

- Hangings are almost always suicidal
- Mass suicides do occur sporadically
- Suicide pacts common
- Bound limbs seen also in suicides

Points against suicide:

- No suicide note
- Diary entries did not show intention to die
- In fact showed intention to live and improve living conditions
- Motive to commit suicide not found

Accidental Hanging

- Points against:
- Accidental hanging usually seen in infants or children
- Not common in adults except Autoerotic hanging
- Mass accidental hangings not reported in literature
- Speculation how death occurred in spite of 6 free hands?
- Was death instantaneous that they could not survive or help each other?

Accidental

Points in favor:

- Absence of intention to die
- Belief of surviving the act
- Evidence of similar ritual with success in the past
- Hanging deaths are instantaneous leaving no time to change mind at the last second.

Was this act FAITH?

- Unmistakable religious background to the act
- The symbolism of the banyan tree formation
- Banyan tree is considered sacred in Hinduism and is a symbol of immortality
- “Havan”: a sacred purifying ritual that involves a fire ceremony, offerings to the fire god Agni.
- “Maun vrat”: vow of silence

WAS IT DELUSION?

DELUSION: DSM-5:

- Delusions are fixed beliefs that are not amenable to change in light of conflicting evidence.
- Delusions are deemed bizarre if they are clearly implausible and not understandable to same-culture peers and do not derive from ordinary life experiences.
- Their content may include a variety of themes (e.g., persecutory, referential, somatic, grandiose, **RELIGIOUS**)

Religious delusions

- Religious or spiritual content.
- Religious delusions are not caused by excessive religious belief
- Delusions reflects the predominant interests and concerns.
- These may be combined with other delusions, such as grandiose delusions, delusions of control, or delusions of guilt.

Difference between religious beliefs and religious delusions

- Delusion is held without any doubt.
- Religious belief is held with some doubts, or at least an understanding that others could have doubts about what I believe.

"EXTRAORDINARY CONVICTION"

Diagnosing delusion

- Conviction
- Preoccupation
- Extension
- Bizarreness
- Disorganization
- Affective response
- Deviant behavior/Morbid behavior

Shared delusional disorder

- Folie à deux, shared psychosis, or shared delusional
- Delusional belief and hallucinations are transmitted from one individual to another.
- Observed among people who live in close proximity and in close relationships.
- *folie à trois*, *folie à quatre*, *folie en famille* , *folie à plusieurs*

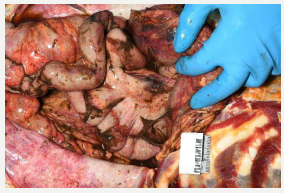
HARRIS COUNTY INSTITUTE OF FORENSIC SCIENCES

THE PERFORATED JEJUNUM: A CASE SERIES

HANNAH C JARVIS
MBBS AICSM BSC(HONS) MRCS(ENG)

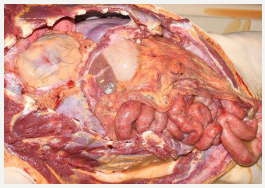
INTRODUCTION

- Intestinal perforation is due to an insult or injury to the bowel wall
- Peritonitis - major complication with significant mortality rate



INTRODUCTION

- Intestinal perforation
  - –Up to 40% of hospital admissions due to an acute abdomen
  - –Surgical emergency



- Presentation
  - –Features of obstruction or perforation, or both

INTRODUCTION

- Incidence of small bowel perforation
  - 1 in 300,000 to 350,000
  - Duodenum > Ileum > Jejunum
  - Typhoid infection is the most common aetiology on a global scale
    - Usually involves the ileum

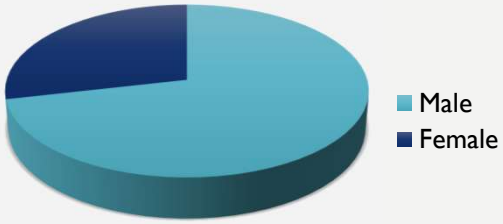
AETIOLOGY: SMALL BOWEL PERFORATION

- Trauma
- Foreign bodies
- Iatrogenic
- Irradiation
- Obstruction
- Inflammatory diseases
- Atherosclerosis
- Peptic ulcer disease
- Vascular disease
- Drugs
- Tumours
- Congenital abnormalities
- Graft versus host disease

METHODS

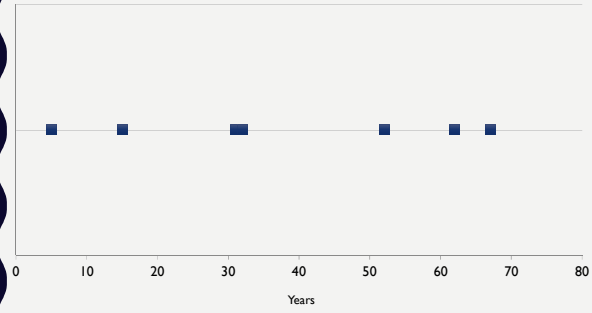
- Harris County Institute of Forensic Sciences, Houston, Texas
- Database searched: 2006 – 2019
  - 19 fatalities certified due to small bowel perforation
    - 7 due to perforation of the jejunum
    - 12 cases did not specify the exact site

SEX

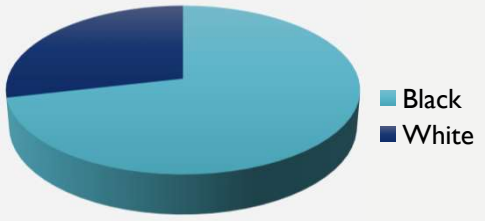


AGE

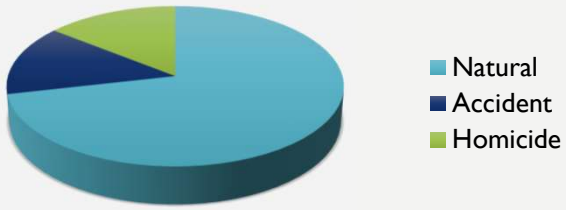
- Mean average age: 38 years



RACE



MANNER OF DEATH

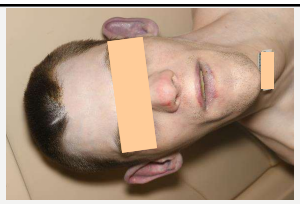


NATURAL DEATHS

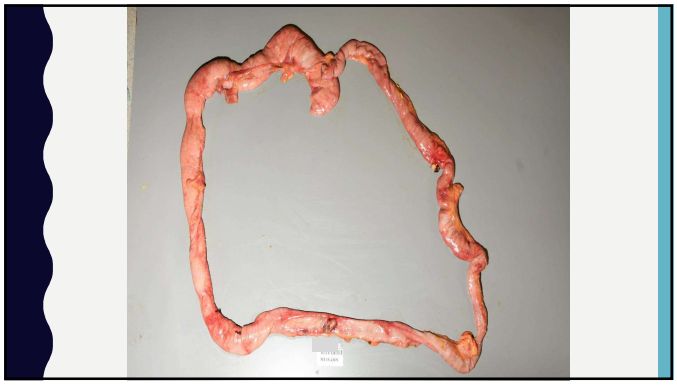
5

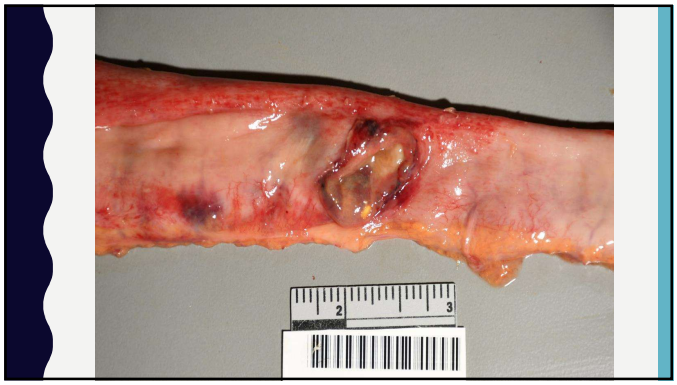
- Two cases: perforation of undetermined aetiology
- Perforation of adynamic ileus
- Perforation following surgical repair of a hernia
- Perforation associated with Zollinger-Ellison syndrome

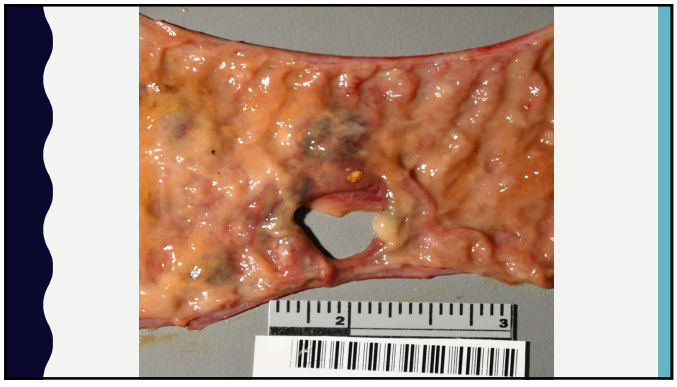
CASE 1



- 32 year old man, mental retardation, autism
- Non-verbal but ambulatory
- Found dead in bed at care home
- No apparent distress the previous evening

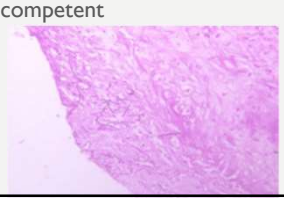






DISCUSSION: CASE 1

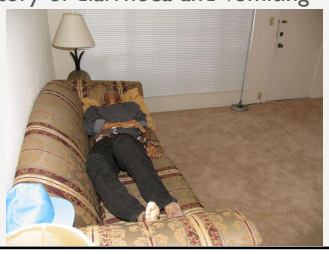
- No underlying aetiology identified
- Fungi within jejunal wall
  - Case reports of duodenal candidiasis and perforation in immunocompetent patients

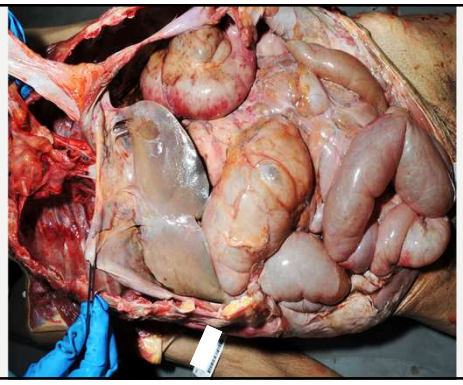


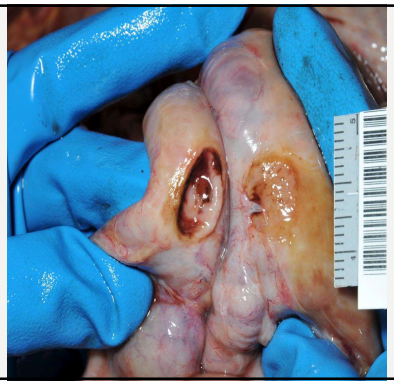
Jain A, Lohith P, Garg L, Ghullani D, Khurana N. Duodenal candidiasis: a rare cause of giant duodenal perforation in immunocompetent patient. Int Surg J 2018;5:749-51

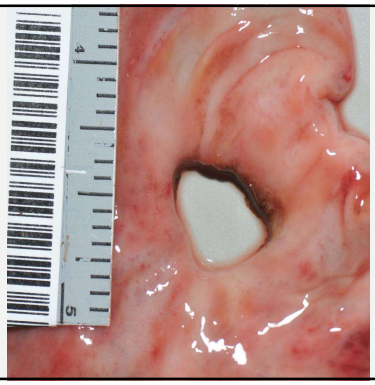
CASE 2

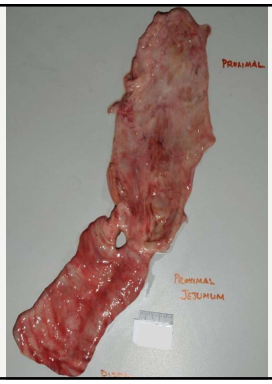
- 67 year old man
- 2 day history of diarrhoea and vomiting





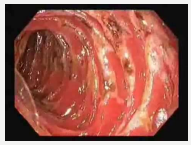





PROXIMAL
PROXIMAL
JEJUNUM

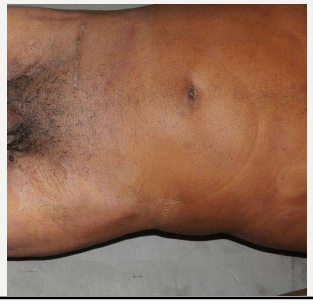
DISCUSSION: CASE 2

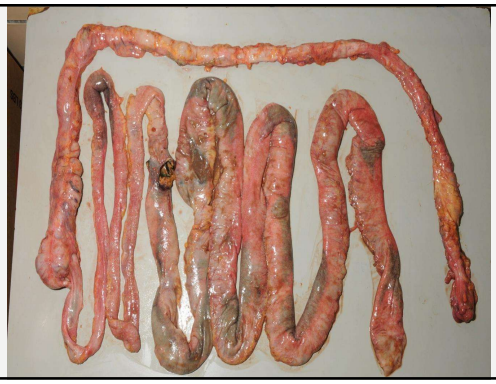
- Peripancreatic mass with neuroendocrine features
- Zollinger-Ellison syndrome
  - Multiple , recurrent ulcers
  - Often in atypical locations, such as jejunum

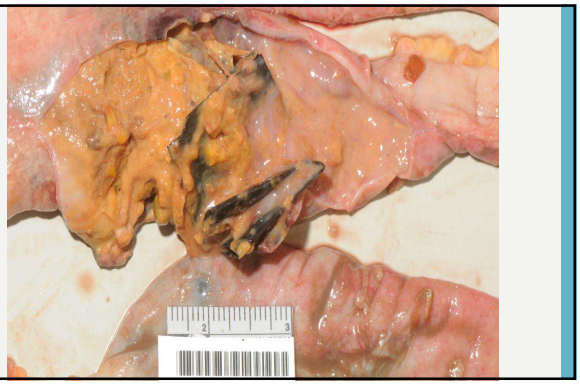


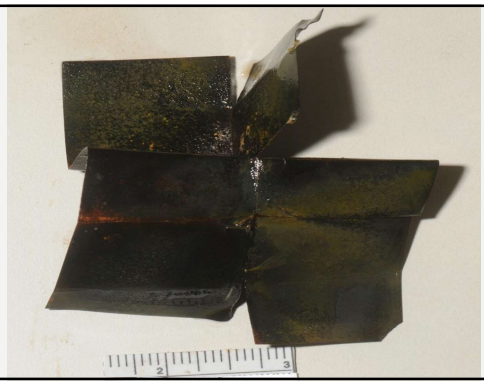
ACCIDENT: CASE 3

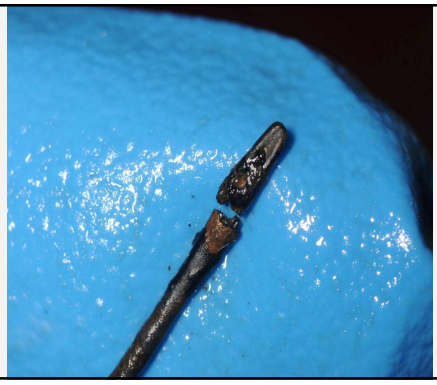
- 52 year old man, schizophrenia
- Recent inguinal hernia repair
- Collapsed in bathroom





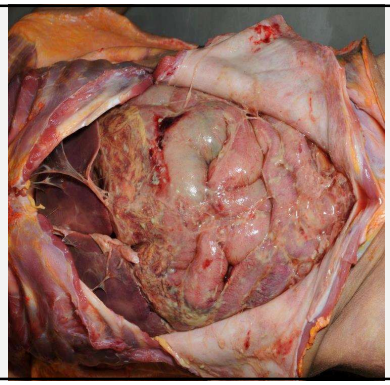


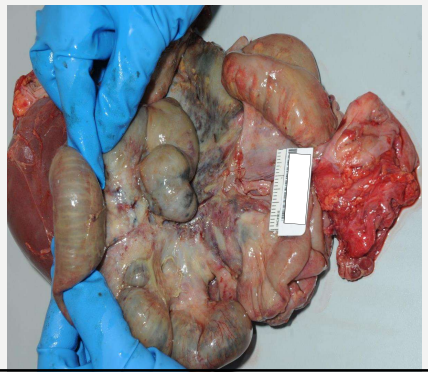


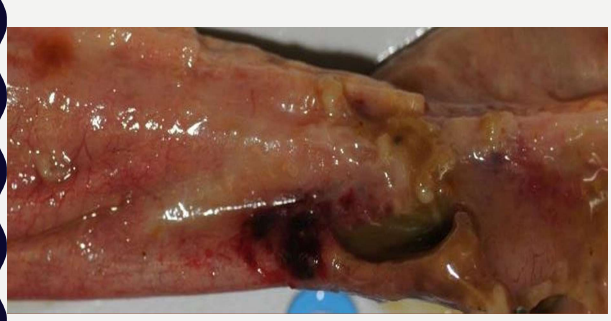


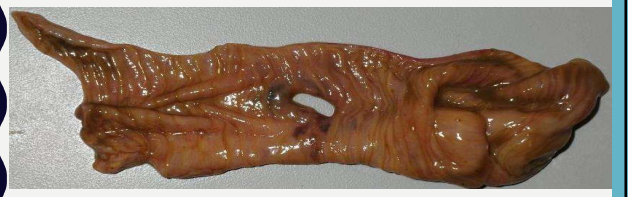
HOMICIDE: CASE 4

- 5 year old, cerebral palsy, seizures
- Found dead underneath siblings bed







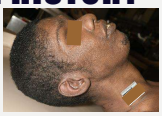


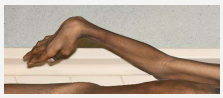
BLUNT FORCE TRAUMA OF THE ABDOMEN

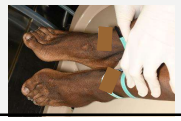
- Bowel perforation occurs in 1 – 7% of paediatric cases
- Isolated jejunal perforation occurs in less than 1% of cases
- Mortality 30%

ASSOCIATED MEDICAL HISTORY

- Schizophrenia
- Cerebral Palsy
- Trisomy 9
- Autism, mental retardation

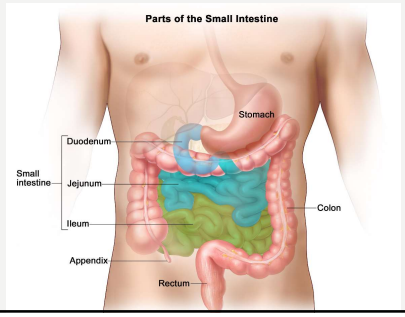






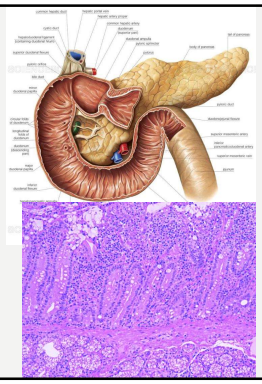
DIAGNOSIS AT AUTOPSY

GROSS ANATOMY



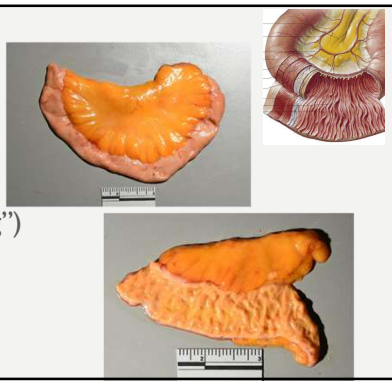
DUODENUM

- First part of small intestine
- Retroperitoneal except for first inch
- Opening of pancreatic and common bile ducts



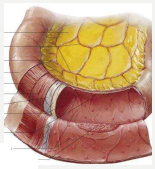
JEJUNUM

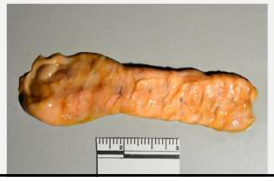
- Second part of small intestine
- From the Latin, jejunus ("fasting")
  - –Often empty after death
- Plicae circularis

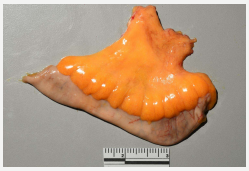


ILEUM

- Third part of small intestine
- Peyer's patches

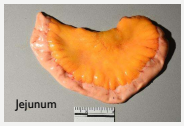


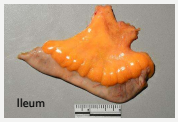




JEJUNUM VERSUS ILEUM

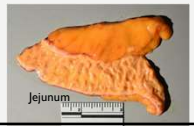
- No distinct line or anatomic landmark between them
- Plicae circularis become smaller and absent in terminal ileum
- No Peyer's patches in the jejunum
- Ileum has a smaller luminal diameter and thinner wall





JEJUNUM VERSUS ILEUM

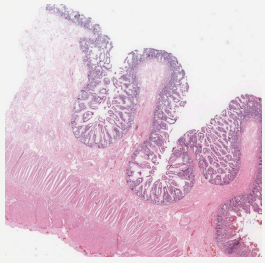
- Jejunum: left upper and central abdomen
- Ileum: right lower and central abdomen
- Mesentery of ileum has more adipose tissue
  - –Vessels more prominent in jejunal mesentery



HISTOLOGY

Jejunum

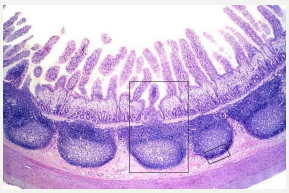
Characteristic features
- Villi
- Crypts of Lieberkühn
- Paneth cells
- No Brunner's glands
- No Peyer's patches



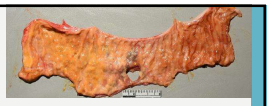
HISTOLOGY

Ileum

Characteristic features
- Peyer's patches



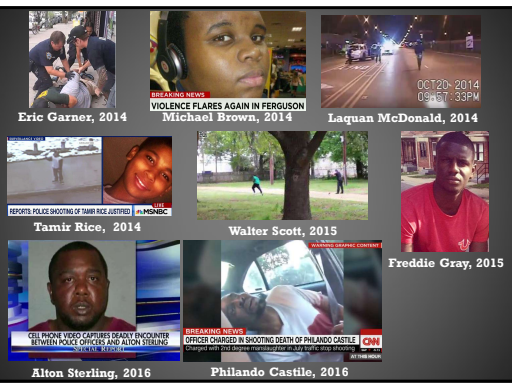
CONCLUSIONS



- Perforation of the jejunum is rare
- Possible association with mental illness or retardation
- Mostly natural deaths
- Identification of the precise location within the small intestine at autopsy

A Review of Police-Involved Fatalities from Regions of Texas

Jessica B. Dwyer, MD
Southwestern Institute of Forensic Sciences
Dallas, TX



Eric Garner, 2014 | Michael Brown, 2014 | Laquan McDonald, 2014

Tamir Rice, 2014 | Walter Scott, 2015 | Freddie Gray, 2015

Alton Sterling, 2016 | Philando Castile, 2016

Police-Involved Fatalities

- Notoriously underreported:
  - Supplementary Homicide Reports (SHRs) from the FBI Uniform Crime Reports system
    - voluntary program
  - National Vital Statistics System
    - surveys death certificates
  - Arrest-Related Deaths program
    - currently suspended

Police-Involved Fatalities

- National Violent Death Reporting System (NVDRS)
  - state-based surveillance system of violent deaths:
    - pools data elements from multiple sources
  - as of 2018, all 50 states, Puerto Rico, and DC

Police-Involved Fatalities

- very few case series
- So what about the police-involved fatalities that come through our office?

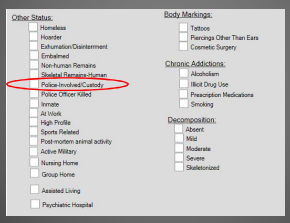
Dallas, TX

Dallas County Medical Examiner's Office
(Southwestern Institute of Forensic Sciences)

- 2018:
  - 4500 postmortem examinations
  - 3700 autopsies
    - 330 homicides
- cover Dallas county and multiple surrounding smaller counties
  - 2018:
    - 1420 autopsies from outside jurisdictions

Methods

- JusticeTrax LIMS-plus database:

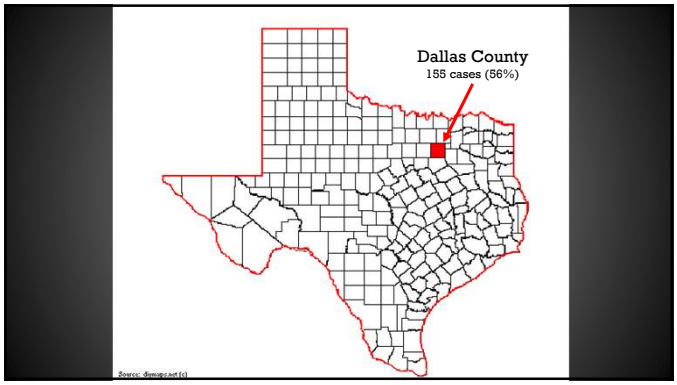


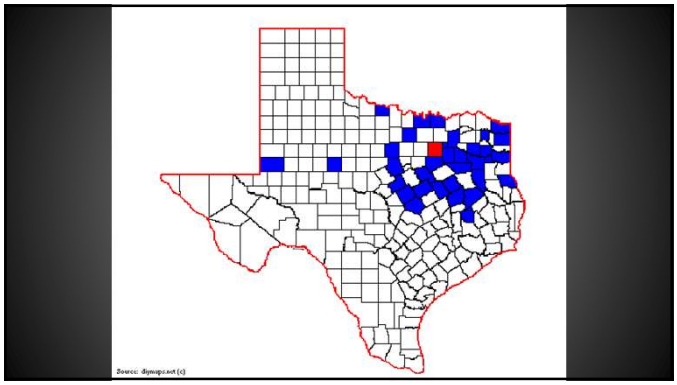
Methods

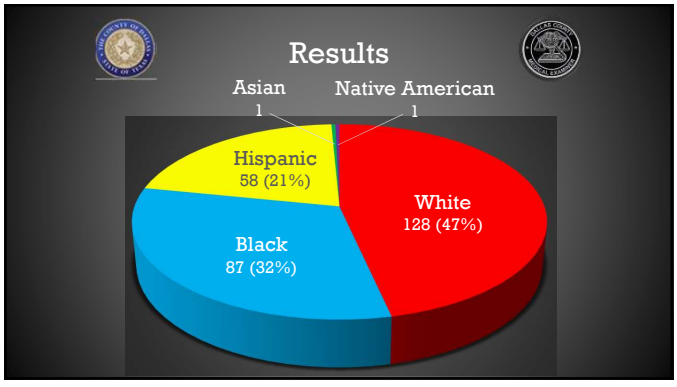
- Police-Involved Fatalities:
  - deaths occurring in proximity to law enforcement during the processes of:
    - apprehension
    - arrest
    - early incarceration

Results

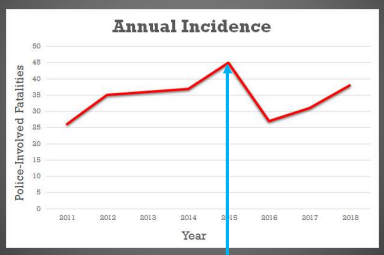
- April 2011 – December 2018:
  - 338 "Police-Involved/Custody" deaths
  - **275** classified as police-involved fatalities:
    - 259 men (94%), 16 women
    - Average age 34.9 years (median 33 years)


Dallas County
155 cases (56%)



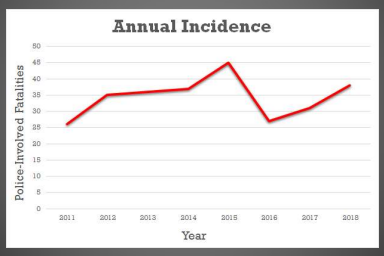

Results
Asian
1
Native American
1
Hispanic
58 (21%)
White
128 (47%)
Black
87 (32%)

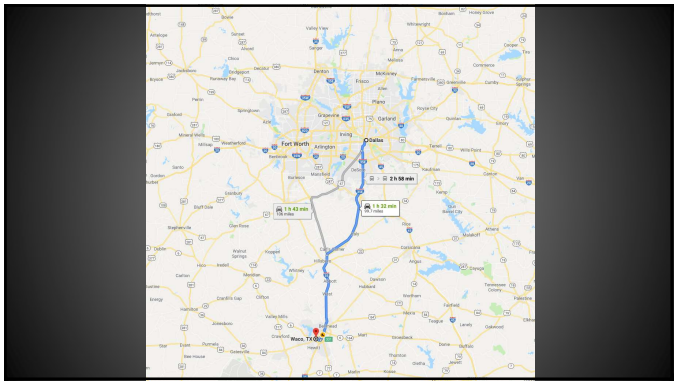
Results



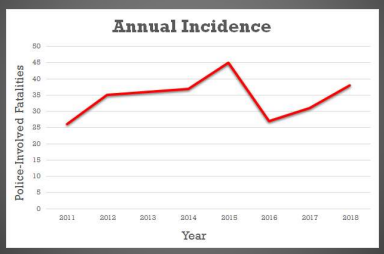
44 deaths, 35 homicides

Results

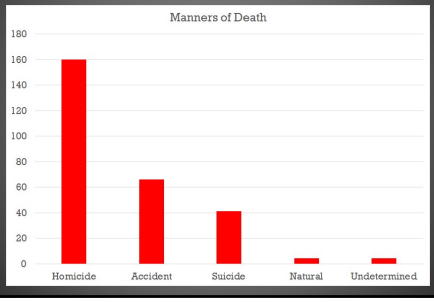




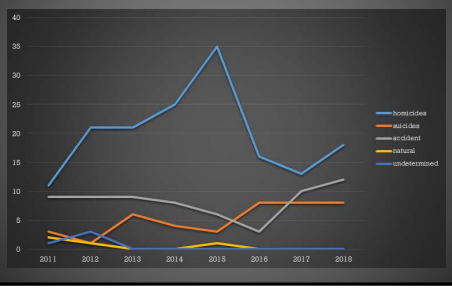
Results



Results

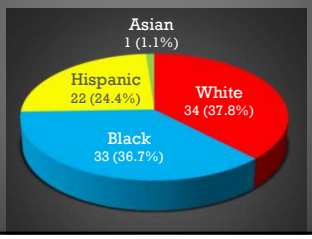


Results

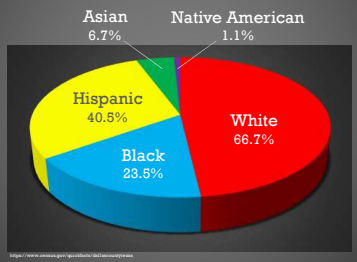


Results

- 160 **Homicides**:
  - 90 (56%) within Dallas County:



Dallas County, TX



Results

90 Police-involved Homicides (Dallas County)	
White	37.8%
Black	36.7%
Hispanic	24.4%
Asian	1.1%

Dallas County (General Population)	
White	66.7%
Black	23.5%
Hispanic	40.5%
Asian	6.7%

Results

90 Police-involved Homicides (Dallas County)	
White	37.8%
Black	36.7%
Hispanic	24.4%
Asian	1.1%

Dallas County (General Population)	
White	66.7%
Black	23.5%
Hispanic	40.5%
Asian	6.7%

Results

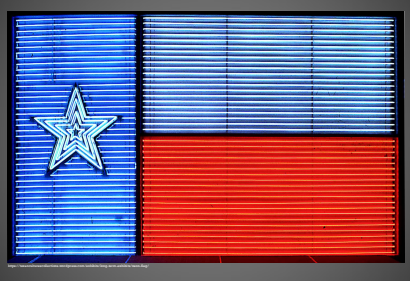
- 160 **Homicides**:
  - Causes of death:
    - Firearm wounds (148; 93%)
    - Toxic effects of drugs in conjunction with physiologic stress/excited delirium (8)
    - Complications of blunt force injuries (1)
    - Blast injuries (1)

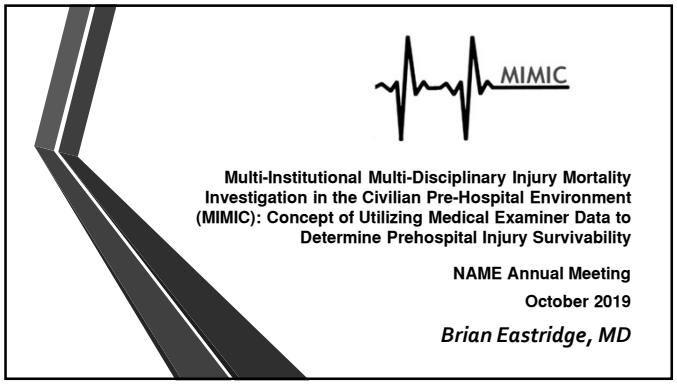
Results

- Toxicology:
  - 237 individuals (86%)
  - most commonly detected substances
    - marijuana (85)
    - ethanol (80)
    - methamphetamine (62)
    - cocaine (44)

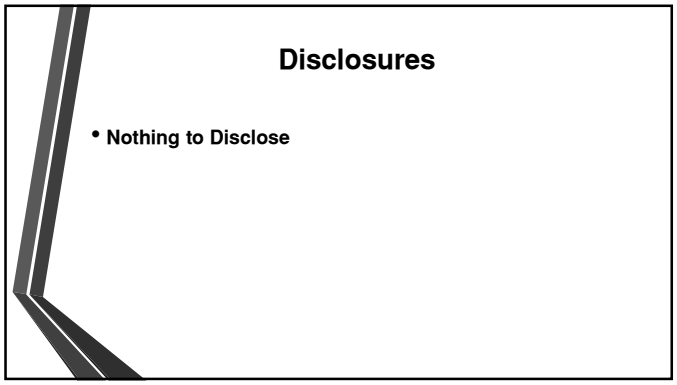
Conclusion

- review of police-involved deaths within a specific region of the United States
- need for uniform tracking on both local and national levels

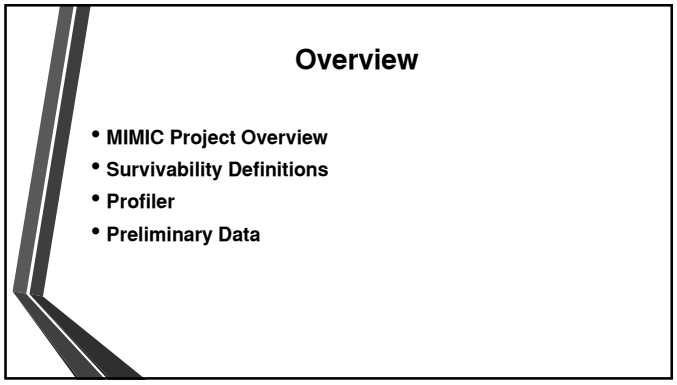



MIMIC
Multi-Institutional Multi-Disciplinary Injury Mortality Investigation in the Civilian Pre-Hospital Environment (MIMIC): Concept of Utilizing Medical Examiner Data to Determine Prehospital Injury Survivability
NAME Annual Meeting
October 2019
Brian Eastridge, MD

1


Disclosures
• Nothing to Disclose

2


Overview
• MIMIC Project Overview
• Survivability Definitions
• Profiler
• Preliminary Data

3

MIMIC Project Overview

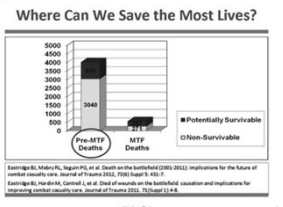
4

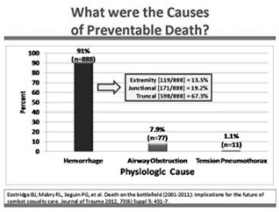
DoD Broad Agency Announcement (BAA) Grant

- Department of Defense (BAA $3,979,380)
- PI: Brian Eastridge, MD
  Professor, Department of Surgery
  Division Chief, Trauma and Emergency General Surgery
  Jocelyn and Joe Straus Endowed Chair in Trauma Research
  University of Texas Health Science Center at San Antonio
- Co-PIs: Kurt Nolte, MD
  Professor of Pathology
  University of New Mexico
  Director of Radiology-Pathology Center for Forensic Imaging
  Chief Medical Investigator, Office of the Medical Investigator
  Ellen MacKenzie, PhD
  Dean, Johns Hopkins Bloomberg School of Public Health
  Bloomberg Distinguished Professor

5

Background/Scientific Rationale Pre-Hospital Mortality Combat



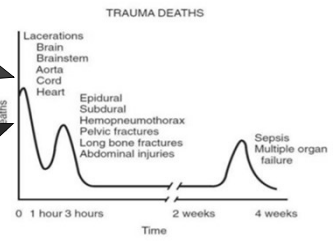


6

Background/Scientific Rationale Pre-Hospital Mortality Civilian

Poorly defined

NASEM Report Emphasis



7

Why is the MIMIC study unique?

- It replicates what other small studies have done.
- Provides a multi-disciplinary review team with granular injury details to determine survivability.
- Allows reviewers to determine survivability.
- Utilizes death data from autopsy reports to determine survivability.
- The MIMIC study is the only study that has examined pre-hospital trauma deaths to determine ways to improve outcomes.

Medrano NW, Villarreal CL, Price MA, et al. Multi-Institutional Multi-Disciplinary Injury Mortality Investigation in the Civilian Pre-hospital Environment (MIMIC). Trauma Surgery and Acute Care Open. 2019.

8

Study Hypotheses

- Substantial opportunity to further reduce deaths in pre-hospital setting.
  - Potential liabilities in civilian and military pre-hospital care must be identified and remediated in order to reduce the number of potentially preventable deaths on the battlefield and in the civilian environment.

9

MIMIC Objectives

- **Objective #1:** ***Develop a framework and methodology*** for evaluating pre-hospital deaths
- **Objective #2:** Organize and standardize a ***multidisciplinary, multi-institutional network of experts*** to identify the causes of pre-hospital deaths due to trauma and estimate the potential for survivability.
- **Objective #3:** ***Define the causes and pathophysiologic mechanisms of 3,000 pre-hospital deaths***, and estimate the potential for survivability
- **Objective #4:** ***Describe the epidemiology of pre-hospital mortality*** in the context of trauma system development and estimate its impact on society.
- **Objective #5:** ***Develop a blueprint for a sustained effort*** identifying high priority areas for injury prevention, trauma systems performance improvement and research and development.

10

System Benefits

Trauma

- Performance improvement
  - Engineering
  - Medical devices / procedures
  - EMS value validation
  - Injury Prevention
  - Collaboration between trauma and ME communities

Medical Examiner

- Funding for advanced radiological imaging
- Improve mechanistic information
- Interaction between trauma and ME communities
- Bridge the gap between ME and TS data sets

11

Study Population

- **Inclusion Criteria:**
  1. Pre-hospital deaths (at scene, en route to hospital or DOA defined as no vitals upon arrival at hospital)
  2. Blunt, Penetrating, Thermal, and Suicides are included
- **Exclusion Criteria:**
  1. Non-mechanical causes of death – poisoning, drug overdoses, hangings, drowning (unless associated with trauma)
  2. Decomposed remains only (not fully fleshed with distinguishable organs)

12

Forensic Record

Medical Examiner cases may involve any of the following:

- External examination
- Internal examination
- Investigator reports
- Toxicology Report
- Radiographs- CT Reports will be uploaded. Actual images will be uploaded if available and when a case requires adjudication.

13

Study Setting
Six Regions in the Country

(Centralized ME systems and utilizing electronic case management system to collect uniform data on all deaths)

1. **State of Connecticut**. Serves a population of 3.6 million. They perform approximately 2,200 autopsy examinations at a single, centralized facility annually.
2. **Johnson County, Iowa.** Serves a population of 142,000. In 2014 JCME accepted jurisdiction of 380 deaths and performed 118 autopsies.
3. **State of Maryland.** Serves a population of approximately 6.0 million residents . They perform 4,220 autopsies at the single, centralized facility annually.
4. **State of New Mexico.** Serves a population of 2.0 million. They perform approximately 2,100 full autopsy examinations annually
5. **State of Oklahoma.** Serves a population of 3.8 million and conducts investigation of roughly 4,000 deaths annually.
6. **The District of Columbia.** Serves a population of 659,000. They perform approximately 1,110 examinations annually.

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Estimates of Number of Injury Deaths

(Blunt, Firearm and Other Sharp Forces)

OCME	2012	2013	2014	Total
Connecticut	684	621	692	1997
Johnson Co, Iowa	133	128	110	371
Maryland	1509	1200*	1200*	3909
Oklahoma	1044	1153	1007	3204
New Mexico	823	778	906	2507
Washington, DC	232	267	254	753
Total	**4,425**	**4,147**	**4,169**	**12,741**

* Estimates

15

MIMIC Final Subject Selection

ME Site	Number of Cases
Connecticut	427
Johnson Co, Iowa	47
Maryland	848
Oklahoma	341
New Mexico	1,243
Washington, DC	152
Total	**3,058**

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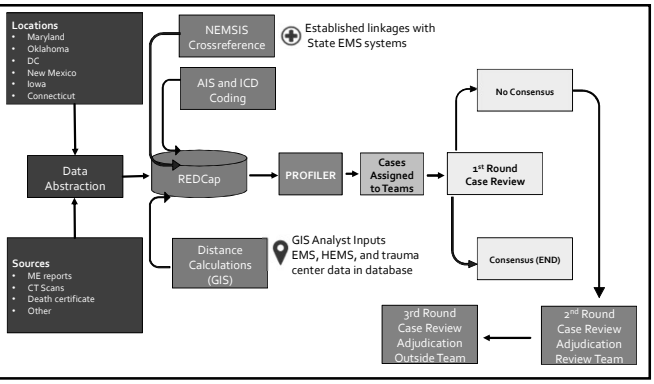
Case Review Methods

- Steering Committee (Military and Civilian) defined definitions and process
- Expert review panels (~ 80 Military and Civilian reviewers) (6 individuals are on each panel)
  - 4 Surgeons
  - 1 Emergency Medicine/EMS
  - 1 Forensic Reviewer
- Panels will each review a certain number of cases using the **PROFILER** and assign a determination of survivability to each case
- Reviewers will review cases independently. Throughout the course of the study approximately **250 cases** will be reviewed by each team panel.
- Discrepancies in determination of survivability will be identified and non-consensus will be reviewed by an adjudication team

17



18

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Survivability Definitions

- **Non-Survivable-** Death as a result of catastrophic anatomic injuries
- **Possibly Survivable -** Anatomic injuries that were severe but medically survivable
- **Definitely Survivable-** Minimal anatomic injuries with a high likelihood of survival
- **Cannot Judge-** information insufficient to make a determination

20

Anatomic Survivability

Medically Non-Survivable (MNS)

- Dismemberment / decapitation
- Traumatic Brain evisceration
- Cervical cord transection (above C_3)
- Airway transection within thorax
- Cardiac injury > 2cm
- Uncontained hemorrhage, thoracic aorta
- Uncontained hemorrhage, pulmonary artery
- Hepatic avulsion
- Junctional lower extremity amputations with open pelvis
- Injuries to the deep CNS nuclei, brainstem, or massive brain tissue injury
- Massive Pulmonary Tissue Disruption

Medically Potentially Survivable / Definitely Survivable

- All other

21

Profiler

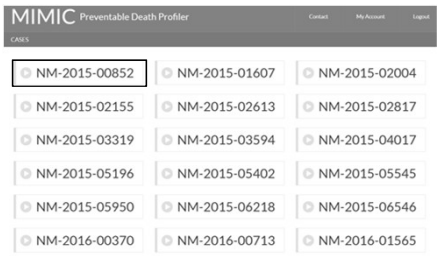
22

Profiler

1) **Open medical examiner case in Profiler**
2) **Review case**
   - Medical examiner data (left side of page)
   - Injury cause / circumstance
   - Injury severity
   - First Discovery & Response
   - EMS Care
   - Access to EMS and Trauma Center
3) **Causation and survival determination**
   - Primary cause of death (may choose multiple but must be associated with severe injury)
   - Assuming immediate access to trauma care
   - Actual conditions
   - Opportunities for improvement (free text)

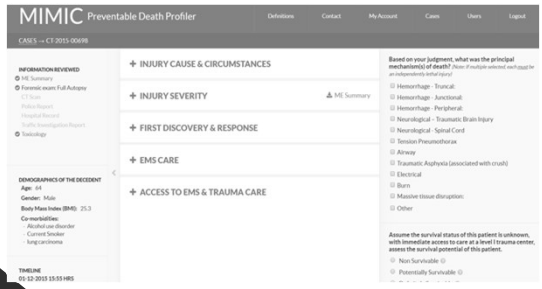
23

Open Medical Examiner Case in Profiler



24

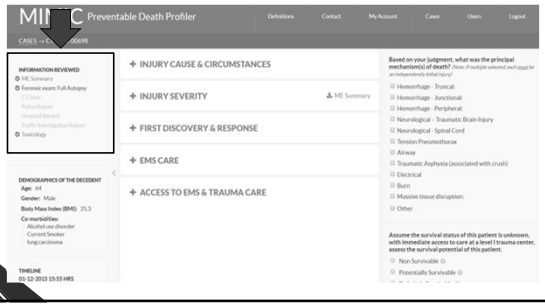
Open Medical Examiner Case in Profiler



25

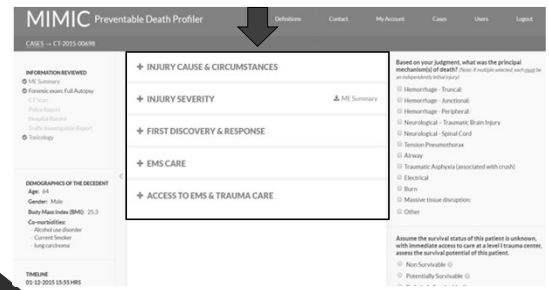
Review Case

Medical Examiner Data



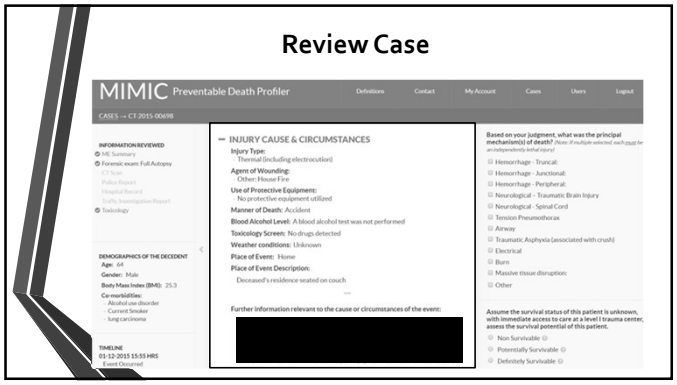
26

Review Case



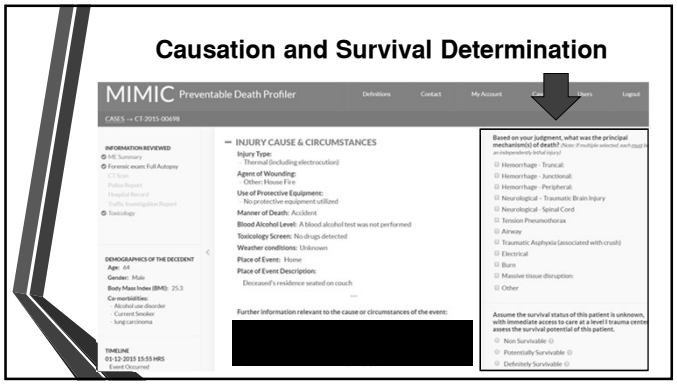
27

Review Case



28

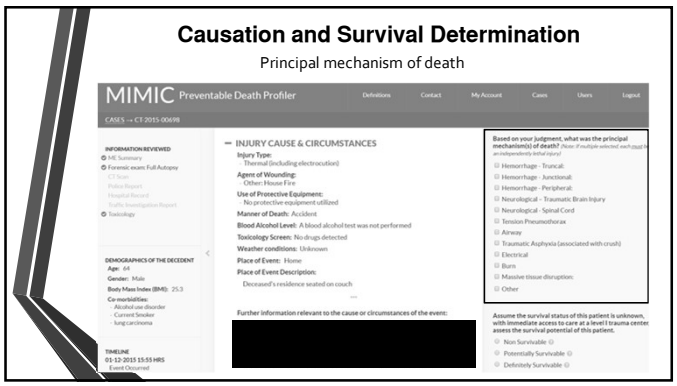
Causation and Survival Determination



29

Causation and Survival Determination

Principal mechanism of death



30

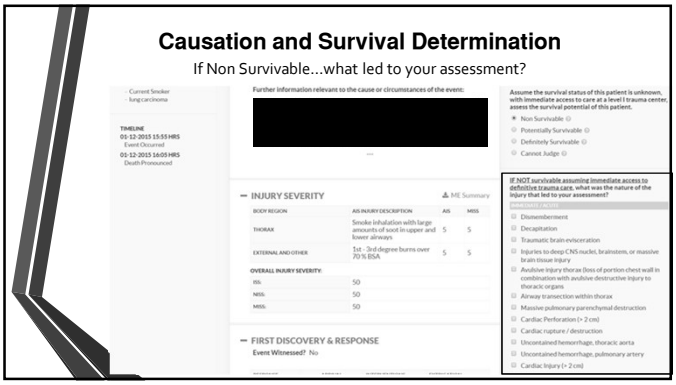
Causation and Survival Determination

Assuming immediate access to care…rate the likelihood of survival

31

Causation and Survival Determination

If Non Survivable…what led to your assessment?



32

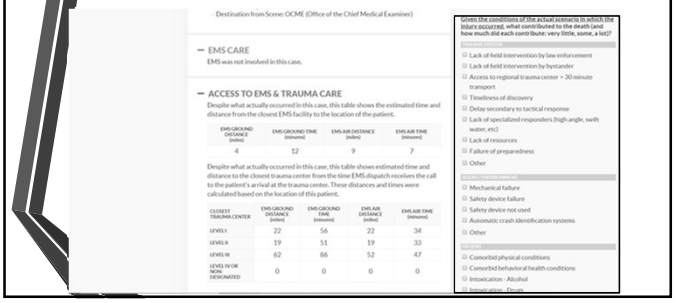
Causation and Survival Determination

Given the condition of the actual scenario…rate the likelihood of survival

33

Causation and Survival Determination

What contributed to the death?



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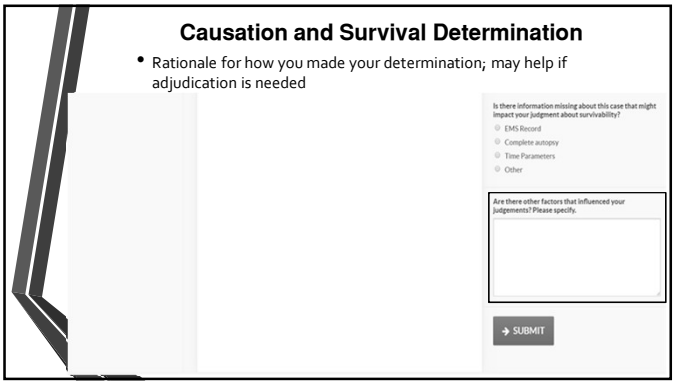
Causation and Survival Determination

- Rationale for how you made your determination; may help if adjudication is needed



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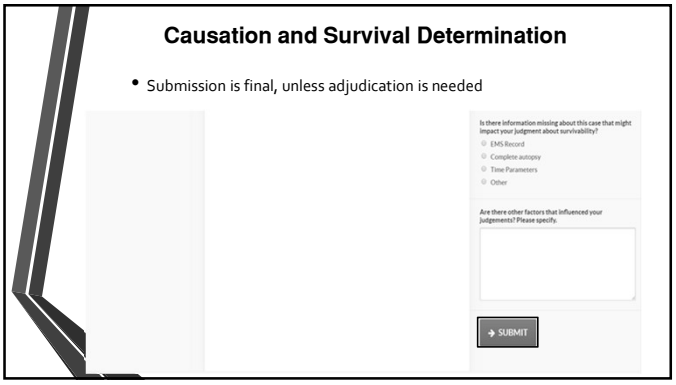
Causation and Survival Determination

- Submission is final, unless adjudication is needed



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Preliminary Data

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Case Reviews

Study Round	Number of Cases Released	Case Completion
Round 1 Status *Began 1-16-2019*	260 Cases Released	240 Cases Completed
Round 2 Status *Began 3-25-2019*	240 Cases Released	240 Cases Completed
Round 3 Status *Began 6-13-2019*	300 Cases Released	150 Cases Completed

- 13 review team panels
- Study will consist of 10 rounds
- Reviewers are reporting being able to complete each case review in about 10-15 minutes

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Questions Used to Determine Consensus

- **Consensus must be reached on both Survivability Questions:**
  - Assume the survival status of this patient is unknown, ***with immediate access to care at a level I trauma center***, assess the survival potential of this patient.
  - Assume the survival status of this patient is unknown, ***given the conditions of the actual scenario*** in which the injury occurred (i.e. discovery, EMS response, access to trauma center, weather etc.), assess the survival potential of this patient.

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Case Consensus Definition

- 5 reviewers are used to determine consensus. The ME/Forensic reviewer is not calculated in consensus as this analysis is kept separate.
- Each variable is independent. So it must be 3 or more reviewers answering the same on one specific category. (For example: 3 agree the case is Potentially Survivable)
  - If one reviewer selects non-survivable and the other 4 select either potentially, definitely survivable, or cannot judge, that case goes to adjudication
  - If two reviewers select cannot judge, but the other three are able to make a determination, the case goes to adjudication

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Case Adjudication

Study Round	Number of Cases That Did Not Reach Initial Consensus	Cases Resolved During Team Adjudication	Cases Still In Team Adjudication	Could Not Reach Consensus, Pushed for Outside Adjudication
Round 1 Status	61 cases	44 cases	3 cases	14 cases
Round 2 Status	49 cases	21 cases	20 cases	8 cases
Round 3 Status	36 cases	9 cases	24 cases	3 cases

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Preliminary Round 1 and Round 2 Data

- Q1: Based on your judgment, what was the principal mechanism(s) of death?

Principal Mechanism(s) of Death	Frequency
Neurological – Traumatic Brain Injury	1342
Hemorrhage – Truncal: Thorax	354
Neurological – Spinal Cord	256
Hemorrhage – Truncal: Abdomen / Pelvis	136
Burn	133
Airway	79
Massive tissue disruption: CNS	67
Asphyxia	65
Massive tissue disruption: Whole Body	59
Massive tissue disruption: Thorax	41
Tension Pneumothorax	32
Hemorrhage – Junctional: Cervical	29
Massive tissue disruption: abdomen	28
hemorrhage - peripheral: upper extremity	21

Note: Cases with multiple causes are counted multiple times. (Round 1 and 2)

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Preliminary Round 1 and Round 2 Data

- Q2: Assume the survival status of this patient is unknown, with immediate access to care at a level I trauma center, assess the survival potential of this patient.

Immediate Access Survivability	Frequency for reviewers reaching consensus	Frequency for medical examiners
	262 (77%)	269 (79%)
	75 (22%)	46 (14%)
	2 (1%)	5 (1%)
	0	19 (6%)

RESEARCH AND DEVELOPMENT OPPORTUNITIES TO INFORM INJURY PREVENTION

Note: Using 339 cases that have reached consensus on survivability assessments for Q2

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Preliminary Round 1 and Round 2 Data

- Q3: Assume the survival status of this patient is unknown, given the conditions of the actual scenario in which the injury occurred (i.e. discovery, EMS response, access to trauma center, weather etc.), assess the survival potential of this patient

Actual Scenario Survivability	Frequency for reviewers reaching consensus	Frequency for medical examiners
	341 (93%)	325 (89%)
	26 (7%)	22 (6%)
	0	0
Cannot Judge	0	20 (5%)

OPPORTUNITIES TO IMPROVE CURRENT TRAUMA SYSTEM

Note: Using 367 cases that have reached consensus on survivability assessments

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Immediate Access Survivability	Frequency for reviewers reaching consensus	Frequency for medical examiners
Non-survivable	262 (77%)	269 (79%)
Potentially Survivable	75 (22%)	46 (14%)
Definitely Survivable	2 (1%)	5 (1%)
Cannot Judge	0	19 (6%)

RESEARCH AND DEVELOPMENT OPPORTUNITIES TO IMPROVE FUTURE TRAUMA SYSTEMS

Actual Scenario Survivability	Frequency for reviewers reaching consensus	Frequency for medical examiners
Non-survivable	341 (93%)	325 (89%)
Potentially Survivable	26 (7%)	22 (6%)
Definitely Survivable	0	0
Cannot Judge	0	20 (5%)

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Preliminary Round 1 and Round 2 Data

- Q4: Which injury prevention programs/devices or interventions might have improved the chances of survival for this individual?

Prevention Program(s)	Frequency
Behavioral health	777
Alcohol / drug	469
Seat belt	149
Airbag	55
Helmet	34
Child Restraint	5
Protective Clothing	5
Personal Flotation Device	4

***Note:** Using records from all reviewers in Round 1 and Round 2.*

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Questions

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Summary

The goal of the research is to identify liabilities in trauma systems and develop mitigation strategies with translation potential for realistic and relevant improvements in trauma systems and medical examiner systems. The research intends to identify ways that the ME and trauma communities can improve linkages to foster in-depth reviews of trauma mortality.

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Future Directions

- Submission of an NIH R-24 award to fund a PEDS-MIMIC project
- Looking for funding opportunities aimed at building the ME system
- Exploring funding opportunities that focus on suicides

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Team Acknowledgment

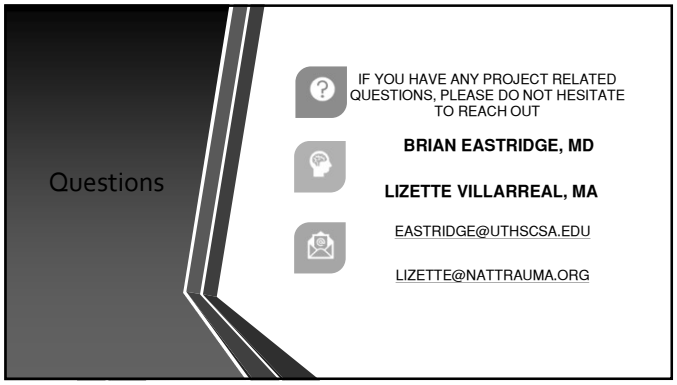
- Authors: Villarreal CL, Medrano NW, MacKenzie E, Nolte KB, Phillips MJ, Price MA, Eastridge BJ
- MIMIC Steering Committee
- MIMIC Forensic Reviewers
  - Kurt Nolte, Edward Mazuchowski, Roger Mitchell, Stacy Drake, Marcus Nashelsky, David Fowler, Greg Davis, James Gill, Joseph Hunt

50

Team Acknowledgment

Study Sites	Medical Examiner	Data Abstractors
New Mexico	Kurt Nolte	Garon Bodor Victoria Chavez Kayla Moorman Susan Catlett Yvette Gonzalez
Maryland	David Fowler	Ling Li Haitaio Bi
Washington, DC	Roger Mitchell	Chikarlo Leak Ameerah Battle
Oklahoma	Eric Pfeifer	Lynda Goldberg-Baedke
Connecticut	James Gill	Michelle Clark Jessica Crowson
Iowa	Marcus Nashelsky	Heather Sanderson

51


Questions
IF YOU HAVE ANY PROJECT RELATED QUESTIONS, PLEASE DO NOT HESITATE TO REACH OUT
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52

Around the World in 180 days

How Much Has Twitter "Disrupted" Hierarchies in Forensic Pathology?

Ken Obenson MD FRCPC FNAME
Saint John Regional Hospital
Saint John New Brunswick
Canada

No conflicts to declare

Can hierarchies really be flattened?

Humans tend to form groups and groups are eventually sorted into hierarchies depending on the ambitions of the individual group members

What is Twitter?

- A microblogging service
- Tweet within a 280 character limit on any topic that you fancy
- You have a “following” and you “follow” (others to receive their tweets)
- ~ 126 million daily users (worldwide)
- ~ 48.65 million active users in the US

Was limited to 140 characters till November 2017

Leading countries based on number of Twitter users as of July 2019 (in millions)

US: 48.65
Japan: 36.7
UK: 14.1
Saudi Arabia: 9.9
Turkey: 8.6
Brazil: 8.28
India: 7.75
Mexico: 7.02
Spain: 6.71
Russia: 6.63

Source: Clement J. Social Media & Generated Content
https://www.statista.com/statistics/242606/number-of-active-twitter-users-in-selected-countries/July 2019

Anatomy of the FP Twitter "group"

- 31 accounts on Twitter identified as belonging to those of a forensic pathologist (per their profiles)
- 15 are US based
- 4 - Canada
- 3 - UK
- 2 – Australia, Indonesia, Malaysia,
- 1 - Denmark, NZ , South Africa
- 17 female – 14 male

2 fellows, 5 residents and 1 medical student

Characteristics of followers

- Total of 82k+
- Range of 25 to 45,400
- Three had > 4k
- **Most had less than 1k**

"Followers" refers to people who find the opinions of the FPs worthy of consideration

Characteristics of "following"

- Total of 28,776
- Range of 36 to 9.9k
- **Most FPs followed < than 2k people**

"Following" in this context refers to people whose opinions the FPs may find worthy of consideration

Tweet characteristics 2009-19

- **Total tweets 90,498!***
- **51% (16) tweeted >1k times**
  - 6.5% (2) - > 10k
  - 32% (10) – between 2k & 10 k
- 19% (6) – between 500 and 2000
- 39% (12) - had 500 tweets or less

*Tweets include both forensic and non forensic topics

How much forensic content* did they tweet about?

Of 100 sequential tweets of the top 10 Tweeters

- **30% of forensic related content (2)**
- 9% to 20% forensic content (4)
- 5% forensic content (4)

*Forensic content defined by the following criteria: Death investigation, autopsy, recruitment, teaching cases, testifying, images

What was the forensic content?

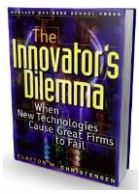
- Retweets of forensic cases or opinions
- Responses to general questions and queries
- Original posts on forensic cases
- Opinions on death investigation processes
- Adverts for training positions/jobs
- Responds to queries on recommended texts
- On SUDC
- Links to teaching cases
- Training of medical undergrads in the basics of forensic medicine and pathology

When did they join Twitter?

- 77% (24) joined ***after*** 2010
- Almost 50% joined after 2014
- 29% (9) *joined* ***in 2018-19***
- ***None*** were registered on the platform when company started in March 2006

Disruption (in business)

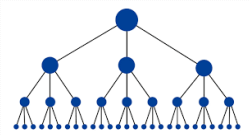
- Clayton Christensen's 1997 book *The Innovator's Dilemma*.
- However Joseph Schumpeter described the term "*creative destruction*" in 1949, which he in turn had adapted from Karl Marx



Either make stuff for the least discriminating customer or develop product which customer did not know that they needed

What **hierarchies** are disrupted?

- Traditional "command and control"



- Revenue?
- Organization?
- **Influence?**
- **Information and learning?**

The Wirearchy

- **A term coined by John Husband (1999)**
- "..Power structure created as the Information Age unfolded, disrupting hierarchical organizations and the fundamental construct of access to knowledge"

See References

Main concept:

That the "Internet and its associated networks are moving the world away from the "master-servant" archetype of the Industrial Age to a more open, social, and collaborative relationship".

See References

Metrics of Disruption

- Number of inquiries to forensic fellowships?
- Number of fellows increased?
- Number of resident & medical student members of NAME?
- Number of resident & medical student attendees at NAME & other forensic meetings?
- Inquiries made by the public to self identified experts?
- Number and frequency of connections made peer to peer?

Number and frequency of connections made peer to peer

- Probably the most easily measurable index
- Twitter is free & requires **no permissions** to follow a particular individual unless the account holder specifically requires it
- In general the more followers you have the more influential you are (unless your followers are bots!!)
- Take advantage of the many opportunities to teach and share knowledge

Securing the "new" environment

- Polite and respectful interactions are encouraged – avoid racist, sexist and abusive language
- No need to tolerate abusive or offensive commentary from anyone
- The more followers you have **the more careful you need to be** especially when discussing professional opinions – they carry a lot of weight

In short….

- Your name is your brand which you ***should*** protect
- People often tweet racist or offensive comments particularly about public figures
- If you value your current or future employment you should either ignore the comment or condemn it

Summary

- Twitter is a useful tool that facilitates **peer to peer interactions (especially among FPs)**
- **Few** FPs have professional accounts on Twitter
- It is **too early** to tell what other effects it will have on recruitment
- A willingness to interact directly with the general public, medical students and residents may help attract them into the profession (controlling for other factors i.e. money et al)

Conclusion

The wealth of opportunities to interact with directly with experts around the world breaks down barriers to communication and increases opportunities to learn and collaborate (so called **flattening of the knowledge** hierarchy or “wirearchy”).

The more (FPs sign on) the merrier

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Unexplained Pediatric Deaths: Investigation, Certification & Family Needs

Procedural guidance and key considerations developed by the

National Association of Medical Examiner's Panel on Sudden Unexpected Death In Pediatrics

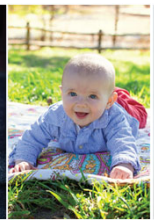
NAME 2019 Annual Meeting
Kansas City, Missouri
October 13, 2019

Disclosures

- NAME panel work funded by SUDC Foundation.
- Reference to book published by AFP.
- Employed by or receiving funding from:
  - NIH (M. Sens, R.Goldstein)
  - SUDC Foundation (L. Crandall)
  - Montgomery County Forensic Services (K. Pinneri)
  - Washoe County Regional Medical Examiner's Office (L. Knight)
  - University of North Dakota (M. Sens)
  - Vermont Office of the Chief Medical Examiner (E. Bundock)
  - National Association of Medical Examiners (M. Sens)
  - Boston Children's Hospital (R. Goldstein),
- Private Consultation Services
  - Knight Forensics, PLLC (L. Knight)
  - Gray Matter Forensic Consulting, LLC (E. Bundock)

The Beginnings

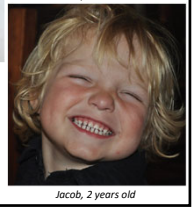
Vivienne, 3 years old



Keegan, 8 months old

Adeline, 14 months old

Slade, 18 months



Jacob, 2 years old

With parent permission

Background

- Challenge of infant deaths – NAME audience discussion 2013/2014
- 2016: AAP and NAME - revision of Child Abuse and SIDS paper
- Funding modeled after Opiate Grant / SUDC Funded
  - Committee of NAME / AAP; library support; advisory members (Feds, researchers, SUDC)
  - Two face-to face meetings; teleconferences
- Manuscript / position paper NAME / AAP

Response (single NAME post; one week)

- 32+ NAME members
  - More as project evolved
- 6 AAP members (+ others)
- Volunteer librarian – NYU
- SUDC, NYU, other researchers
- NIH (3 institutes), CDC

- Initial: One committee of 17
- Plan B: "Main" committee with members chairing subcommittees; subcommittee members not at in-person meetings
- Final:
  - Everyone on "main committee" and invited to face to face meetings
  - Multiple subcommittees based on initial question plan and evolving needs

Responding:

NAME Fellows / Members

- Tom Andrews
- Roger Byard
- Elizabeth Bundock
- Rudi Castellani
- Tracey Corey
- Giancarlo DiVella
- Eric Eason
- Wendy Gunther
- Heather Jarrell
- Laura Knight
- Kristin Landi
- Kelly Lear-Kaul
- Adele Lewis
- Evan Matshes
- Anna McDonald
- Othon Meda
- Nathaniel Patterson
- Kathryn Pinneri
- Donald Pojman
- Reade Quinton
- Valerie Rao
- Lakshmanan Sathyavagiswaran
- Mary Ann Sens
- Christina Stanley
- Jane Willman Turner
- Steven M White

Investigator / Coroner

- Stacey Drake
- Jennifer Winner
- Karla Orozco
- Dotti Owen
- Rose Psara
- Beoncia Loveless

Fellow

- Brandi McCleskey

National

- NIH: Ruth Brenner, Valerie Maholmes, Kristin Burns, Marion Koso-Thomas
- CDC: Margaret Warner, Carrie Shapiro-Mendoza, others
- NCHS / US WHO: Robert Anderson

Experts, AAP, SUDC

- Michael Ackerman
- Isabel Barata
- Susan Berry
- Erin Bowen
- Derek Bruce
- Frank Cecchin
- Ruey-Kang Chang
- Laura Crandall
- Orrin Devinsky,
- Arline Faustin
- Amanda Kay
- Declan McGuone
- Rachael Moon
- Vince Palusci
- James Robinson
- Nori Williams

Librarians

- Aileen McCrillis
- Cynthia Schmidt

National Association of Medical Examiner's Panel on Sudden Unexpected Death In Pediatrics

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- Elizabeth A. Bundock, Co-Chair and Editor
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- Thomas A. Andrew
- Isabel Barak
- Derek Bruce
- Susan Berry
- Erin Bowen
- Kristin Burns
- Rudolph Castellani
- Laura Gould Crandall
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- Eric Eason
- Wendy Gunther
- Amanda J. Kay
- Laura Knight
- Kristen Landi
- Kelly Lear
- Adele Lewis
- Evan Matshes
- Brandi McCleskey
- Rachel Y. Moon
- Vincent J. Palusci
- Kathryn Pinneri
- Cynthia Schmidt
- Mary Ann Sens
- Carrie Shapiro-Mendoza
- Jane W. Turner
- Margaret Warner
- Steven White
- Nori Williams

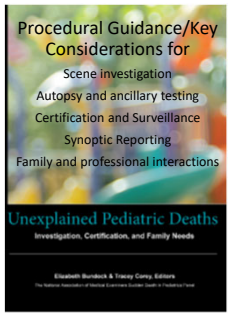
Workshop Presenters

Preliminary Framing Questions and Initial Committees

- All pediatric sudden deaths
- Potential mechanisms, evidence available, evidence needed
  - Neuropath / Neurologic
  - Infectious
  - Cardiac
  - Genetic
  - Metabolic / other natural
  - Asphyxia / other un-natural
- Basic and optimal death investigation needed, variations for age
- Risk factors, prevention
- Autopsy performance and ancillary testing
- Communication needed: Family, professionals, health systems, public health
- Certification (what information, where should it go, alternative models, manner, risk factors, etc.)
- Reporting, tracking, evaluation
- Research needs and direction

Results

- Large, fluid committee and subcommittees
- Over three years of work – started in late 2016
  - Massive reference collection, organization and review
  - 19 main committee conference calls (1 – 4+ hours in length); other subcommittee activities; spirited and passionate discussion
  - Two in-person 2 day meetings; one lunch in person meeting at NAME; editors retreat
- Support by SUDC:
  - Anticipated publication of book, Nov, 2019
- Heroic efforts of Tracey Corey and Elizabeth Bundock
- Collaboration with Radcliffe project – shaped discussions



The 3rd International Congress on Sudden Death in Infants and Children,

Radcliffe Institute for Advanced Study, Harvard University November 26-27, 2018

Inconsistent Classification of Unexplained Sudden Deaths in Infants and Children Hinders Surveillance, Prevention and Research. FSMP, Online 9/9/19

Authors on Publication:
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Barbara Himes
Susan Hollander
Ingrid A. Holm
Christine Keywan
Betty McEntire
Edwin A. Mitchell
Jan Sperhake
Barbara Samplson
Mark Super

Workshop Presenter

TOPICS COVERED

Medicolegal Death Investigation

Workshop Presenter: Kathryn Pinneri, MD.

Medicolegal Death Investigation

- Children are not small adults
  - Infants, toddlers, school aged children, pre-teens, tweens, teenagers
  - All have different concerns, developmental abilities and milestones
- Any child death falling under the jurisdiction of a medical examiner/coroner should be investigated by a certified medicolegal death investigator, independent from law enforcement
- Information obtained relies on parents, caregivers and other relatives
  - Often distraught at the scene/hospital
  - May or may not have played a role in the death
  - Delicate balance: obtaining information needed for investigation while being sensitive to the family's grief

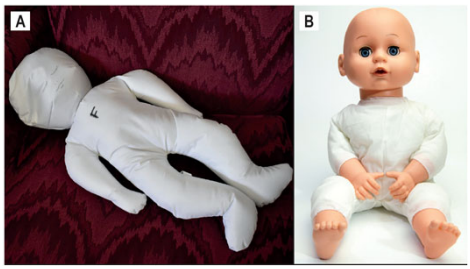
Medicolegal Death Investigation

- Scene investigation is critical
  - Should be performed within 24 hours even when the child has been transported to the hospital, to include evaluation of any potential hazards or exposures
  - Individual death scene investigation requirements will vary based on the circumstances surrounding the death and the age and developmental capabilities of the child
  - The child's environment plays a much larger role in death investigation than most adults
- In cases of death during apparent sleep, the sleeping environment should be documented to include softness, such as the presence of a pillow top mattress and excessive bedding materials

Medicolegal Death Investigation

- Must visit and photograph the environment where the child was initially found
- Doll reenactment is recommended for deaths during apparent sleep of all children up to 24 months of age, developmentally delayed children, and children with a seizure history to document the position of the child when placed to sleep and when found
- Best to use a doll brought with you; avoid using something in the residence if possible
  - Store bought baby doll
  - Weighted featureless doll (purchased online)
- Use placards denoting "found" and "placed"

Doll Reenactment



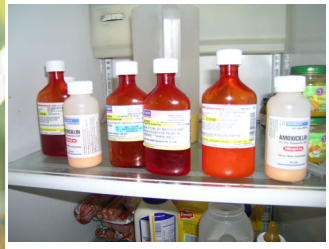
Doll Reenactment

Medicolegal Death Investigation

- Photographic documentation of the scene is required
  - Permanent record that can be viewed at a later date when necessary
  - Overall views of the environment
  - Availability of food and necessary care items (e.g., diapers, formula, baby bottles)
  - Focused views of the sleeping environment and the presence of any body fluids near the child
    - May have appropriate sleeping environment available (crib or bassinette); however, not utilizing them
  - Use of a ruler/scale is recommended for injuries and sleeping environment (demonstrating the thickness of the bedding/dimensions of the crib/bassinet) for all cases in which the child apparently dies during sleep

Medicolegal Death Investigation

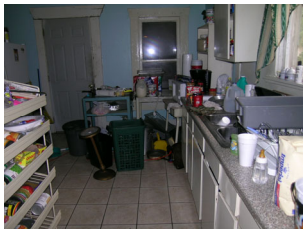
Medicolegal Death Investigation



Medicolegal Death Investigation

- The condition of the residence should be documented
  - Lighting, power and heat sources
  - Ambient temperature and humidity (where applicable)
- The clothing of any adults or siblings should be viewed and photographed for infants/children found dead while sharing sleep surfaces, either by law enforcement or the medicolegal death investigator, depending on the jurisdiction

Medicolegal Death Investigation




Medicolegal Death Investigation

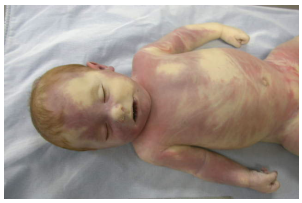
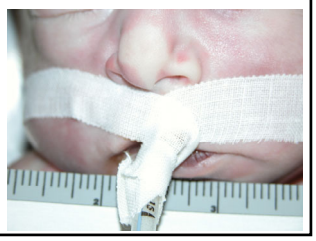
- Documentation of the body
  - The type and amount of clothing and blankets on and around the child

Medicolegal Death Investigation

- Documentation of the body
  - The type and amount of clothing and blankets on and around the child
  - Other objects near child

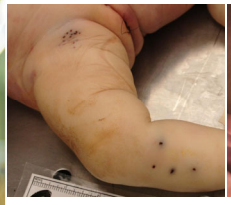
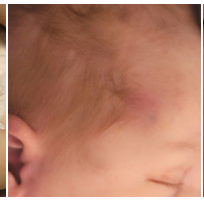
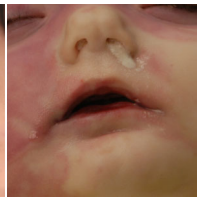
Medicolegal Death Investigation

- Documentation of the body
  - The presence and pattern of lividity
  - The presence of rigor mortis

Medicolegal Death Investigation

- Documentation of the body
  - Evidence of medical intervention
  - Visible injuries and transient findings

Medicolegal Death Investigation

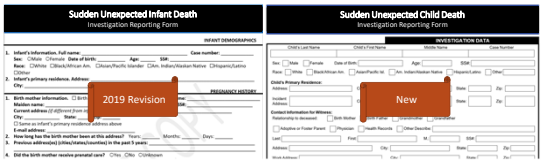
- Video surveillance (e.g., crib monitors, home security systems, law enforcement body cameras) should be inquired about and viewed when available
- Many infants/children are transported to the hospital with attempts at resuscitation
  - Parents/caregivers should be interviewed as soon as possible – even at the hospital

Medicolegal Death Investigation

- Use of an infant/child death reporting form is recommended
  - Ensures required information is gathered uniformly, including housing and living environment, developmental milestones passed, caregiver arrangements, and school information (when applicable)
  - As a standard practice, may help the family feel less interrogated
  - Provides background information for obtaining necessary records
- Best practice: ask all the questions, all the time, as soon as possible

Medicolegal Death Investigation

- Sudden unexplained infant and child death reporting forms
  - Checklist with all information needed for pediatric death investigation
  - Infant form recently revised by CDC
  - Childhood form developed by Panel

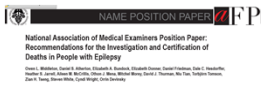


Medicolegal Death Investigation

- Questions on checklist
  - Who normally cares for the child?
  - Who lives in the home with the child?
  - Any sick contacts?
  - Recent illness or fever?
  - Any recent changes in behavior or activity level?
  - What does the child eat and when were they last fed?
    - Collect bottle/cup when possible
  - Where does the child normally sleep? Any sleep-surface-sharing?
  - Any known medical history? Medications?

Medicolegal Death Investigation

- Seizure history
  - Age at onset, etiology
  - Known triggers, Febrile
  - Frequency and type (s); Last seizure
  - Medication/dosage, recent medication changes
  - Family history of seizures
- Developmental milestones are important!!
  - Vary with age
  - Rolling over, crawling, cruising, walking, etc
  - Delayed children will have altered milestones – get as specific information as possible



Medicolegal Death Investigation

- Information/records needed for sudden unexplained pediatric deaths
  - Mother's obstetrician
  - Birth hospital
    - Gives starting point for weight and length
    - Provides type of delivery and any complications
  - Pediatrician
    - Request all visits, including growth charts, newborn screening results and immunizations
  - Terminal hospital/ER records
  - Prior ER/hospital records
  - EMS records
    - May need documentation of type of CPR performed
    - Provides great initial information (scene environment, body position, cardiac rhythm, capillary blood glucose

Medicolegal Death Investigation

- School records may be requested for those children of school age
- The medical examiner/coroner should work with local hospitals and other agencies to obtain and store records and/or gain electronic off-site access
  - Case management software must be secure, access-controlled, and have the capability to store third party records

Medicolegal Death Investigation

- Cell phone and social media photographs and videos of the child prior to death may be obtained from the parents/caregivers.
- The death investigator should be familiar with current social media platforms and work with parents/law enforcement agencies to gain access to electronic devices when necessary.

Medicolegal Death Investigation

- Removal of the child from the residence should be performed with care and compassion
  - Recommended that the child be wrapped in a sheet or blanket and carried to the transport vehicle, to be placed inside a body bag and/or transport box
- Some states/jurisdictions have laws allowing viewing of a deceased child
  - Usually requires supervision
  - Be as accommodating as possible without jeopardizing the investigation

Autopsy and Ancillary Testing

Workshop Presenter: Laura Knight, MD.

Autopsy and Ancillary Testing

- What is a complete autopsy?
- What is a complete pediatric autopsy?
- To what extent must we preserve biospecimens for future analysis with advances in testing?
- Research?
- Resources?
  - Equipment and supplies
  - Storage capacity, freezers
  - Funding
  - Personnel/staffing

Autopsy and Ancillary Testing

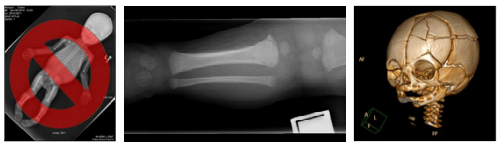
Procedural Guidance

- **An autopsy must be performed in all sudden unexpected deaths in infants and children**
  - unless prohibited by law (such as in cases of religious objection in certain states).
- **The autopsy should be performed promptly** and as soon as practical following death, to preserve the quality of diagnostic specimens
  - including those for microbiological, genetic, and metabolic studies.

Autopsy and Ancillary Testing

Procedural Guidance

- **A radiologic skeletal survey should be performed** in all infants and young children.
  - Consultation with a pediatric radiologist, if available, may be considered.
  - Memoranda of understanding may be established with local hospitals to obtain postmortem skeletal surveys in cases in which the infant or child is transported to the hospital.



Autopsy and Ancillary Testing

Procedural Guidance

- **Histology and comprehensive toxicology must be performed** in all sudden unexpected deaths in infants and children.
- In deaths that remain unexplained after gross autopsy examination, additional testing should be performed:
  - **Microbiological cultures** (and other related studies), directed by the case history and autopsy findings.
  - **Molecular testing** may be performed in conjunction with cultures, and specimens should be preserved for additional **infectious disease-related** molecular testing methods if indicated later.
  - **Chemical analysis of vitreous fluid** for electrolytes and glucose should be performed.

Table 5.3: Histologic Sampling During the Postmortem Examination of an Infant or Child Who Has Died Suddenly and Unexpectedly

Minimum Sections	Supplemental/Discretionary Sections
Central Nervous System*	
Cortex and white matter at frontal watershed, with leptomeninges, basal ganglia, thalamus, level of lateral geniculate nucleus, rostral medulla, cerebellum; grossly apparent lesions that cannot be diagnosed without histology	Basal ganglia with insular cortex, amygdala, thalamus, midbrain, pons, cervical spinal cord
Cardiovascular System*	
Left and right ventricles, interventricular septum, grossly apparent lesions	Atria (to include right and left atrioventricular grooves with coronary arteries), cardiac conduction system (SA and AV nodal regions)
Respiratory System	
Each lobe of both lungs (including peripheral and central areas), trachea (extra- and intra-thoracic)	Lobar bronchi, true vocal cords, epiglottis/aryepiglottic folds
Hepatobiliary System	
Liver	
Genitourinary System	
Each kidney	Bladder, gonads
Endocrine System	
Each adrenal gland, thyroid gland, pancreas	Pituitary gland
Gastrointestinal System	
Stomach, small intestine, colon	Esophagus
Immune System	
Spleen, thymus, bone marrow*	Tonsil
Musculoskeletal System	
	Diaphragm, rib with chondrosternal junction
Gross Abnormalities	
Needing a histopathologic correlate	At pathologist's discretion

See Chapter 5 *Unexplained Pediatric Deaths: Investigation, Certification and Family Needs*. AFP 2019

Autopsy and Ancillary Testing

Procedural Guidance

Genetic testing

- **Preserve specimen to allow for later genetic testing**
  - a lavender top EDTA tube of blood at minimum
- **Ideally, screening tests for cardiac channelopathies and cardiomyopathies should be performed when all other testing is negative**, *prior* to finalizing cause of death as undetermined or equivalent.
- Other genetic studies (for metabolic and neurologic disorders, or directed genetic testing for specific cardiomyopathy) may be appropriate based on medical history, circumstances of death, and autopsy findings.
- It is understood that the yield of genetic testing is low in SUIDs, but somewhat higher in SUDC. It is critical to order in SUDC cases.
- DNA banking may be offered to families (at their cost) in "undetermined" cases with negative genetic screens.

Autopsy and Ancillary Testing

Procedural Guidance

Metabolic testing

- Must be performed whenever the clinical history or autopsy findings suggest a diagnosis of inborn error of metabolism;
  - clinical consultation may be useful in appropriately targeting the testing.
- **Routine** metabolic screening on all sudden unexplained infant and child deaths is **extremely low-yield**, and a negative result from a limited postmortem panel may provide false reassurance.
- At minimum, a metabolic blood/bile spot card should be prepared at the time of autopsy and held (to be later sent if indicated by unexpected findings).

Autopsy and Ancillary Testing

Procedural Guidance

Examining the brain

- The pediatric brain and spinal cord **should be preserved in formalin prior to sectioning,** photography, and histologic sampling if organ retention is not precluded by statute and the autopsy has not revealed a definitive cause of death. The intracranial dura may be examined with or without fixation.
- Examination by a neuropathologist experienced in forensic cases is recommended but at the discretion of the autopsy pathologist if resources are limited or retention of organs is restricted.; some offices do this as a matter of routine on SUID/SUDC cases

Autopsy and Ancillary Testing

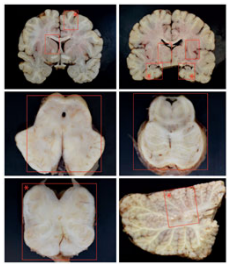
Procedural Guidance

Examining the brain

Table 8.1: Histologic Sections for Neuropathologic Examination

Brain Region	Reason for Evaluation
* Cortex and white matter at frontal watershed, with leptomeninges	Assess cortical development; identify neuronal necrosis; screen for neuronal storage disorder; exclude meningitis and encephalitis
* Hippocampi, right and left, at level of lateral geniculate nucleus	Assess development; screen for neuronal or causes of seizure; identify neuronal necrosis
* Medulla, rostral	Contains centers for cardiorespiratory regulation and arousal
* Cerebellum	Involved in autonomic regulation; atrophy associated with epilepsy; identify neuronal necrosis
* Grossly apparent lesions that cannot be diagnosed without histology	Microscopic confirmation is needed for diagnosis
Basal ganglia with insular cortex	Insular cortex involved in autonomic regulation; screen for neuronal storage disorder and periventricular lesions associated with premature birth
Amygdala	Implicated in epilepsy and apnea; screen for gliosis and neuronal loss as sequelae of temporal lobe seizures
Thalamus	Screen for neuronal storage disorder and gliosis
Midbrain and Pons	Contains centers for cardiorespiratory regulation and cranial nerve nuclei
Cervical spinal cord	Necessary for cardiorespiratory regulation

* Recommended minimum sampling



See Chapter 8 *Unexplained Pediatric Deaths: Investigation, Certification and Family Needs*. AFP 2019

Autopsy and Ancillary Testing

Procedural Guidance

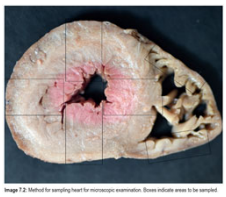
Examining the heart and great vessels

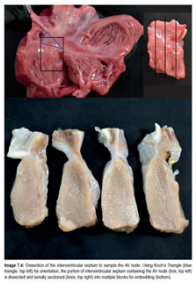
- The orientation of the heart and great vessels must be **examined *in situ*** in all pediatric cases. When abnormalities are already apparent, the heart, lungs, and thoracic aorta should be **removed *en bloc*** for further examination. Otherwise, the method of removal is **at the discretion** of the pathologist.
- In infants, the heart should be opened along lines of blood inflow and outflow.
- In older children, the adult method (transverse apical sections, followed by dissection of the heart base by blood inflow and outflow method) may be used.

Autopsy and Ancillary Testing

Procedural Guidance

Examining the heart and great vessels





See Chapter 7 *Unexplained Pediatric Deaths: Investigation, Certification and Family Needs*. AFP 2019

Table 5.2: Special Dissections and Their Indications

Special Dissection	Indication
Removal of the parietal pleura to expose the ribs	Routine
Opening petrous ridges to visualize/culture middle ear canal	History or suspicion of otitis media; known upper respiratory infection
Removal of spinal cord	Routine; ideal practice to include spinal cord, dura mater, and pituitary gland with brain for neuropathology examination
Anterior neck dissection with removal of tongue, laryngohyoid complex and trachea as a block	Routine; examine anterior neck soft tissues, laryngohyoid structures, and pre-vertebral fascia and retropharynx
Posterior neck dissection	Suspicion of trauma to this region; clarify suspected cervical spine injuries (including alleged or suspected shaking/whiplash); evaluate extent of impact injury; refine evidence of strangulation or neck pressure
Removal of ocular globes with optic nerves for further examination after fixation	Suspicion of child abuse; presence of craniocerebral trauma or intracranial hemorrhage
Subcutaneous dissection of back and extremities to examine soft tissue and muscles	Suspicion of child abuse; evaluation for evidence of impact or application of pressure
Dissection of skeletal elements; specimen radiographs	Radiological finding of fracture or suspected injury of bone, or other radiological abnormality having a histopathologic correlate
Cervical spine removal *en bloc*	Suspicion of blunt head impact and/or shaking injury; findings of unexplained subdural and subarachnoid hemorrhage; further refine evidence of head and neck trauma

See Chapter 5 *Unexplained Pediatric Deaths: Investigation, Certification and Family Needs*. AFP 2019

Autopsy and Ancillary Testing

Procedural Guidance

- **Communication should be considered a step in the autopsy.**
- Preliminary results to family, law enforcement, other stakeholders within 48 hours
  - anticipated scope of testing
  - turnaround times
  - who they should contact for updates or questions.
- Final results and the cause of death to the family
  - verbally (by scheduled appointment, either via telephone or in-person)
  - and in writing (ie, report if desired)
  - Include a cover letter warning family what is enclosed (ie, autopsy report)
  - A written request from the family for this information may be required in some states.
- Family should have the opportunity to ask questions of the pathologist in order to best understand the findings in the report.

Autopsy and Ancillary Testing

Procedural Guidance

- **The autopsy report should include a detailed opinion section that explains the rationale** for the cause and manner of death determination
  - written in a manner accessible to the lay reader,
  - questions about unusual results or circumstances should be anticipated and explained proactively
- The opinion section may include recommendation for clinical evaluation and genetic testing for surviving family members when a genetic condition remains in the differential diagnosis.
  - Or this recommendation may be made in a separate letter to the family
- Synoptic reporting and death certificate completion, up next

Autopsy and Ancillary Testing

- **Greater financial support MUST be provided to death investigation systems** to provide adequate training, FP staffing, supporting staffing, and needed facilities, equipment, supplies, and budget to perform recommended procedures, consultations, and testing.
  - Completeness of investigations
  - Timeliness of results and reports
  - Care and counseling of family
- Provide financial incentives to enter FP workforce (shortage); encourage dual training in FP plus PP, NP, or CvP.

Synoptic Reporting

Workshop Presenter: Mary Ann Sens, MD., Ph.D.

Synoptic Reporting

- For deaths in which the cause of death cannot be determined, the autopsy report should contain:
  - At minimum, a synoptic report, including the following elements: cause of death, manner of death, investigation, medical history, sleep environment concerns, other environmental concerns, other objective concerns, autopsy, toxicology, ancillary studies, and radiologic studies, and;
  - Ideally, an organized, well-written summary section that details a rationale for the chosen cause of death statement, highlighting influential aspects of the history, investigation, or autopsy.

Why a Synoptic Report?

Challenges with Certification

- Rich and detailed investigation cannot be conveyed
- Data elements for public health / research not readily gathered
  - Poor surveillance tool for interventions, trends
- Wording on DC may totally change intent of certifier

Goals with Certification

- Wanted to convey some major scene / investigation points
- Wanted clarity in diagnosis and certification

Why a Synoptic Report?

Desired Solution

- Certification terminology that CANNOT be incorrectly coded
- Certification that permits identification of areas for surveillance

- Report details of scene and autopsy findings
- Include level of investigation and testing

- Standardized certification choices
- Synoptic reporting of pediatric sudden deaths

Synoptic Report:

What:	• Concise, structured data collection of data pairs
Why:	• Optimize collection, reporting, research and validation
How:	• CAP Cancer Protocols initial synoptic report – now widespread

Key Components of Synoptic Report

- Data: Response format (may be pre-populated)
- Separate lines for each data / response pair
- All responses are together; can be anywhere in report
- Additional items allowed but required data elements must all be present
- Narrative comments permitted BUT THEY ARE NOT a substitute

Pathology Report Cancer Synoptic (for senior FP)

Final data pairs shown; may result from drop-down or other menu

CARCINOMA OF THE PROSTATE

TUMOR SUMMARY:	Prostate, prostatectomy
Procedure:	Radical Prostatectomy
Type:	Adenocarcinoma
Grade:	Gleason grade 3+4 = 7 (Group 3)
Gleason tertiary pattern:	Not applicable
Tumor size:	at least 1.1 cm as measured from the glass slide
Extraprostatic extension:	None
Urinary bladder neck invasion:	None
Seminal vesicle invasion:	None
Margins:	Positive, focal, left posterior
Treatment effect, primary site:	None
Lymph nodes, # sampled:	0
Stage (AJCC 8):	mpT2 pNX

Checklist – paper or within EMR

Gastrointestinal Stromal Tumor (GIST)

Based on AJCC/UICC TNM, 8th edition

Procedure
___ Local excision
_X_ Resection
Specify type (eg, partial gastrectomy): ____total gastrectomy____
___ Metastasectomy
___ Other (specify) _____
___ Not specified

Tumor Site
Specify (if known): __gastric body_____
___ Not specified

Tumor Size
Greatest dimension: _5.3_ cm
*Additional dimensions: _4.8_ x _4.5_ cm
___ Cannot be determined (see "Comment")

Cannot have text only, even if all elements are present

Kidney, Left (Radical Nephrectomy):

Clear cell adenocarcinoma, Furhman nuclear grade 3, 8.3 cm, unifocal involving upper pole of kidney and extending into the renal vein with the renal vein margin positive. Sarcomatoid features not identified.

No lymph nodes submitted, adrenal gland uninvolved, lymphatic invasion present, no venous large vessel invasion, pT3, Nx. No significant pathologic alterations identified.

Application to Pediatric Sudden Death

- Good Death Investigation and Autopsy = Lots of Data
- Check list of elements to consider in investigation / autopsy

- Consistent data collection in standard reporting format
- Ability to assess detail of investigation and autopsy

- Proven ability of synoptic reports to improve quality

Synoptic Report Basic Elements

I. Cause
II. Manner
III. Investigation
IV. Medical History
V. Sleep environment
VI. Other environment
VII. Other objective concerns
VIII. Autopsy
IX. Toxicology
X. Ancillary Studies
XI. Radiologic Studies
XII. Comments

Investigation:
- Medicolegal investigation with scene visit and doll reenactment
- Medicolegal investigation with scene visit, no doll reenactment
- Medicolegal investigation without scene visit
- Other (state)

Environment, other:
- Markedly elevated temperature / excess bundling
- Markedly cold temperature
- Cigarette smoking in or outside home
- Marijuana use in or outside home

Data Element	Response
Cause of Death:	Unexplained Sudden Death
Manner of Death:	Undetermined
Investigation:	• Medicolegal investigation with scene visit and doll reenactment • Medicolegal investigation with scene visit, no doll reenactment • Medicolegal investigation without scene visit • Other (state)
Medical History:	• Decedent medical history reviewed, no causative or contributory factors, or risk factors identified • Decedent medical history reviewed, minor findings (state) • Decedent medical history reviewed, potential causative or contributory factors, or risk factors identified (state) • Incomplete medical record review • No medical record review • Medical records unavailable or nonexistent
Sleep environment concerns:	• Supine sleeping on safe surface (alone, on surface designed for infant sleep, with firm mattress and fitted sheet and absent additional soft bedding and objects) • Prone sleeping on safe surface • Supine sleeping on unsafe surface • Prone sleeping on unsafe surface • Sleep surface sharing with one or more other children • Sleep surface sharing with one adult • Sleep surface sharing with more than one adult • Sleep surface sharing with adult(s), and other children • Complex sleep surface sharing (other circumstances not covered above, such as with intoxicated adult) • Unknown/unconfirmed sleep environment

Additional Comments: Free text available for additional findings deemed appropriate by the pathologist

Data Element	Response
Other environmental concerns	• Markedly elevated temperature in home or excess bundling • Markedly cold temperature in home • Cigarette smoking in or outside home • Marijuana use in or outside home
Other objective concerns	• Postmortem changes out-of-keeping with stated history • Non-lethal injury or injuries • Non-lethal illness or disease process • Illness or injury of unknown significance • Non-lethal toxicologic finding • Toxicologic finding of unknown significance
Autopsy	• Complete autopsy (macroscopic and microscopic examination of thoracic, abdominal and pelvic organs, brain and spinal cord) • Subspecialty pathologists consulted (pediatric, cardiac and/or neuro-pathologists) • Incomplete autopsy (specify in Comments) • Autopsy not performed
Toxicology	• Complete toxicology (alcohol, illicit, prescribed and non-prescribed drugs) • Toxicology testing not performed due to inadequate or absent specimens • Toxicology testing not performed
Ancillary studies	• Bacterial cultures done • Viral cultures / studies done • Vitreous electrolytes done • Genetic cardiac studies done • Metabolic screen done • Ancillary studies not performed due to inadequate, inappropriate or absent specimens • Ancillary studies not performed

Outcomes of Synoptic Reporting

Certification clarity

- More standardized and accurate certification to allow INTENT of certifier to be accurately captured
- Improved surveillance opportunities and stratification of cases

Use / recognition of data gathered

- Evolution of synoptic reporting in a field
  - Verification of type, number of basic elements
  - Improve of choices of sub-data for clarity and actual use

Outcomes of Synoptic Reporting

Use and Improvements in Synoptic Reporting

- Requires peer and expert review in quality process
- Requires investment by ultimate stakeholders – national organizations / members, public health, national demographic / statistical units (CDC, Census, NIH, HRSA, NIJ, others) for improving data accuracy and completeness

Current Procedural Guide and Considerations

Deaths should be certified in consistent way to reflect accuracy and intent of certifier while maximizing surveillance opportunities

For deaths in which the cause of death cannot be determined, the autopsy report should contain:

- At minimum, a synoptic report, including the following elements: cause of death, manner of death, investigation, medical history, sleep environment concerns, other environmental concerns, other objective concerns, autopsy, toxicology, ancillary studies and radiologic studies
- Organized, well-written summary section that details a rationale for the chosen cause of death statement, highlighting the influential aspects of the history, investigation and autopsy

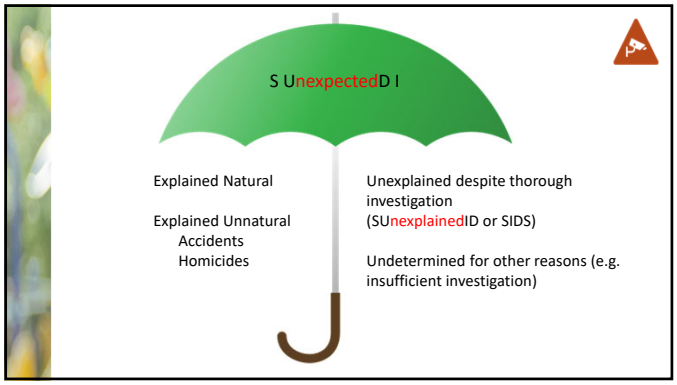
Death Certification and Surveillance

Workshop Presenter: Elizabeth Bundock, MD., Ph.D.

Sudden Infant Death Syndrome (SIDS)

"Sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history."

* Willinger M, James LS, Catz C. Pediatr Pathol 1991; 11(5):677-684



Inclusion of Risk Factors on DC

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

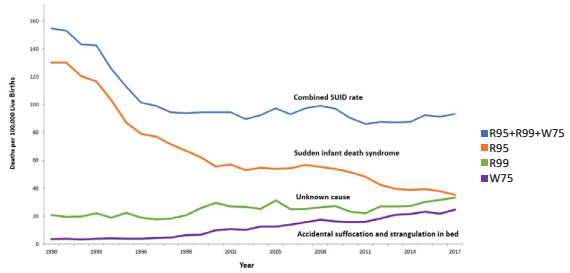
IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Sudden Unexplained Infant Death
Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b.
Due to (or as a consequence of):
c.
Due to (or as a consequence of):
d.

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I
Sharing sleep surface with two adults

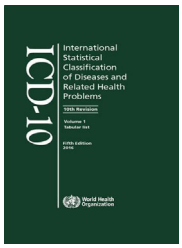
33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No

"Diagnostic Shift"



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality Files https://www.cdc.gov/sids/data.htm

Primer on Coding for Certifiers



ICD-10 Codes for Unexplained Deaths

ICD-10 Code	Title	Applies when
R95	Sudden Infant Death Syndrome	Age <365 days, COD is unexplained and includes the words "sudden" and "death"
R96	Other sudden death, cause unknown	Age ≥ 365 days, COD is unexplained and includes the word "sudden"; excludes sudden cardiac death
R99	Other ill-defined and unspecified causes of mortality	Any age, COD is unexplained but does not specifically indicate "sudden"

2005-2007

ORIGINAL ARTICLE

A Functional Approach to Sudden Unexplained Infant Deaths

Tracey S. Corey, MD, Randy Hanzlick, MD,† John Howard, MD,‡ Clifford Nelson, MD,§ and Henry Krous, MD‖*

Endorsed by the NAME board of directors on October 14, 2005, at the annual meeting in Los Angeles, CA. AJFMP 2007 28(3) 271-277.

Sudden Unexplained Infant
Death Investigation

A Systematic Training Program for the Professional
Infant Death Investigation Specialist

CDC

Infants Certified with Sudden and Death

- If the cause of death is certified as any combination of "Sudden" and "Death"
  - sudden infant death syndrome,
  - sudden unexplained infant death, or
  - unexplained sudden death

and is not followed by a better-defined, coded condition in Part I,

the underlying cause code will be R95

Effect of Sequence and Part II on Coding When Cause of Death Includes "Sudden" and "Death"

Part I/COD, Line A	Due to Part I/COD, Line B	Part II/CCOD	ICD-10 Underlying Cause Code	Code Title
Sudden infant death syndrome OR Sudden unexplained infant death			R95	Sudden Infant Death Syndrome
"		Risk factors: Bed sharing, prone sleep	R95	Sudden Infant Death Syndrome
"	Possible asphyxia due to bed sharing		R95	Sudden Infant Death Syndrome

Effect of Sequence and Part II on Coding When Cause of Death Includes "Sudden" and "Death"

Part I/COD, Line A	Due to Part I/COD, Line B	Part II/CCOD	ICD-10 Underlying Cause Code	Code Title
Sudden infant death syndrome OR Sudden unexplained infant death	Possible overlay while bed sharing		W75	Accidental suffocation and strangulation in Bed
"		Possible overlay while bed sharing	R95	Sudden Infant Death Syndrome

Overlay will be used as the Underlying Cause when it appears in Part I, but not Part II.

Infant or Child Certified as COD: Undetermined

- If the cause of death is entered as "undetermined", the underlying cause code will be R99,

  except when another better-defined, coded condition is present.

  In which case, "undetermined" is ignored and the Underlying Cause of Death will be coded according to the codable entity.

Effect of Part II on Coding When Cause of Death is "Undetermined"

Part I/COD	Part II/CCOD	ICD-10 Underlying Cause Code	Code Title
Undetermined		R99	Other ill-defined and unspecified causes of mortality
Undetermined	Risk factor: Bed sharing, Prone sleep	R99	Other ill-defined and unspecified causes of mortality
Undetermined	Risk factors: Bed sharing, Acute tracheitis	J041	Acute tracheitis

One Story, Three Codes

Part I/COD	Part II/CCOD	ICD-10 Underlying Cause Code	Code Title
Sudden infant death syndrome OR Sudden unexplained infant death	Possible asphyxia due to bed sharing	R95	Sudden Infant Death Syndrome
Undetermined	Risk factor: Bed sharing	R99	Other ill-defined and unspecified causes of mortality
Undetermined	Possible asphyxia due to bed sharing	W75	Accidental suffocation and strangulation in Bed

10 Leading Causes of Death by Age Group, United States – 2017

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 4,580	Unintentional Injury 1,267	Unintentional Injury 718	Unintentional Injury 860	Unintentional Injury 13,441	Unintentional Injury 25,689	Unintentional Injury 22,828	Malignant Neoplasms 39,266	Malignant Neoplasms 114,810	Heart Disease 519,052	Heart Disease 647,457
2	Short Gestation 3,749	Congenital Anomalies 424	Malignant Neoplasms 418	Suicide 517	Suicide 6,252	Suicide 7,948	Malignant Neoplasms 10,900	Heart Disease 32,656	Heart Disease 80,102	Malignant Neoplasms 427,896	Malignant Neoplasms 599,108
3	Maternal Pregnancy Comp. 1,432	Malignant Neoplasms 325	Congenital Anomalies 188	Malignant Neoplasms 437	Homicide 4,905	Homicide 5,488	Heart Disease 10,401	Unintentional Injury 24,461	Unintentional Injury 25,406	Chronic Low Respiratory Disease 136,139	Unintentional Injury 169,936
4	SIDS 1,363	Homicide 303	Homicide 154	Congenital Anomalies 191	Malignant Neoplasms 1,374	Heart Disease 3,681	Suicide 7,335	Suicide 8,561	Chronic Low. Respiratory Disease 18,667	Cerebro-vascular 125,853	Chronic Low. Respiratory Disease 160,201
5	Unintentional Injury 1,317	Heart Disease 127	Heart Disease 75	Homicide 178	Heart Disease 913	Malignant Neoplasms 3,616	Homicide 3,351	Liver Disease 8,312	Diabetes Mellitus 14,904	Alzheimer's Disease 120,107	Cerebro-vascular 146,383
6	Placenta Cord. Membranes 843	Influenza & Pneumonia 104	Influenza & Pneumonia 62	Heart Disease 104	Congenital Anomalies 355	Liver Disease 918	Liver Disease 3,000	Diabetes Mellitus 6,409	Liver Disease 13,737	Diabetes Mellitus 59,020	Alzheimer's Disease 121,404
7	Bacterial Sepsis 592	Cerebro-vascular 66	Chronic Low. Respiratory Disease 59	Chronic Low Respiratory Disease 75	Diabetes Mellitus 248	Diabetes Mellitus 823	Diabetes Mellitus 2,118	Cerebro-vascular 5,198	Cerebro-vascular 12,708	Unintentional Injury 50,951	Diabetes Mellitus 83,564
8	Circulatory System Disease 449	Septicemia 48	Cerebro-vascular 41	Cerebro-vascular 56	Influenza & Pneumonia 190	Cerebro-vascular 593	Cerebro-vascular 1,811	Chronic Low. Respiratory Disease 3,975	Suicide 7,982	Influenza & Pneumonia 46,862	Influenza & Pneumonia 55,672
9	Respiratory Distress 440	Benign Neoplasms 44	Septicemia 33	Influenza & Pneumonia 51	Chronic Low Respiratory Disease 188	HIV 513	Septicemia 854	Septicemia 2,441	Septicemia 5,838	Nephritis 41,070	Nephritis 50,633
10	Neonatal Hemorrhage 379	Perinatal Period 42	Benign Neoplasms 31	Benign Neoplasms 31	Complicated Pregnancy 168	Complicated Pregnancy 512	HIV 831	Homicide 2,275	Nephritis 5,071	Parkinson's Disease 31,177	Suicide 47,173

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

10 Leading Causes of Death by Age Group, United States – 2017

SUDC R96-99*=243

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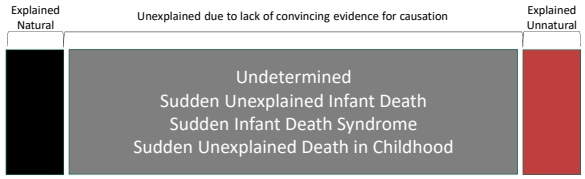
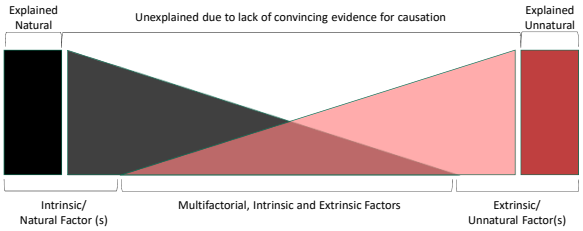
Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

*R96-99 is defined in ICD-10 as "ill-defined and unknown cause of mortality" and is currently our only measure to assess the incidence of SUDC. If included in the leading cause of death chart, SUDC in toddlers would rank 8th.

Sudden Unexpected Pediatric Deaths



Sudden Unexpected Pediatric Death



Death Certification and Surveillance

- When cause of death cannot be determined, one of the following cause statements are recommended as applicable :
  - Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors).
  - Unexplained Sudden Death (Intrinsic Factors Identified).
  - Unexplained Sudden Death (Extrinsic Factors Identified).
  - Unexplained Sudden Death (Intrinsic and Extrinsic Factors Identified).
  - Undetermined (Not further specified).
  - Undetermined (Insufficient Data).

Intrinsic Factors

- natural conditions or risk factors associated with abnormal physiology or anatomy that are concerning as contributors to death but are insufficient as a cause
  - (e.g. low birth weight, preterm birth, small for gestational age, concurrent non-lethal illness, history of febrile seizures),
- or natural conditions of unknown significance
  - (e.g. cardiac channelopathy or seizure gene variants of unknown significance).

Extrinsic Factors

- conditions in the child's immediate environment that are a potential threat to life but cannot be deemed the cause of death with reasonable certainty,
  - (e.g. side or prone sleep if unable to roll to supine, over-bundling without documented hyperthermia, objects in immediate sleep environment, sleep environment not specifically designed for infant sleep, soft or excessive bedding, and sleep-surface sharing),
- injuries or toxicologic findings that are either non-lethal or of unknown lethality, or
- circumstances/findings otherwise concerning for unnatural death.

COD: Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors)

Criteria for Infants:

1. Infant less than one year of age in apparent good health that dies suddenly and unexpectedly.
2. For Sleep Related Deaths:
   a) Placed alone, supine, in infant-specific sleep environment (e.g. crib, bassinet, portable crib, play pen) with flat, firm sleep surface, uncluttered by objects, and without potential areas of entrapment.
   b) Found unresponsive or dead, in the same sleep environment, with no obstruction of the nose and/or mouth or compression of neck/chest to cause asphyxia given the developmental abilities of the infant, as described by finder and demonstrated by doll reenactment.
3. The infant was not overly dressed or bundled for the environmental temperature.
4. Competent caregiver not impaired by drugs or alcohol.
5. Physical findings on body and at scene consistent with history provided by caregiver.

6. Completion of scene investigation and doll reenactment unless caregiver declines.
7. Review of child medical records and family health history.
8. Complete autopsy with histology, comprehensive toxicology testing (including vitreous chemistries if possible), and skeletal survey.
9. No anatomic, metabolic, toxicologic, chemical, historical, or external cause of death identified. Genetic testing is recommended but not required for this certification.
10. No extrinsic or intrinsic risk factors are identified.

COD: Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors)

Criteria for Children greater than 12 months of age:

1. Child greater than 12 months of age in apparent good health that dies suddenly and unexpectedly.
2. For sleep related deaths: Found unresponsive or dead, with no obstruction of the nose and/or mouth or compression of neck/chest considered sufficient to cause asphyxia given the developmental abilities of the child (prone position without obstruction of nose and/or mouth may be present).
3. Physical findings on body and at scene consistent with history provided by caregiver.
4. Competent caregiver not impaired by drugs or alcohol.
5. Completion of scene investigation and doll reenactment if age or circumstance appropriate and caregiver cooperative.
6. Review of child medical records and family health history.
7. Complete autopsy with histology, comprehensive toxicology testing of blood (including vitreous chemistries if possible).
8. No anatomic, metabolic, toxicologic, chemical, historical or external cause of death identified. Genetic testing is recommended but not required for this certification.
9. No extrinsic or intrinsic risk factors are identified.

COD: Unexplained Sudden Death (Intrinsic Factors Identified)

A cause of death cannot be determined and criteria for Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors) are not met due to

- intrinsic/natural abnormalities that are either known risk factors for sudden death

  (including, but not limited to, low birth weight, preterm birth, small for gestational age, concurrent non-lethal illness, febrile seizures)
- or are of unknown significance (including, but not limited, to mutations of unknown significance).
- Trauma and other unnatural etiologies are sufficiently excluded.

COD: Unexplained Sudden Death (Extrinsic Factors Identified)

A cause of death cannot be determined and criteria for Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors) are not met due to

- the presence of unintentional extrinsic factors that increase risk for unnatural death.
  - For infants this includes, but is not limited to, side or prone sleep if unable to roll to supine, overheating, objects in sleep environment, infant in sleep environment not specifically designed for infant sleep, soft or excessive bedding, and sleep-surface sharing.
  - At all pediatric ages this may include, but is not limited to, non-lethal injuries or injuries of unknown significance, non-lethal toxicologic findings of unknown significance, or circumstances otherwise concerning for unnatural death.

COD: Unexplained Sudden Death (Intrinsic and Extrinsic Factors Identified)

A cause of death cannot be determined and criteria for Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors) are not met due to

- a combination of intrinsic and extrinsic factors as described above.

COD: Undetermined (Not further specified)

A cause of death cannot be determined due to circumstances or findings that make the above classifications inapplicable.

- Examples may include
  - Inconsistent histories and/or other evidence that raise uncertainty about manner of death,
  - Competing causes of death
  - Cases which remain undetermined but were not sudden.

COD: Undetermined (Insufficient Data):

A cause of death cannot be determined because

- investigation, death scene examination, or autopsy were substantially limited, incomplete, or insufficient.

Examples may include

- legal/religious restrictions
- delayed report of death that limits scene investigation,
- decomposition.

Death Certification and Surveillance

- The following criteria for certification of an infant death as being caused by an asphyxia etiology are recommended:
  - The case must have a complete/full autopsy.
  - Toxicology, histology, vitreous electrolytes, cultures, and review of medical history are to be performed, as necessary as determined by investigation and autopsy.
  - The infant must have obstruction of both nose and mouth or compression of the neck or chest, that is reliably witnessed or demonstrated by doll reenactment, or other reliable evidence of overlay or entrapment.
  - Asphyxiation must be probable given infant's age and stage of development.
  - There cannot be a reasonable competing cause of death.

Death Certification and Surveillance

R95 or R96 depending on age on certificate**

Unexplained Sudden Death (No Identified Intrinsic or Extrinsic Factors).
Unexplained Sudden Death (Intrinsic Factors Identified).
Unexplained Sudden Death (Extrinsic Factors Identified).
Unexplained Sudden Death (Intrinsic and Extrinsic Factors Identified).

R99

Undetermined (Not further specified).
Undetermined (Insufficient Data).

****To better represent the current and future data captured by R95/MH11, it is recommended that the title of this code be changed to "Unexplained Sudden Death in Infancy or Sudden Infant Death Syndrome."

Development of extension codes by the NCHS to capture data included within parentheses is recommended.

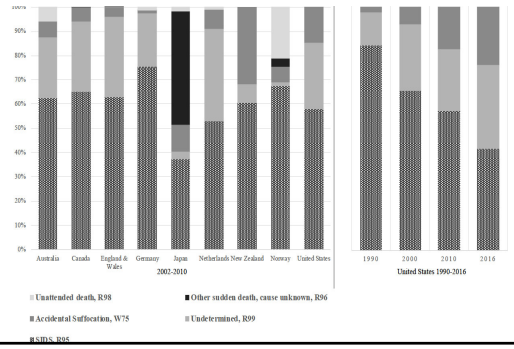
The 3rd International Congress on Sudden Death in Infants and Children

Workshop Presenter: Richard D. Goldstein, MD.

ICD-10 Codes

R95 Sudden Infant Death Syndrome
R96 Other sudden death, cause unknown
(recommended code for SUDC)
R99 Ill-defined and unknown cause of mortality
W75 Accidental suffocation and strangulation in bed

ICD-11 being finalized (MH11, MH12, MH14, PB00-PB0Z)



Accommodations by WHO Certifiers

R95 (SIDS):
Deaths under 1 year with the following inclusion terms:
Cot death, Crib death, SDII, SID, SIDS, SUD, SUDI, SUID
Sudden (unexpected) (unattended) (unexplained), death (cause unknown) (in infancy)(syndrome), infant death (syndrome)

R96 (intended SUDC):
Deaths 1 year of age and older with all the above inclusion terms
Coded to Instantaneous Death - R96.0

BUT: Undetermined with *possible* asphyxia, or risk in sleep environment, etc. will elevate to ASSB **W75**

The 3rd International Congress on Sudden Death in Infants and Children

Radcliffe Institute for Advanced Study, Harvard University

Robert N. Anderson, PhD, National Center for Health Statistics, North American Collaborating Centre for the WHO Family of International Classifications, Hyattsville, MD, USA

Peter S. Blair, PhD, University of Bristol, International Society for the Study and Prevention of Perinatal and Infant Death, UK

Elizabeth A. Bundock, MD, PhD, Office of the Chief Medical Examiner, National Association of Medical Examiners, Vermont, USA

Laura G. Crandall, SUDC Registry and Research Collaborative, New York University Langone Medical Center, New York, NY, USA

Robert A. Darnall, MD, Dartmouth Geisel School of Medicine, American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, Dartmouth, NH, USA

Richard Goldstein, MD, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

Fern Hauck, MD, MS, University of Virginia Health System, American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, International Society for the Study and Prevention of Perinatal and Infant Death, Charlottesville, VA, USA

Robin L. Haynes, PhD, Boston Children's Hospital, Boston, MA, USA

Barbara Himes, IBCLC, First Candle/National SIDS Alliance, USA

Susan Hollander, CJ Foundation for SIDS, USA

Ingrid A. Holm, MD, MPH, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

Christine Keywan, LCGC, Boston Children's Hospital, Boston, MA, USA

Henry F. Krous, MD, Rady Children's Hospital and UCSD School of Medicine, San Diego, CA, USA

Betty McEntire, PhD, American SIDS Institute, American Association of SIDS Prevention Physicians, International Society for the Study and Prevention of Perinatal and Infant Death, USA

Edwin A. Mitchell, FRACP, University of Auckland, NZ

Rachel Y. Moon, MD, University of Virginia Health System, Chair, American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, International Society for the Study and Prevention of Perinatal and Infant Death, Charlottesville, VA, USA

Torleiv Rognum, MD, PhD, MHA, Oslo University Hospital, University of Oslo, Norway

Mary Ann Sens, MD, PhD, University of North Dakota School of Medicine and Health Sciences, National Association of Medical Examiners, USA

Carrie Shapiro-Mendoza, PhD, MPH, Centers for Disease Control and Prevention, USA

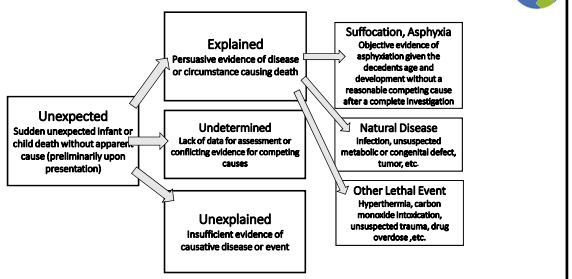
Jan Sperhake, MD, University Medical Center Hamburg-Eppendorf, Germany

Barbara A. Sampson, MD, PhD, Chief Medical Examiner, New York, NY, USA

Mark Super, MD, Merced County Sheriff - Coroner's Office, CA, USA

Guiding principles

- Consensus
- Standardization
- Reliability



3 Categories

- **Undetermined** because you don't have enough to make a conclusion
- **Explained** by evidence that is not circumstantial or based only on risk **Thorough and Conclusive**
  - Persuasive evidence of lethality
- **Unexplained** after a credible, realistic process **Thorough and Conclusive**

Consensus Classification of Unexplained Sudden Deaths in Infants and Children

Proposed ICD-11 Code	*Current ICD-10 Code*	*Proposed ICD-11 Stem Code/Classification*	*ICD-10 Classification*
UNEXPLAINED MH11	R95	**Unexplained sudden death in infancy** or Sudden Infant Death Syndrome	Sudden Infant Death Syndrome
UNEXPLAINED MH12	R96	Unexplained sudden death in children and adults	Other sudden death, cause unknown
UNDETERMINED MH14	R99	Other Ill-Defined or Unspecified Causes of Death (Undetermined)	Other Ill-Defined or Unspecified Causes of Death
EXPLAINED PB00-PB0Z	W75-W84	Unintentional threat to breathing (accidental asphyxia)	Unintentional threat to breathing by external compression of airways or chest; Unintentional threat to breathing by unspecified means

MH11: Unexplained sudden death in infancy or SIDS

The sudden *unexpected* death of an apparently healthy infant under one year of age that *remains unexplained* after a thorough case investigation, including performance of a complete autopsy with ancillary testing, examination of the death scene, and review of the clinical history. (based upon NAME)

MH12: Unexplained sudden death in children and adults

The sudden unexpected death of a person *one year of age or older* that remains unexplained after a thorough case investigation, including performance of a complete autopsy with ancillary testing, and review of the clinical history and circumstances of death.

MH14: Other Ill-Defined or Unspecified Causes of Death (Undetermined)

Cases may be certified as Undetermined when:

1. The investigation, death scene examination, or autopsy was *substantially limited, incomplete or insufficient*, for example legal/religious restrictions, delayed report of death that limits scene investigation, or decomposition; or
2. Inconsistent accounts or other findings raise *competing conclusions* about the cause of death.

PB00-PB0Z: Unintentional threat to breathing (accidental asphyxia)

Certification of asphyxia: Adequate evidence must be documented to substantiate asphyxiation, given the decedent's age and stage of development. There cannot be a reasonable competing cause of death after a complete autopsy with ancillary testing, examination of the death scene (with a doll re-enactment when appropriate), and review of the clinical history.

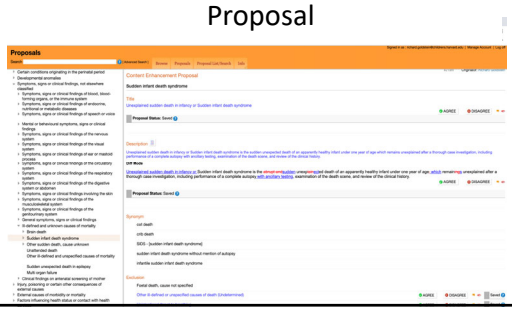
In infants, bed/sleep surface sharing, soft bedding, or prone sleep, without adequate evidence for airway obstruction or chest wall compression, are insufficient to certify a death as due to asphyxia. These deaths may be more appropriately certified as unexplained sudden death or SIDS. The use of "possible" or "probable" asphyxia will result in the death being classified as asphyxia.

Rises to the level of *Explained*

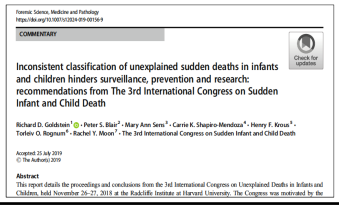
Implications

- Global reliability and standardization
- Thorough careful work is reflected in the "unexplained" diagnosis
- Lack of resources and variable standards are reflected in "undetermined"
  - Frustrated assessments
  - Accurate portrayal that insufficient resources can limit assessments
- Explanation is not the presence of risk but an *assessment of the lethality* of those factors in an individual case
- Legitimate conclusion of asphyxia is clearly stated

WHO ICD Content Enhancement Proposal



- Invited NAME participation, all suggested by NAME President included (Kim Collins)
- Reviewed by NAME panel before proposal was finalized
- Published Open Access in a forensic pathology journal
- Intended to incorporate concerns NAME and its members have expressed for decades


Forensic Science, Medicine and Pathology
https://doi.org/10.1007/s12024-019-00156-9

COMMENTARY

Inconsistent classification of unexplained sudden deaths in infants and children hinders surveillance, prevention and research: recommendations from The 3rd International Congress on Sudden Infant and Child Death

Richard D. Goldstein[1] · Peter S. Blair[2] · Mary Ann Sens[3] · Carrie K. Shapiro-Mendoza[4] · Henry F. Krous[5] · Torleiv O. Rognum[6] · Rachel Y. Moon[7] · The 3rd International Congress on Sudden Infant and Child Death

Accepted: 25 July 2019
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Abstract

This report details the proceedings and conclusions from the 3rd International Congress on Unexplained Deaths in Infants and Children, held November 26–27, 2018 at the Radcliffe Institute at Harvard University. The Congress was motivated by the

Family Needs & Professional Relations

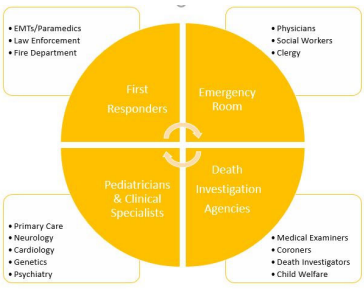
Workshop Presenter: Laura Crandall

Family Needs & Professional Relations

Guidance for Professional Relations

- Establish trauma-informed inter-agency care protocols
- Training for first response teams
- Education for hospital teams about the local medicolegal death investigation system
- Medical Training
  - Multidisciplinary approach
  - Access for Debriefings/Panel Discussions
  - Develop Network of Suitable Consultants
- Role of child death review committees

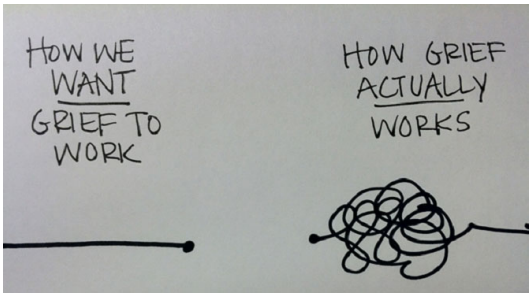
Family Needs & Professional Relations



Family Needs & Professional Relations

Grief

- Parental Bereavement- Hardest of Losses to Bear
- In the Blink of an Eye
- First 72 Hours is Chaos for Families
  - Confusion, lack of control…
  - Multiple Agencies/Professionals Involved- none of their choosing
- What does it look like?
  - 5 Stages: Denial, Anger, Bargaining, Depression and Acceptance
  - Or…



Procedural Guidelines for Family Needs

- To prevent further trauma, complete thorough investigations and foster positive outcomes
- Maintain an unbiased, non-accusatory approach to parents
- Respect for privacy, dignity, and comfort for families
- Opportunity to see and hold the infant in supervised conditions once death has been pronounced and before transport.
- Timely communication associated with positive long-term bereavement outcomes
- Open communication with MDI and single point of contact for families
  - Information in multiple formats - written (Help For Families Brochure), verbal, through clinicians, etc.

Procedural Guidelines for Family Needs

- Provide services or referrals to address
  - Grief support for surviving family members
  - Medical follow-up (Cardiac/Genetic consults etc.) and related referrals (as clinically indicated by investigation)
  - Home Visits
- Opportunity for Post-autopsy conference with family members and stakeholders/clinicians
- Investigation becomes part of each family's history

Family Needs & Professional Relations

- INSERT VIDEO

We are what we repeatedly do.
Excellence, then, is not an act, but a habit.
~ **Aristotle**

It always seems impossible until it is done.
~ **Nelson Mandela**

Thank you!

- All committee members who donated their time and expertise to see this project to completion
- SUDC Foundation for grant support for this project, the ability to publish the book and to provide complimentary copies to all NAME members
- NAME for administrative and organizational support.
- American Academy of Pediatrics for organizational support.
- Academic Forensic Pathology for the opportunity to publish this work in a volume adequate to address the complexity and depth of the issues.

PHARMACOKINETICS

Laura M. Labay, Ph.D., F-ABFT, DABCC-TC

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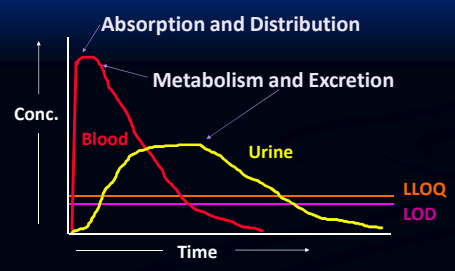
WHAT THE BODY DOES TO THE DRUG



ABSORPTION

MOVEMENT OF DRUG FROM SITE OF ADMINISTRATION
TO THE BLOODSTREAM

https://www.ntnu.com/news/2017/06/researchers-use-light-launch-drugs-red-blood-cells

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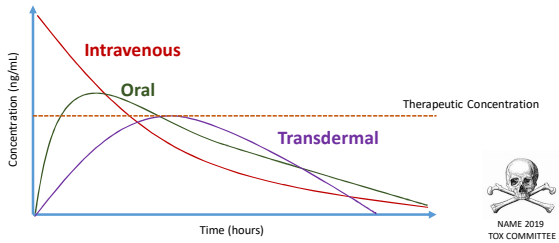
BIOAVAILABILITY - AUC

The proportion of a drug that enters the circulation when introduced into the body and so is able to have an active effect.



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DETERMINANTS

- Physicochemical properties
- Formulation
- Route of administration

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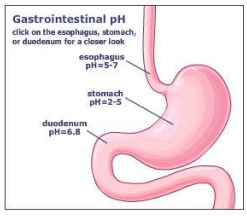
DEGREE OF IONIZATION

Degree of ionization → pK_a

pK_a → the pH at which the ionized and unionized forms exist in equal concentrations

The more the drug is in its unionized form, the more likely it is to be lipid-soluble and transferred by passive diffusion through the membrane.



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pK_a RULES

pK_a RULES
pK_a is defined as the pH were a drug exists as 50% ionized and 50% unionized
If pK_a - pH = 0, then 50% of drug is ionized and 50% is unionized
Acidic groups become less ionized in an acidic environment Basic groups become less ionized in an alkaline environment

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QUANTIFYING THE DEGREE OF IONIZATION

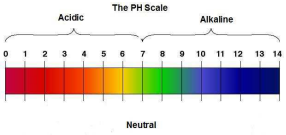
For every unit by which pH is changed, the ratio of unionized to ionized molecules changes 10-fold

EXAMPLE:

- When the pH is 2 units less than the pK_a, molecules of an acidic drug become 100x more un-ionized

pH = 3

pK_a = 5



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PRACTICE QUESTIONS

1) The pK_a of sodium pentothal is 7.4 and the drug is acidic. If a patient is given sodium pentothal orally instead of by IV, will it put the patient to sleep? _____
2) Absorption from the GI tract is determined by:
   a) The pH of the medium and the pK_a of the drug
   b) The fraction of the drug that is non-ionized
   c) Lipid solubility of the non-ionized drug
   d) All of the above
   e) None of the above
3) Given a weak acid (pk_a 8.0), the ratio of ionized to non-ionized form of the drug at pH 4.0 most closely approximates:
   a) 2:1
   b) 1:1
   c) 1:1000
   d) 10,000:1
   e) None of the above
4) Compared to a weak acid (pK_a 8.0), another weak acid (pK_a 5.3), other factors being equal, would be:
   a) Absorbed from the GI tract at approximately the same rate
   b) Absorbed from the GI tract more slowly
   c) Absorbed from the GI tract more rapidly
   d) Unabsorbed from the GC tract
   e) More completely inactivated by gastric juice

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PRACTICE QUESTIONS - ANSWERS

1) The pK_a of sodium pentothal is 7.4 and the drug is acidic. If a patient is given sodium pentothal orally instead of by IV, will it put the patient to sleep? YES
2) Absorption from the GI tract is determined by:
   a) The pH of the medium and the pK_a of the drug
   b) The fraction of the drug that is non-ionized
   c) Lipid solubility of the non-ionized drug
   d) All of the above
   e) None of the above
3) Given a weak acid (pk_a 8.0), the ratio of ionized to non-ionized form of the drug at pH 4.0 most closely approximates:
   a) 2:1
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   d) 10,000:1
   e) None of the above
4) Compared to a weak acid (pK_a 8.0), another weak acid (pK_a 5.3), with all other factors being equal, would be:
   a) Absorbed from the GI tract at approximately the same rate
   b) Absorbed from the GI tract more slowly
   c) Absorbed from the GI tract more rapidly
   d) Unabsorbed from the GC tract
   e) More completely inactivated by gastric juice

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DISTRIBUTION

MOVEMENT OF A DRUG FROM ITS POINT OF ENTRY THROUGHOUT THE SYSTEMIC CIRCULATION AND INTO VARIOUS TISSUES

GOAL: FOR THE DRUG TO REACH ITS INTENDED SITE OF ACTION

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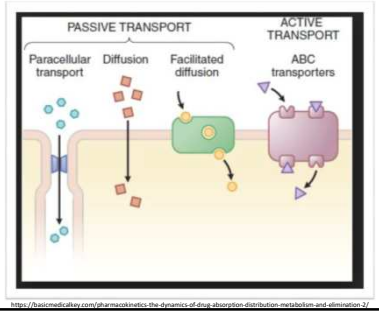
TRANSMEMBRANE MOVEMENT

- Molecular Size
- Drug Polarity
- Lipid Solubility
- Membrane Structure



https://basicmedicalkey.com/pharmacokinetics-the-dynamics-of-drug-absorption-distribution-metabolism-and-elimination-2/

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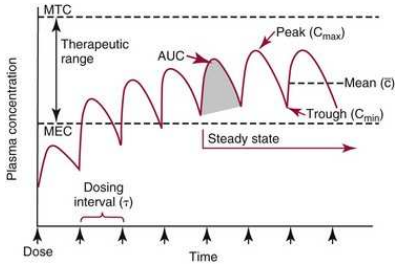
STEADY STATE CONCENTRATIONS



https://basicmedicalkey.com/therapeutic-drugs-and-their-management/

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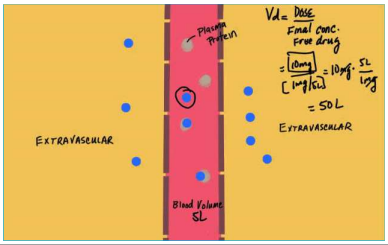
VOLUME OF DISTRIBUTION

A *HYPOTHETICAL* VOLUME INTO WHICH A DRUG IS DISTRIBUTED

IT IS A MEASURE OF HOW READILY DRUG DIFFUSES OUT OF THE PLASMA INTO TISSUES



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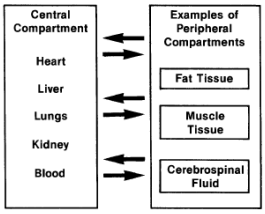
VOLUME OF DISTRIBUTION MEANING

1. Reflects the extent of drug distribution
2. In general,
   - Low V_d → Drug confined to plasma
   - High V_d → Drug equilibrates with tissues & extravascular fluids



https://www.ashp.org/-/media/store%20files/pi2418-sample-chapter-1.pdf

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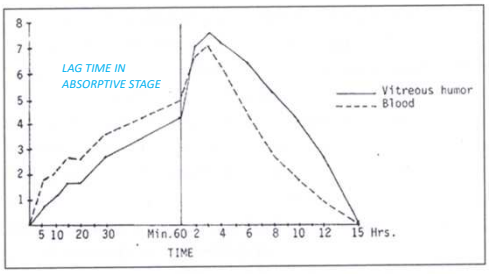
DISTRIBUTION – VITREOUS FLUID



Hentsch R, Mueller Hp. [Animal Experimental Studies On The Concentration Of Ethanol In The Blood And Vitreous Body After Peroral Administration]. Albrecht Von Graefes Arch Ophthalmol. 1965 May 13;168:330-4. German.

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CASE EXAMPLE

BRIEF CASE HISTORY (Attach Investigator Report If Possible)

2 year 4 month old female toddler found dead on floor of residence. Foul play suspected.

Positive Findings:

Compound	Result	Units	Matrix Source
Ethanol	133	mg/dL	001 - Heart Blood
Blood Alcohol Concentration (BAC)	0.133	g/100 mL	001 - Heart Blood
Ethanol	97	mg/dL	006 - Gastric Fluid
Isopropanol	5.1	mg/dL	006 - Gastric Fluid
Acetaldehyde	1.3	mg/dL	006 - Gastric Fluid
Acetone	1.7	mg/dL	006 - Gastric Fluid
Ethanol	216	mg/dL	004 - Vitreous Fluid
Acetone	5.4	mg/dL	004 - Vitreous Fluid
Sodium (Vitreous Fluid)	128	mmol/L	004 - Vitreous Fluid
Potassium (Vitreous Fluid)	>20	mmol/L	004 - Vitreous Fluid
Chloride (Vitreous Fluid)	115	mmol/L	004 - Vitreous Fluid
Urea Nitrogen (Vitreous Fluid)	59	mg/dL	004 - Vitreous Fluid
Creatinine (Vitreous Fluid)	1.3	mg/dL	004 - Vitreous Fluid
Ethanol	217	mg/dL	003 - Urine
Acetone	5.4	mg/dL	003 - Urine
Quinine	380	ng/mL	003 - Urine

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CALCULATION

$$Dose = Cp \times Vd \times Wt$$

Cp → Plasma Drug Concentration (mg/L)
Vd → Volume of Distribution (L/Kg)
Wt → Weight (Kg)

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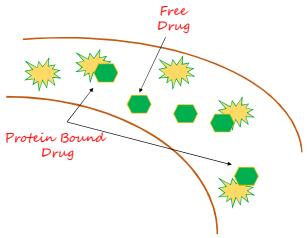
PROTEIN BINDING

Protein bound drug is:

- Not metabolized or excreted
- Inactive
- Confined to a specific tissue or site
- High plasma protein binding decreases V_d



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PROTEIN BINDING AND DISEASE

DRUG	UNBOUND %	UNBOUND % - DISEASE
Diazepam	2%	6% in liver disease
Furosemide	2%	6% in nephrotic syndrome
Phenytoin	9%	19% in renal disease
Triamterene	19%	40% in renal disease
Theophylline	35%	71% in liver disease
Digoxin	75%	82% in renal disease

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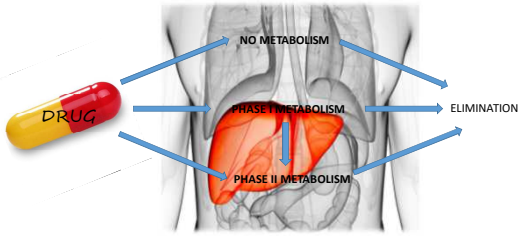
METABOLISM

BIOTRANSFORMATION OF PHARMACEUTICAL SUBSTANCES IN THE BODY



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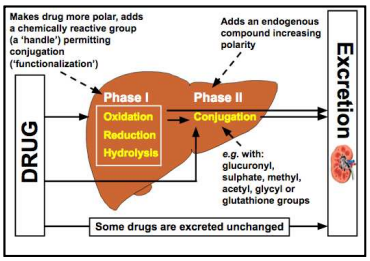
PHASE I AND II - OVERVIEW



https://www.studyblue.com/notes/note/n/pharmacology-elementary-drug-metabolism-and-renal-excretion-of-drug/deck/15711438

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PHASE I METABOLISM

Chemical reactions – oxidation, reduction, hydrolysis

Oxidation reactions are catalyzed by cytochrome p450 enzymes

Isoenzyme	Comments
CYP1A	Important for methylxanthines and paracetamol; induced by smoking
CYP2A	Limited number of substrates; significant interindividual variability
CYP2B	Limited number of substrates
CYP2C	CYP2C9 is an important isoform; CYP2C19 shows genetic polymorphism
CYP2D	Metabolises numerous drugs; CYP2D6 shows genetic polymorphism
CYP2E	Metabolises alcohol
CYP3A	Main isoform in liver and intestine; metabolises 50–60% of current drugs
CYP4	Metabolises fatty acids

Extreme caution should be taken if co-administration with a CYP3A4 inhibitor or inducer is unavoidable

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CYTOCHROME p450 INTERACTIONS

1) COMPETITION
If the drugs are substrates for the same CYP isoform, the metabolism of each may be _____.

2) INHIBITION
In general, inhibition _____ plasma concentrations of substrate drugs, but _____ concentrations may be decreased.

3) INDUCTION
In general, induction _____ plasma concentrations of substrate drugs.

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CYTOCHROME p450 INTERACTIONS

COMPETITION
If the drugs are substrates for the same CYP isoform, the metabolism of each may be inhibited.

INHIBITION
In general, inhibition increases plasma concentrations of substrate drugs, but prodrug concentrations may be decreased.

INDUCTION
In general, induction decreases plasma concentrations of substrate drugs.

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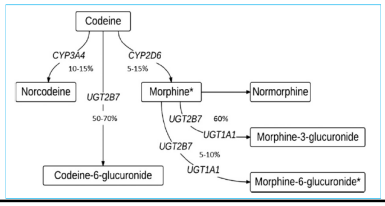
PHASE II METABOLISM

"CONJUGATION REACTIONS"

1. Substrates are coupled covalently to an endogenous molecule
2. Transferases catalyze the reaction
3. The resulting molecule is polar and able to be excreted in urine



https://pediatrics.aappublications.org/content/pediatrics/138/1/e20153479.full.pdf

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METABOLIZER FORMS

- Rapid metabolizer
- Normal metabolizer
- Intermediate metabolizer
- Poor metabolizer

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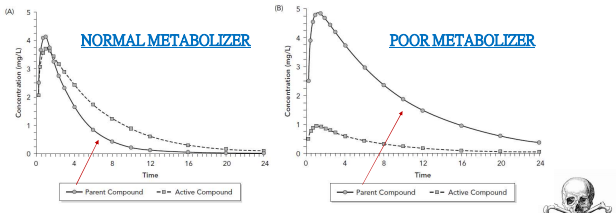
CONCENTRATION AND TIME PROFILE EXAMPLES



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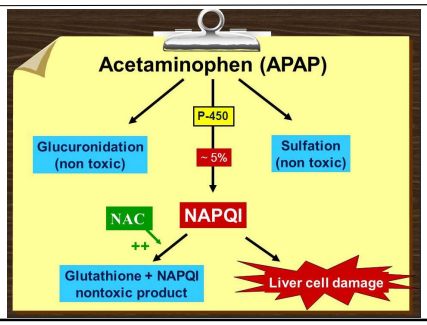
http://samples.jbpub.com/9781449652739/Chapter2.pdf

METABOLIC SYSTEMS AT CAPACITY



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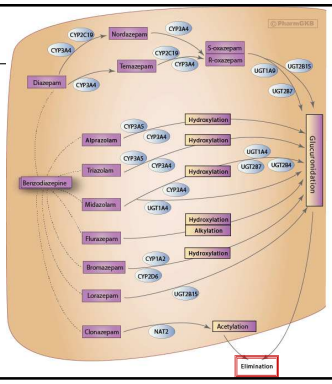
ELIMINATION

PROCESSES BY WHICH A DRUG IS REMOVED IN AN UNALTERED FORM AND/OR MODIFIED AS A METABOLITE



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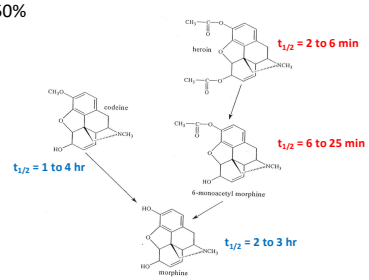
https://www.pharmgkb.org/pathway/PA165111375

HALF-LIFE ($t_{1/2}$)

THE TIME IT TAKES FOR THE CONCENTRATION OF A DRUG IN PLASMA TO DECREASE BY 50%



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FIRST ORDER ELIMINATION

Most drugs undergo first order elimination

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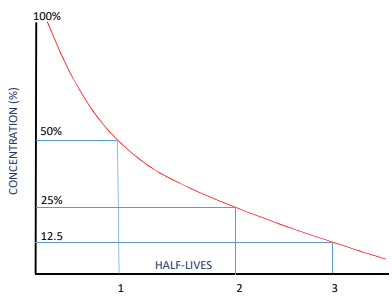
FIRST ORDER ELIMINATION



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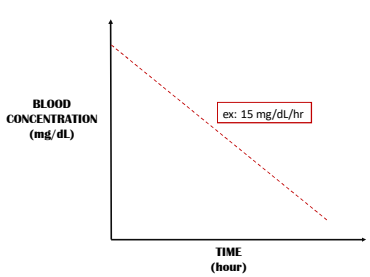
ZERO ORDER KINETICS

DEFINITION: A constant amount of drug is eliminated per unit time



Example:

100 mg/dL

↓

85 mg/dL

↓

70 mg/dL

↓

55 mg/dL

↓

Etc.

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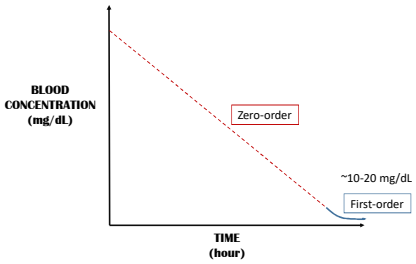
ZERO ORDER TO FIRST ORDER – ETOH EXAMPLE



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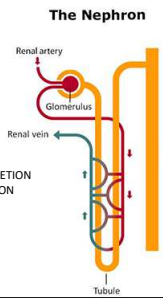
FACILITATION OF ELIMINATION BASED ON pH

MATRIX	pH
URINE	4.8 to 8.0
BLOOD	7.4

URINE pH AFFECTS DRUG EXCRETION

EXAMPLES:

METHAMPHETAMINE → ACIDIC URINE → INCREASES EXCRETION
BARBITURATE → ACIDIC URINE → INCREASES REABSORPTION



https://www.niddk.nih.gov/health-information/kidney-disease/kidneys-how-they-work

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ELIMINATION - QUESTION

A patient has presented to the Emergency Department with a Barbiturate overdose. Would you recommend that the urine should be made acidic or alkaline to facilitate excretion?

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ELIMINATION - QUESTION

A patient has presented to the Emergency Department with a Barbiturate overdose. Would you recommend that the urine should be made acidic or alkaline to facilitate excretion?

I would want to make the urine alkaline.

Why? This would cause the Barbiturate, a weakly acidic drug, to be ionized and not amenable to reabsorption.

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POSTMORTEM PHARMACOKINETICS

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From OXYCONTIN® Package Insert for Oxycodone HCl Controlled-Release Tablets

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

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ASSUMPTIONS

- The drug was ingested and all of it was absorbed at the time of specimen collection.
- The drug was ingested only one time (e.g., a single dose).
- The drug concentration represents the peak (Cmax) blood-drug concentration.
- The drug concentration accurately reflects the circulating blood-drug concentration in the antemortem state in that it has been unaffected by such influences such as postmortem redistribution.
- The presence of metabolites and/or the drug's presence in other matrix types are not represented.
- The volume of distribution (Vd) and the blood to plasma drug ratio (b/p) of the drug is known.

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TRUE or FALSE

1. The conjugation of morphine with glucuronide acid decreases the narcotic activity of the drug hastens excretion.
2. The metabolism of diazepam to nordiazepam is an example of an oxidative (Phase I) reaction.
3. The ionized form of a drug is the form which readily crosses the membrane.
4. If a weakly basic drug is given by IV, it will not be found in the stomach.
5. A weak acid would demonstrate an increased renal clearance if the urine was alkanized.
6. A weakly acidic drug is equally absorbed from the stomach and small intestine.
7. Normally, the blood has a pH of 7.4

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TRUE or FALSE

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7. Normally, the blood has a pH of 7.4 TRUE

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Pharmacokinetics is concerned with the rate at which drugs enter the body, distribute within it, and then leave. Includes metabolism.

Metabolic reactions tend to make a drug progressively more water soluble so it can be eliminated in the urine.

The V_d of a drug is the volume in which it would need to distribute so that the concentration in the body is equal to that of the blood.

Most drugs are eliminated following first-order processes.

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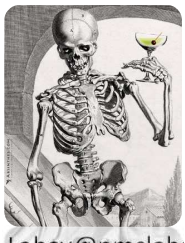
QUESTIONS?



Laura.Labay@nmslabs.com

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Genetic Polymorphisms

Jirair Gevorkyan, Ph.D., F-ABFT

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Objectives

1. Understand the basis and application of genetic information in relation to drug response and toxicity.
2. To distinguish genetics and enzymes behind strong and weak metabolic responders.
3. Understand how genetic polymorphisms can be applied to postmortem toxicology and death investigations.

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Outline

- Introductory Concepts
  - Central Dogma
  - Mutations
  - Structure and Function
- Polymorphisms
  - Consequences in Pharmacology
  - Cytochrome P450s
- Application to Toxicology
  - Relevant Polymorphisms and Drugs
  - Case Examples

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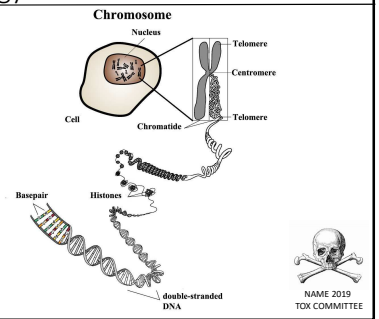
Central Dogma of Biology

Hereditary information
- Humans Chromosome: 46
- Dogs: 78
- Cats: 38
- Fruit Flies: 8

Consistent Differences
- Between species
- Between subpopulations
- Between individuals



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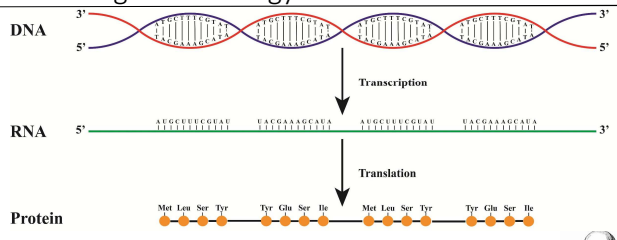
Central Dogma of Biology



But also…
Effects of ribozymes, proteins, metabolites produce bidirectionality
Post transcriptional/translational modifications, somatic epitypes, epigenetics

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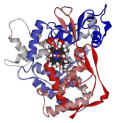
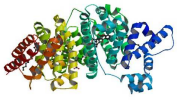
Central Dogma of Biology

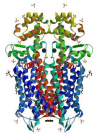
- Structure -> Function
- Genotype -> Phenotype



CYP2C9



Human Serum Albumin



μ-opioid receptor

https://www.raminrahni.com/animation

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Mutations

Single Nucleotide Polymorphisms

3'-ACGCCTTGACGACGCTTAC-5'
5'-TGCGGAACTGCTGCGAATG-3'

3'-ACGCCTTGACGAAGCTTAC-5'
5'-TGCGGAACTGCTTCGAATG-3'

Insertion/Deletion

3'-ACGCCTTGACGACGCTTAC-5'
5'-TGCGGAACTGCTGCGAATG-3'

3'-ACGCCTTGACGAACGCTTAC-5'
5'-TGCGGAACTGCTTGCGAATG-3'

3'-ACGCCTTGACGAGCTTAC-5'
5'-TGCGGAACTGCTCGAATG-3'

Short Tandem Repeat

3'-ACGCCTTGACGACAGCAGCAGCTTAC-5'
5'-TGCGGAACTGCTGACGACGACGAATG-3'

3'-ACGCCTTGACGACAGCAGCAGCAGCAGCTTAC-5'
5'-TGCGGAACTGCTGACGACGACGACGACGAATG-3'

Seond letter

First letter	U	C	A	G	Third letter
U	UUU Phe, UUC Phe, UUA Leu, UUG Leu	UCU Ser, UCC Ser, UCA Ser, UCG Ser	UAU Tyr, UAC Tyr, UAA Stop, UAG Stop	UGU Cys, UGC Cys, UGA Stop, UGG Trp	U C A G
C	CUU Leu, CUC Leu, CUA Leu, CUG Leu	CCU Pro, CCC Pro, CCA Pro, CCG Pro	CAU His, CAC His, CAA Gln, CAG Gln	CGU Arg, CGC Arg, CGA Arg, CGG Arg	U C A G
A	AUU Ile, AUC Ile, AUA Ile, AUG Met	ACU Thr, ACC Thr, ACA Thr, ACG Thr	AAU Asn, AAC Asn, AAA Lys, AAG Lys	AGU Ser, AGC Ser, AGA Arg, AGG Arg	U C A G
G	GUU Val, GUC Val, GUA Val, GUG Val	GCU Ala, GCC Ala, GCA Ala, GCG Ala	GAU Asp, GAC Asp, GAA Glu, GAG Glu	GGU Gly, GGC Gly, GGA Gly, GGG Gly	U C A G

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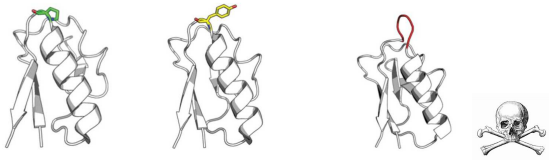
Mutations, Structure and Function

DNA TCATATGCA**CCC**CGT
Peptide S Y A **P** R

Mutation	Silent Substitution	Dissimilar Substitution	Insertion
DNA	TCATATGCACCACGT	TCATATGCATATCGT	TCATATGCAGGAGGCCCCCGT
Peptide	S Y A P R	S Y A Y R	S Y A G G P R



DOI: 10.1042/BJ20121221

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Genetic Polymorphisms

Inter-individual genetic variability

Person 1 Chromosome 5

Copy 1 3'-TGACGATGCTTAC-5'
5'-ACTGCTACGAATG-3'

Copy 2 3'-TGACGAAGCTTAC-5'
5'-ACTGCTTCGAATG-3'

Person 2 Chromosome 5

Copy 1 3'-TGACGATGCTTAC-5'
5'-ACTGCTACGAATG-3'

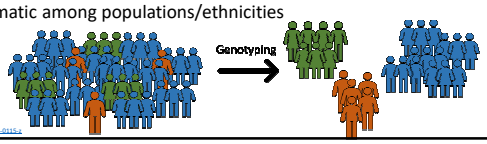
Copy 2 3'-TGACGACGCTTAC-5'
5'-ACTGCTGCGAATG-3'

Person 3 Chromosome 5

Copy 1 3'-TGACGACGCTTAC-5'
5'-ACTGCTGCGAATG-3'

Copy 2 3'-TGACGACGCTTAC-5'
5'-ACTGCTGCGAATG-3'

Systematic among populations/ethnicities



DOI: 10.1186/s12920-015-0115-z

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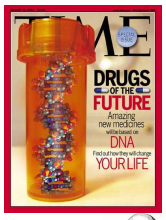
Genetic Polymorphisms

Pharmacogenetics
- Individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response

Pharmacogenomics
- Genomic influence on drug response, often using high-throughput data, sequencing, SNP chip, expression, proteomics

Pharmacodynamic
- Receptors, ion channels, immune molecules

Pharmacokinetic
- Transporters, metabolic enzymes, plasma protein binding



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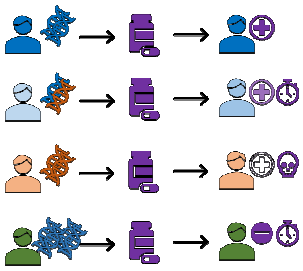
Metabolizer Forms

- Normal metabolizer
- Intermediate metabolizer
- Poor metabolizer
- Ultrarapid metabolizer



Parent drug and metabolite activity are important

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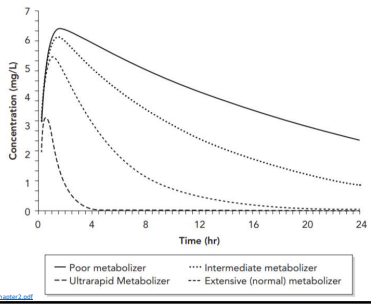
Metabolizer Forms



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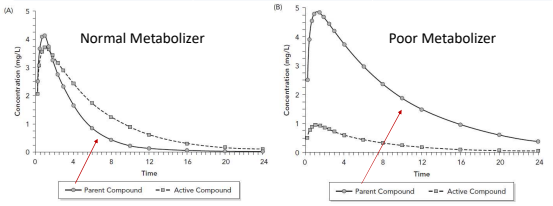
Metabolizer Forms

Analyte	Poor Metabolizer	Ultrarapid Metabolizer
Prodrug, Active Metabolite	poor efficacy, accumulation of prodrug	good efficacy, rapid effect
Active Drug, Inactive Metabolite	good efficacy, but accumulation may have adverse effects	poor efficacy, need a greater dose or slow release formula



http://samples.jbpub.com/9781449627739/27739ch02.pdf

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Practice Question

1) A mutation is defined as any change in a DNA sequence away from normal. A polymorphism is a DNA sequence variation that is common in the population. TRUE or FALSE
2) A poor metabolizer may have one of the following genetic predispositions:
   a) Two functioning alleles related to drug metabolism
   b) One functioning and one non-functioning alleles related to drug metabolism
   c) Two non-functioning alleles related to drug metabolism
   d) More than two functioning alleles related to drug metabolism
3) An ultra rapid metabolizer may have one of the following genetic predispositions:
   a) Two functioning alleles related to drug metabolism
   b) One functioning and one non-functioning alleles related to drug metabolism
   c) Two non-functioning alleles related to drug metabolism
   d) More than two functioning alleles related to drug metabolism
4) Pharmacogenetics is the study of
   a) study of how people respond differently to drug therapy based upon their genetic makeup or genes
   b) how genes affect a person's response to drugs
   c) the science of drugs
   d) the study of genes and their functions

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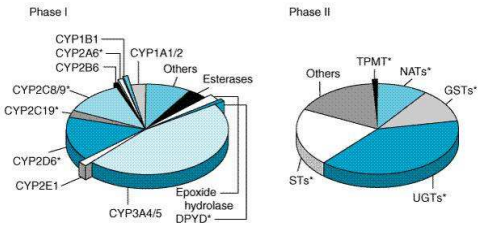
Metabolic Enzymes



Other important genetic polymorphisms outside of metabolic enzymes (VKORC1, ABCE)

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ISBN 0-07-142280-3

Genetic Polymorphisms

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China[17]	Debrisoquin[15] Sparteine[15] Nortriptyline[23] Codeine[27,28]	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 14.6% in China[17] 18% in Japan[33]	Omeprazole[34,35]	Enhanced drug effect[35,37]
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous[38]	Fluorouracil[39,40]	Enhanced drug effect[39,40]
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans[41]	Succinylcholine[9,41]	Enhanced drug effect[9,41]

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

DOI: 10.1056/NEJMra030021

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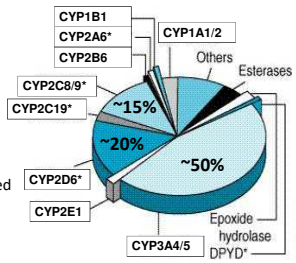
Cytochrome P450 (CYP450)

Critical for metabolism of drugs
- Oxidize drugs
- Making drugs more water-soluble

Clinically relevant if inactivated
- Inhibition (grapefruit)
- Downregulation
- Drug-Drug Interaction
- CYP3A4 covers ~50 %
  - Most consequential if inactivated



CYP2C9*2A
- Superfamily
- Family
- Subfamily
- Isozyme
- Allele
- Suballele

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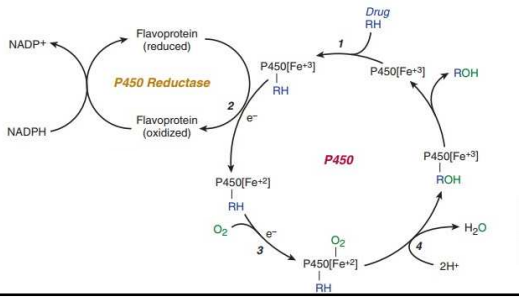
CYP450 Mechanism



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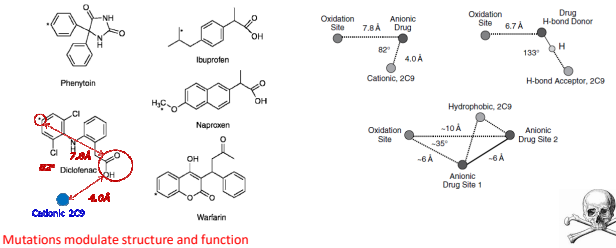
CYP450 Structure and Function

CYP2C9 Substrates



Mutations modulate structure and function
CYP450 Polymorphs vary in activity and affect pharmacokinetics

ISBN: 978-0-1236-9520-8

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CYP450 Polymorphisms

TABLE 1
Importance of Polymorphic CYP for the Metabolism of Drugs and Carcinogens

Enzyme	Substrates	Polymorphism frequency	Functional effects	Most important polymorphic variants
CYP1A1	Carcinogens	Relatively high	Unproven	No important functional variant alleles
CYP1A2	Drugs, carcinogens	High	Rare	CYP1A2*1F, CYP1A2*1K
CYP1B1	Carcinogens, estrogens	Rare null alleles, frequent missense mutations	At least seven haplotypes with similar activity	CYP1B1*3
CYP2A6	Nicotine, drugs, carcinogens	High in Orientals, less frequent in Caucasians	Important for nicotine metabolism	CYP2A6*1B, CYP2A6*4, CYP2A6*9, CYP2A6*12
CYP2B6	Drugs	High	Reduced drug metabolism	CYP2B6*5, CYP2B6*6, CYP2B6*16
CYP2C8	Some drugs	High	Reduced drug metabolism	CYP2C8*3
CYP2C9	Drugs	Relatively rare in Caucasians	Very significant	CYP2C9*2, CYP2C9*3
CYP2C19	Drugs	High	Very significant	CYP2C19*2, CYP2C19*3, CYP2C19*17
CYP2D6	Drugs	Very high	Very significant	CYP2D6*2-to CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17
CYP2E1	Carcinogens, solvents, few drugs	Low	No significant cases have been reported	No important functional variant alleles
CYP3A4	Drugs, carcinogens	Low	No or small	CYP3A4*1B
CYP3A5	Drugs, carcinogens	High	Significant	CYP3A5*3, CYP3A5*6, CYP3A5*7
CYP3A7	Drugs, carcinogens	Low	Some	CYP3A7*2

DOI: 10.1093/toxsci/kfs374

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CYP450 Polymorphisms

Table 3 Mean frequencies of *CYP2C9*, *CYP2C19*, and *CYP2D6* genetic variants in different geographic regions[a]

Variant	Southern Africa	Middle Africa	Western Africa	Eastern Africa	Northern Africa	Mixed Africa[b]	Southern Europe	Western Europe	Northern Europe	Eastern Europe	Mixed Europe[c]
*CYP2C9*2*	0 (30)	0 (98)	0.3 (508)	4.3 (324)	13.4 (932)	1.6 (1650)	14.4 (5518)	12.0 (4388)	11.5 (7978)	11.1 (1052)	13.1 (3156)
*CYP2C9*3*	0 (30)	0 (98)	0.3 (508)	1.2 (324)	10.2 (932)	1.5 (1172)	9.6 (5518)	7.3 (2152)	7.4 (7978)	6.9 (1052)	6.7 (3156)
*CYP2C9*5*	0 (30)	0 (98)	2.0 (318)	0.3 (690)	0 (60)	0.5 (726)	ND	0 (242)	0 (684)	0 (580)	0 (526)
*CYP2C9*11*	0 (30)	2.4 (98)	1.6 (318)	0 (24)	1.7 (60)	2.0 (604)	ND	0.4 (242)	0.6 (284)	ND	0.5 (274)
*CYP2C19*2*	21.7 (152)	ND	13.0 (222)	14.9 (1696)	11.0 (494)	15.0 (938)	13.3 (2634)	14.0 (4140)	16.3 (5262)	11.4 (580)	12.8 (2040)
*CYP2C19*3*	0 (152)	ND	0 (222)	0.7 (1696)	0.2 (494)	1.7 (738)	0 (1992)	0.2 (3392)	0.2 (2478)	0.3 (580)	0.1 (1938)
*CYP2D6*2*	31.5 (182)	55.0 (102)	11.8 (484)	27.2 (1110)	28.3 (60)	23.0 (810)	30.2 (996)	29.3 (1666)	32.4 (878)	31.7 (84)	28.8 (2640)
*CYP2D6*3*	0 (182)	0 (102)	0 (484)	0.1 (1502)	0 (60)	0.4 (1302)	1.5 (3262)	1.1 (3682)	1.9 (3788)	0.8 (954)	1.2 (3568)
*CYP2D6*4*	1.1 (182)	0.7 (102)	6.5 (484)	3.0 (1502)	11.7 (60)	6.8 (1302)	16.8 (3262)	18.9 (3682)	17.6 (3788)	17.5 (954)	19.4 (3568)
*CYP2D6*5*	12.5 (182)	5.7 (102)	5.4 (484)	3.9 (1110)	3.3 (60)	6.6 (1302)	2.1 (2696)	5.1 (1666)	2.6 (1726)	1.5 (954)	2.8 (3568)
*CYP2D6*6*	0 (30)	0 (102)	0 (484)	0 (370)	0 (60)	0.4 (502)	1.1 (2402)	0.5 (3196)	1.4 (1496)	0.4 (664)	0.8 (2260)
*CYP2D6*9*	0 (30)	0 (102)	0 (484)	0 (24)	0 (60)	0.2 (502)	1.5 (702)	3.5 (1666)	2.0 (934)	0 (84)	2.1 (2260)
*CYP2D6*10*	0 (30)	4.2 (102)	4.5 (484)	5.2 (670)	0 (60)	5.6 (810)	2.4 (702)	2.9 (1666)	1.4 (920)	2.4 (664)	4.8 (2640)
*CYP2D6*17*	18.7 (182)	7.9 (102)	17.5 (484)	18.4 (1110)	8.3 (60)	20.6 (1302)	0.1 (492)	0 (488)	0 (316)	0 (84)	0.5 (2640)
*CYP2D6*29*	3.1 (30)	3.1 (102)	9.1 (98)	18.2 (236)	0 (60)	7.2 (502)	0 (100)	0 (98)	0 (316)	0 (84)	0.1 (1344)
*CYP2D6*41*	0 (30)	0.7 (102)	6.2 (98)	0 (24)	8.3 (60)	ND	4.5 (100)	7.1 (98)	4.9 (316)	11.4 (84)	14.0 (500)
*CYP2D6*1xN*	7.1 (30)	6.7 (102)	0 (98)	1.7 (236)	0 (60)	1.2 (502)	0.4 (702)	0.6 (1666)	2.6 (316)	0.6 (664)	1.2 (916)
*CYP2D6*2xN*	0 (30)	0 (102)	1.9 (484)	8.8 (458)	28.3 (60)	2.0 (1302)	2.0 (2682)	1.2 (1666)	1.5 (920)	1.5 (664)	3.3 (2224)
*CYP2D6*4xN*	0 (30)	0.7 (102)	7.0 (98)	2.5 (236)	0 (60)	0.3 (502)	0.8 (702)	0.5 (1666)	0 (316)	0 (664)	0.1 (916)
*CYP2D6*10xN*	0 (30)	0 (102)	0 (98)	0 (24)	0 (60)	ND	0.4 (492)	0 (488)	0 (316)	0 (84)	0 (500)
*CYP2D6*41xN*	0 (30)	0 (102)	0 (98)	0 (24)	0 (60)	ND	0 (100)	0 (98)	0 (316)	0 (84)	0.8 (500)

Variant	Western Asia	Southern Asia	Eastern Asia	South-Eastern Asia	Mixed Asia[d]	Melanesia	Australia	Northern America	Central America	South America	Chromosomes Total
*CYP2C9*2*	8.6 (1366)	5.6 (2396)	0.1 (7798)	0.6 (756)	2.4 (156)	0 (78)	ND	1.5 (404)	7.0 (386)	5.7 (2380)	41354
*CYP2C9*3*	9.0 (1366)	7.6 (2396)	3.8 (9186)	3.0 (756)	4.8 (156)	6.3 (78)	ND	3.0 (404)	4.0 (386)	4.4 (2380)	40028
*CYP2C9*5*	ND	0 (714)	0 (2646)	0 (442)	0 (156)	0 (78)	ND	ND	0 (196)	ND	8186
*CYP2C9*11*	ND	ND	0 (1282)	0 (22)	0 (68)	0 (78)	ND	ND	ND	ND	3384
*CYP2C19*2*	13.2 (1614)	33.5 (1646)	31.2 (7654)	29.0 (2954)	27.8 (550)	60.2 (11878)	35.5 (454)	15.7 (410)	9.7 (692)	8.3 (1934)	47944
*CYP2C19*3*	0.4 (1454)	0.6 (1646)	8.7 (7654)	4.6 (2954)	6.8 (550)	15.7 (11878)	14.3 (454)	0 (410)	0.1 (692)	0.1 (1934)	43308
*CYP2D6*2*	30.1 (1378)	30.8 (1614)	15.8 (2842)	9.0 (22)	ND	0 (78)	3.8 (478)	ND	22.2 (1284)	27.8 (706)	17414
*CYP2D6*3*	0 (1378)	<0.1 (1826)	0 (2050)	0 (232)	ND	0 (78)	0 (478)	0 (410)	0.4 (1884)	0.1 (978)	28200
*CYP2D6*4*	7.0 (1580)	8.2 (3788)	3.5 (3292)	1.4 (232)	ND	0 (78)	1.5 (478)	5.3 (410)	9.6 (1884)	11.2 (978)	31606
*CYP2D6*5*	2.6 (1580)	2.9 (1826)	6.4 (3288)	4.8 (232)	ND	1.5 (78)	7.5 (478)	ND	1.0 (1494)	2.1 (798)	23624
*CYP2D6*6*	1.1 (1206)	0 (720)	0 (1726)	0 (22)	ND	0 (78)	0 (478)	0 (180)	0.1 (700)	3.0 (810)	17486
*CYP2D6*9*	0.1 (1206)	0 (720)	0 (1280)	1.7 (232)	ND	0 (78)	0 (478)	ND	0 (310)	0 (556)	11708
*CYP2D6*10*	4.1 (1580)	6.9 (1826)	38.3 (3288)	52.0 (232)	ND	2.3 (78)	0.8 (478)	2.6 (410)	5.6 (1884)	5.0 (736)	19260
*CYP2D6*17*	1.5 (1580)	0 (1614)	0 (1604)	0.3 (232)	ND	0 (78)	0.2 (478)	ND	1.1 (1284)	0.4 (358)	14488
*CYP2D6*29*	0 (296)	0.2 (720)	0 (1280)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0 (116)	5582
*CYP2D6*41*	16.9 (296)	10.5 (720)	3.8 (1280)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0 (116)	4024
*CYP2D6*1 × N*	3.8 (1206)	0.5 (720)	0.2 (2138)	0.5 (232)	ND	11.6 (78)	ND	ND	3.2 (1284)	0.2 (358)	11308
*CYP2D6*2 × N*	3.9 (1580)	0.6 (720)	0.5 (1692)	0 (22)	ND	0 (78)	0 (478)	ND	2.4 (586)	2.8 (116)	15864
*CYP2D6*4 × N*	0.1 (1206)	<0.1 (720)	0 (1922)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0.1 (358)	9698
*CYP2D6*10 × N*	0 (398)	0 (720)	0.8 (1726)	0 (22)	ND	0 (78)	ND	ND	0.5 (586)	0 (116)	5840
*CYP2D6*41 × N*	0 (296)	0 (720)	0.1 (480)	0 (22)	ND	0 (78)	ND	ND	0 (100)	0 (116)	3224

ND, not detected.
[a]Number of studied chromosomes is given in parentheses, for data on individual populations, see Supplementary Tables 1–3.
[b]Includes populations defined as African Pygmies, African American, Black American.
[c]Includes populations defined as European, Caucasian, Caucasian American, European American, White, Ashkenazi Jews, Sephardic Jews.
[d]Includes populations defined as Asian, East Asian, Southeast Asian.

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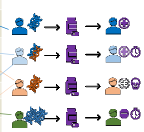
CYP2D6 Polymorphisms Examples

Table 1 | **Cytochrome P450 2D6 (*CYP2D6*) alleles and their effects on CYP2D6 enzyme activity**

CYP2D6 alleles	Allele designation	Enzyme activity	Allele abbreviation
*1, *2, *33, *35	Normal or wild type	Normal	EM
*3, *4, *5-*8, *11-*16, *18-*21, *36, *38, *40, *42, *44, *56, *62	Null	No protein, inactive or negligible	PM
*9, *10, *17, *29, *41, *59	Reduced activity	Decreased	IM
*22-*28, *30-*32, *34, *37, *39, *43, *45-*55	Unknown activity	Unknown	Not applicable
Duplicated alleles			
*1×*N*, *2×*N*, *35×*N*	Multiplication of normal alleles	Increased	UM
*10×*N*, *17×*N*, *29×*N*, *41×*N*	Multiplication of reduced activity alleles	Decreased	IM
*4×*N*, *6×*N*, *36×*N*	Multiplication of null alleles	Inactive or negligible	PM
*43×*N*, *45×*N*	Multiplication of alleles of unknown activity	Unknown	Not applicable

EM, extensive metabolizer allele; IM, intermediate metabolizer allele; PM, poor metabolizer allele; UM, ultra-rapid metabolizer allele.



Drug efficacy is different for each metabolizer form depending on substrate (prodrug vs active drug)

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Practice Question

1) Cytochrome P450s catalyze
   a) Hydrolysis
   b) Redox reactions
   c) Dealkylation
   d) Deamination
   e) All of the above
2) Most clinically relevant inhibitory interactions are the consequence of inactivation of which enzyme?
   a) CYP1A2
   b) CYP2D6
   c) CYP2C9
   d) CYP2C19
   e) CYP3A4
3) What type of metabolizer form would be expected for an individual with multiple copies of non-functioning a cytochrome P450? ______________
4) Which of the two following CYP450 isozymes exhibit significant genetic polymorphism?
   a) CYP1A1
   b) CYP2B6
   c) CYP2D6
   d) CYP2C19
   e) CYP2E1

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Practice Question

1) Cytochrome P450s catalyze
   a) Hydrolysis
   b) Redox reactions
   c) Dealkylation
   d) Deamination
   e) All of the above
2) Most clinically relevant inhibitory interactions are the consequence of inactivation of which enzyme?
   a) CYP1A2
   b) CYP2D6
   c) CYP2C9
   d) CYP2C19
   e) CYP3A4
3) What type of metabolizer form would be expected for an individual with multiple copies of non-functioning a cytochrome P450? Poor metabolizer
4) Which of the two following CYP450 isozymes exhibit significant genetic polymorphism?
   a) CYP1A1
   b) CYP2B6
   c) CYP2D6
   d) CYP2C19
   e) CYP2E1

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Application to Toxicology

- Pharmacogenetics based dose and clinical outcome
- Phenotype consideration in death investigations

Enzyme	Drug Metabolized
CYP2C19	Amitriptyline, Imipramine, Diazepam, Citalopram, Carisoprodol, Clopidogrel, Desipramine, Omeprazole, Phenytoin
CYP2D6	**Amphetamines**, Codeine, Oxycodone, Hydrocodone, Methadone, Tramadol, Dextromethorphan, Metoclopramide, Desipramine, Metoprolol, Amitriptyline, Duloxetine, Fluoxetine, Haloperidol, Risperidone, Thioridazine
CYP2C9	**NSAIDs,** Valproic acid, Warfarin, Phenytoin, Glipizide, Ibuprofen, Celecoxib, Fluvastatin
CYP3A4	**Benzodiazepines**, Fentanyl, Methadone, Buprenorphine, Cocaine, Zolpidem, **Antibiotics, Calcium Channel Blockers, Statins, Steroids**
CYP2E1	Ethanol, Acetaminophen

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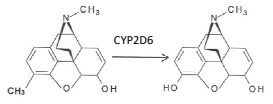
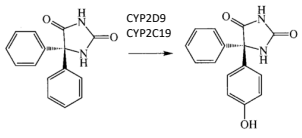
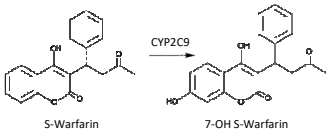
Application to Toxicology



Codeine Morphine



Phenytoin 4'-HPPH



S-Warfarin 7-OH S-Warfarin

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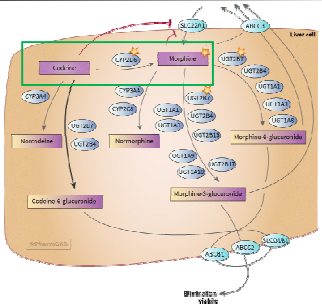
Application to Toxicology

Codeine Metabolism
- CYP2D6
- Prodrug, Active Metabolite

- poor efficacy, accumulation of prodrug

- good efficacy, rapid effect



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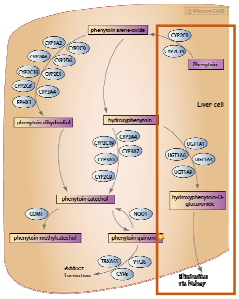
Application to Toxicology

Phenytoin Metabolism
- CYP2D9, CYP2C19
- Active drug, Inactive metabolite

- good efficacy, but accumulation may have adverse effects

- poor efficacy, need a greater dose or slow release formula



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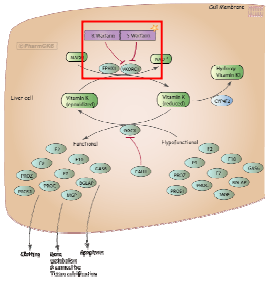
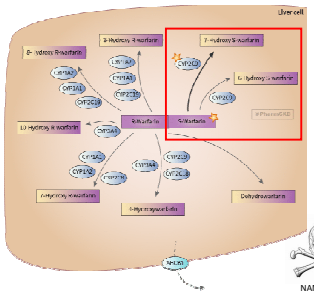
Application to Toxicology





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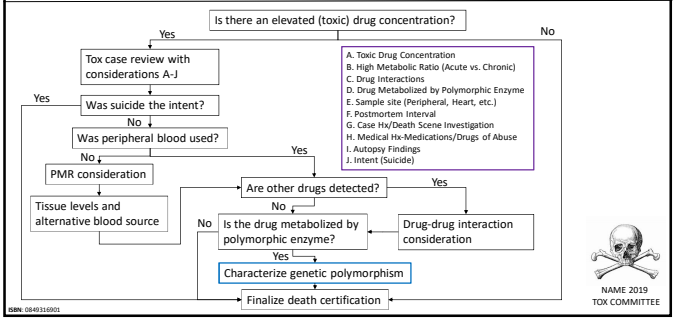
Application to Death Investigation



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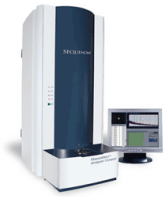
Methodology

- Collection and preparation of samples
- Extraction by ionic resins or commercial kits (QIAGEN)
- Separation of DNA by gel electrophoresis
- Genotyping
  - Real-Time PCR System
  - Capillary Electrophoresis
  - MALFI-TOF



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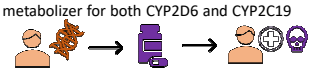
Case 1 (2D6 and 2C19 Poor Metabolizer)

- 46 year old Caucasian male diagnosed with depression
- Desipramine 50-250 mg daily over 1 month treatment as part of a safety and efficacy study
- Chest tightness occurring about 2 hours after desipramine dose, always while he was at rest
- Hospitalized when chest pain lasted 1 hour, ECG consistent with acute anterior wall myocardial ischemia
- Plasma desipramine concentration at 764 ng/mL
- Patient was studied with the drug-metabolizing probes, debrisoquin, mephenytoin, and dapsone
- Found to be poor metabolizer for both CYP2D6 and CYP2C19



DOI: 10.1038/clpt.1993.13

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Case 2 (2D6 Poor Metabolizer)

- Adopted Caucasian 9 year old with be
- Behavioral issues
- 60 mg methylphenidate, 0.9 mg clonidine, and 80-100 mg fluoxetine daily
- Metabolic toxicity over 10 months
- Status epilepticus, cardiac arrest and death
- High fluoxetine and norfluoxetine
- Led to a legal investigation of the adoptive parents of the child
- Child had a completely defective CYP2D6 gene

TABLE 1. POST-MORTEM TOXICOLOGY RESULTS

Drug or metabolite	*Source*	*Concentration*
Promethazine	Blood	0.044 mcg/mL
Fluoxetine	Blood	21 mcg/mL
	Gastric contents	53 mcg/mL
	Liver	2,800 mcg/g
	Brain	24 mcg/g
	Kidney	38 mcg/g
Norfluoxetine	Blood	21 mcg/mL
	Gastric contents	38 mcg/mL
	Liver	2,200 mcg/g
	Brain	22 mcg/g
	Kidney	34 mcg/g

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DOI: 10.1089/cap.2000.10.27

Case 3 (2D6 Ultrarapid Metabolizer)

- Full-term healthy male infant
- Grey skin and fallen milk intake by day 12, found dead on day 13
- Infant blood morphine 70 ng/mL (vs 0 ng/mL – 2·2 ng/mL)
- Mother prescribed codeine 30 mg and acetaminophen 500 mg (~1 tablet every 12 hrs over 2 weeks)
- Morphine concentration of 87 ng/mL in breastmilk
- Mother found to carry CYP2D6 gene duplication
- Resulted in FDA requiring manufacturers to include information to doctors about codeine and the risk of morphine overdose in breastfed infants

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DOI: 10.1016/S0140-6736(06)69255-6 https://www.fda.gov/media/104268/download

Case 4 (2C9 Poor Metabolizer)

- 64 year old African – American female
- Hx of diabetes, asthma, stroke, depression, hypertension, alcohol abuse
- Placed on 100 mg phenytoin, 3x daily after 5-day hospital visit for status epilepticus
- Slurred speech, mental confusion, memory loss, ataxia 13 days later
- Pharmacogenetic characterization found the patient was homozygous for the null allele CYP2C9*6

Table 1 Actual and expected plasma phenytoin concentrations over the course of 41 days with day 1 as the day of presentation with phenytoin toxicity

Days after presentation with phenytoin toxicity	Actual plasma phenytoin concentration (μg/ml)	Expected plasma phenytoin concentration (μg/ml)
Day 1	49.5	49.5
Day 1 (2nd level)	40.3	47.3
Day 2	38.2	38.8
Day 3	38.8	30.5
Day 4	41.2	22.4
Day 5	38.9	14.7
Day 6	32.8	7.9
Day 7	32.1	2.8
Day 9	32.8	*BLQ
Day 11	30.0	BLQ
Day 12	25.1	BLQ
Day 14	24.9	BLQ
Day 15	22.0	BLQ
Day 16	21.2	BLQ
Day 41	5.3	BLQ

* BLQ (Below the lower limit of quantitation)

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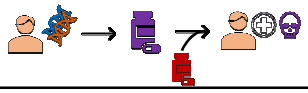
DOI: 10.1097/00008571-200012000-00008

Case 5 (2C9 Poor metabolizer)

- Elderly woman receiving 2.5 mg warfarin daily after a pacemaker one year previously
- Given celecoxib for joint pain 4 weeks prior
- Rx also included digoxin, ranitidine, and atorvastatin
- Developed ecchymoses with a decline in hemoglobin concentration from 160 to 85 g/L over one week
- Was found to be heterozygous for CYP2C9*2 and *3
- Metabolism of warfarin was perturbed and led to bleeding in the presence of variant CYP2C9 genes by coadministration of celecoxib



DOI: 10.1136/jmg.2003.006478

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Limitations

- Genetic variation is only part of the puzzle, context is important
- Does not account for post translational modification
- Does not account for expressional modification
- Studies are primarily clinical, limited in postmortem
- Flat application of ethnic/race to phenotype is strongly discouraged
- Insightful information requires genetic testing
- Must consider postmortem interval, redistribution, age, environmental factors, drug interactions, etc

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Summary

- Genetic polymorphisms are inter-individual variations in genetic code that are also systematic among populations/ethnicities
- Genetic Polymorphisms in metabolic enzymes like CYP2D6 and CYP2C19 contributes to inter-individual differences in drug response
- Examples of drug toxicities that can be predicted by P450 polymorphism include those exerted by codeine, tramadol, warfarin, etc
- Genetic polymorphisms can assist in the interpretation of drug concentrations in postmortem toxicology and drug death certification

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Questions?

"Here's my sequence..."

New Yorker, 2000

Jirair Gevorkyan
Jgevorkyan@outlook.com

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Drug Interactions

Luigino Apollonio, Ph.D.

NAME 2019 Annual Meeting – 20 October 2019

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Outline

- Background
- Types and mechanisms of drug interactions
- Consequences
- Factors influencing interactions
- Avoiding interactions
- Reference information
- Case studies
- Final thoughts

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Objectives

1. To identify the types and mechanisms of drug interactions for consideration in postmortem toxicology and death investigation
2. To identify factors influencing drug interactions, and potential consequences of interactions
3. To become more familiar with key resources on drug interactions, and to explore polypharmacy in case studies

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Background

- Interaction between two or more drugs (or something else!) that prevents them from acting as expected
  - Drug-drug, food/beverage-drug, condition-drug
- A drug interaction may:
  - Affect the total population
  - Affect a particular subset of the population

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Background

- Contraindicated
  - High risk of severe interaction – do not use
- Serious
  - Potential for a serious interaction – may require regular monitoring or alternative medication(s)
- Significant
  - Potential for an interaction – may require monitoring
- Minor
  - Interaction may not be significant or may be unlikely

?

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Background

- Polypharmacy
  - Use of multiple medications
    - Benefit-Risk Assessment
  - Associated risks across general and specialist care
- DIs estimated to cause over 2% of annual hospitalizations in the USA (Carpenter et al 2019)
  - Bethi et al (2018): From a total of 433 prescriptions (46%) had one or more potential DDIs (range of 1-13 DIs per prescription)
    - Older patients and those prescribed >6 drugs were at 'major risk'
  - Gujjarlamudi (2016): Prevalence of 'inappropriate' medication use in the elderly ranges from 11.5-62.5% (citing Guaraldo et al 2011)
    - Risk of DI estimates at 13% for two drugs, 58% for five drugs, and 82% for seven or more drugs (citing Fulton and Allen, 2005)

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Background

- Pharmacokinetic interactions
  - Increase or decrease in:
    - Absorption
    - Distribution
    - Metabolism
    - Elimination
- Additive
- Synergistic
- Antagonistic

- Pharmacodynamic interactions
  - Homodynamic
    (same receptor)
    (pure/partial agonists; competitive/ noncompetitive/uncompetitive antagonists)
  - Heterodynamic
    (different receptors)

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Mechanisms

- Absorption mechanisms
  - Change in intestinal blood flow
  - Change in metabolism in the intestine
  - Change in gastric emptying/intestinal motility
  - Change in gastric acidity
  - Change in intestinal flora
  - Change in solubility
- Distribution mechanisms
  - Effects of body changes – lean muscle, increased fat
  - Changes in protein binding

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Mechanisms

- Metabolism mechanisms
  - Cytochrome p450 effects
    - Leads to changes in the concentration and effect of a drug or its metabolites
    - Enzyme induction
    - Enzyme inhibition
- Elimination mechanisms
  - Renal effects – decrease in renal blood flow, GFR, tubular secretion
  - Urine pH – weak acids or bases in the urine
  - Biliary excretion – reabsorption in the intestine (enterohepatic recirculation)

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Consequences

- Increase or decrease in the beneficial or adverse effects of drugs
  - Reduction in desired effects
    - failure of therapy
    - may need increased dosage
  - Increase in adverse effects
    - Increase in frequency or severity of adverse effects
- May be unpredictable
- May lead to medication non-compliance

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Practice Questions

1) Drug interactions may be categorized (not least) to pharmacokinetic interactions and pharmacodynamic interactions? TRUE or FALSE
2) The risk of an adverse drug event has been estimated at what percent (%) for a person taking five drugs?
   a) 13%
   b) 28%
   c) 58%
   d) 82%
   e) 85%
3) Consequences of drug interactions include which of the following?
   a) Reduction in desired effects
   b) Failure of therapy
   c) Increase in adverse effects
   d) Increase in frequency or severity of side effects
   e) All the above

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Practice Questions

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Factors

- Genetics
- Physiology/pathophysiology/disease (hepatic, renal)
- Age
- Lifestyle
- Dosing regimen
- Duration of therapy
- Time(s) of administration
- Degree of, and agents in, polypharmacy
- Therapeutic index

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How are patients to avoid DIs?

- Ask HCPs about interactions
- Keep a list of current medications
- Inform HCPs of medications, and include OTCs, foods, vitamins, supplements, herbals/traditional medications
- Inform HCPs when medications are stopped/started
- Inform HCPs about lifestyle changes
- Understand why one is taking each medication
- Be aware of side effects
- Try to eliminate unnecessary meds – ask to simplify meds or discontinue if possible
- Take only as prescribed

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Tools: Prescribing Information

- Warnings and Precautions (includes Black Box Warnings)
- Dosage and Administration
- Contraindications
- Adverse Reactions
- Drug interactions
- Use in specific populations

- Examples: Warfarin, Sertraline, Mycophenolic acid, Metoprolol

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Warfarin PI

- Black Box Warning
  - Drugs, dietary changes, and other factors affect INR levels achieved with coumadin therapy.
- Drug Interactions
  - Concomitant use of drugs that increase bleeding risk, antibiotics, antifungals, botanical (herbal) products, and inhibitors and inducers of CYP2C9, 1A2, or 3A4.
  - Consult labeling of all concurrently used drugs for complete information about interactions with [warfarin] or increased risks for bleeding.

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Warfarin PI

- Drug Interactions
  - Drugs may interact with [warfarin] through pharmacodynamic or pharmacokinetic mechanisms.
  - Pharmacodynamic mechanisms for drug interactions with [warfarin] are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and alteration of the physiologic control loop for vitamin K metabolism (hereditary resistance).
  - Pharmacokinetic mechanisms for drug interactions with [warfarin] are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding.
  - It is important to note that some drugs may interact by more than one mechanism.

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Warfarin PI

- Drug Interactions

Table 3: Drugs that Can Increase the Risk of Bleeding

Drug Class	Specific Drugs
Anticoagulants	argatroban, dabigatran, bivalirudin, desirudin, heparin, lepirudin
Antiplatelet Agents	aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine
Nonsteroidal Anti-Inflammatory Agents	celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meflenamic acid, naproxen, oxaprozin, piroxicam, sulindac
Serotonin Reuptake Inhibitors	citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone

Table 2: Examples of CYP450 Interactions with Warfarin

Enzyme	Inhibitors	Inducers
CYP2C9	amiodarone, capecitabine, cotrimoxazole, etravirine, fluconazole, fluvastatin, fluvoxamine, metronidazole, miconazole, oxandrolone, sulfinpyrazone, tigecycline, voriconazole, zafirlukast	aprepitant, bosentan, carbamazepine, phenobarbital, rifampin
CYP1A2	acyclovir, allopurinol, caffeine, cimetidine, ciprofloxacin, disulfiram, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, norfloxacin, oral contraceptives, phenylpropanolamine, propafenone, propranolol, terbinafine, ticlopidine, tolcapone, verapamil, zileuton	nafcillin, omeprazole, phenobarbital, phenytoin, cigarette smoking
CYP3A4	alprazolam, amiodarone, amlodipine, aprepitant, atorvastatin, atazanavir, busulfan, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, cyclosporine, danazol/stanozol, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosaprepitant, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib/nilotinib, nefazodone, nelfinavir, nilotinib, oral contraceptives, posaconazole, ranitidine, ranolazine, ritonavir, saquinavir, telithromycin, tipranavir, voriconazole, zileuton	armodafinil, aminoglutethimide, aprepitant, bosentan, carbamazepine, efavirenz, etravirine, modafinil, nafcillin, phenytoin, pioglitazone, prednisone, rifampin, rufinamide

Some botanicals may cause bleeding events when taken alone (e.g., garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of COUMADIN. Conversely, some botanicals may decrease the effects of COUMADIN (e.g., co-enzyme Q_{10}, St. John's wort, ginseng). Some botanicals and foods can interact with COUMADIN through CYP450 interactions (e.g., echinacea, grapefruit juice, ginkgo, goldenseal, St. John's wort).

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Sertraline PI

- Contraindications
  - Concomitant use of MAOIs, or use within 14 days of stopping MAOIs
  - Concomitant use of pimozide [QT prolongation and ventricular arrhythmias]
  - Concomitant use of disulfiram (oral solution only) [reaction with alcohol]
- Warnings and Precautions
  - Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue [sertraline] and initiate supportive treatment.
    - (also includes amphetamines, TCAs, fentanyl, lithium, tramadol, buspirone, and others)
  - Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk.

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Sertraline PI

- Drug Interactions
  - Protein-bound drugs: Monitor for adverse reactions and reduce dosage of [sertraline] or other protein-bound drugs (e.g., warfarin) as warranted.
  - CYP2D6 substrates: Reduce dosage of drugs metabolized by CYP2D6

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	The concomitant use of SSRIs including ZOLOFT and MAOIs increases the risk of serotonin syndrome.
Intervention:	ZOLOFT is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[See Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.2)]*.
Examples:	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Pimozide	
Clinical Impact:	Increased plasma concentrations of pimozide, a drug with a narrow therapeutic index, may increase the risk of QT prolongation and ventricular arrhythmias.
Intervention:	Concomitant use of pimozide and ZOLOFT is contraindicated *[See Contraindications (4)]*.
Other Serotonergic Drugs	
Clinical Impact:	The concomitant use of serotonergic drugs with ZOLOFT increases the risk of serotonin syndrome.
Intervention:	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of ZOLOFT and/or concomitant serotonergic drugs *[See Warnings and Precautions (5.2)]*.
Examples:	other SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort

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Sertraline PI

Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)	
Clinical Impact:	The concurrent use of an antiplatelet agent or anticoagulant with ZOLOFT may potentiate the risk of bleeding.
Intervention:	Inform patients of the increased risk of bleeding associated with the concomitant use of ZOLOFT and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio *[See Warnings and Precautions (5.3)]*.
Examples:	aspirin, clopidogrel, heparin, warfarin
Drugs Highly Bound to Plasma Protein	
Clinical Impact:	ZOLOFT is highly bound to plasma protein. The concomitant use of ZOLOFT with another drug that is highly bound to plasma protein may increase free concentrations of ZOLOFT or other highly-bound drugs in plasma *[See Clinical Pharmacology (12.3)]*.
Intervention:	Monitor for adverse reactions and reduce dosage of ZOLOFT or other protein-bound drugs as warranted.
Examples:	warfarin
Drugs Metabolized by CYP2D6	
Clinical Impact:	ZOLOFT is a CYP2D6 inhibitor *[See Clinical Pharmacology (12.3)]*. The concomitant use of ZOLOFT with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate.
Intervention:	Decrease the dosage of a CYP2D6 substrate if needed with concomitant ZOLOFT use. Conversely, an increase in dosage of a CYP2D6 substrate may be needed if ZOLOFT is discontinued.
Examples:	propafenone, flecainide, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, thioridazine, tolterodine, venlafaxine
Phenytoin	
Clinical Impact:	Phenytoin is a narrow therapeutic index drug. ZOLOFT may increase phenytoin concentrations.
Intervention:	Monitor phenytoin levels when initiating or titrating ZOLOFT. Reduce phenytoin dosage if needed.
Examples:	phenytoin, fosphenytoin

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Mycophenolic acid PI

- Warnings and Precautions
  - A variety of drugs have potential to alter systemic MPA exposure when co-administered with [MPA].
  - Therefore, determination of MPA concentrations in plasma before and after making any changes to immunosuppressive therapy, or when adding or discontinuing concomitant medications, may be appropriate to ensure MPA concentrations remain stable.
- Drug Interactions
  - See FPI for drugs that may interfere with systemic exposure and reduce [MPA] efficacy: antacids with magnesium or aluminum hydroxide, proton pump inhibitors, drugs that interfere with enterohepatic recirculation, telmisartan, calcium-free phosphate binders.

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Mycophenolic acid PI

Antacids with Magnesium or Aluminum Hydroxide	
Clinical Impact	Concomitant use with an antacid containing magnesium or aluminum hydroxide decreases MPA systemic exposure *[see Clinical Pharmacology (12.3)]*, which may reduce CELLCEPT efficacy.
Prevention or Management	Administer magnesium or aluminum hydroxide containing antacids at least 2h after CELLCEPT administration.
Proton Pump Inhibitors (PPIs)	
Clinical Impact	Concomitant use with PPIs decreases MPA systemic exposure *[see Clinical Pharmacology (12.3)]*, which may reduce CELLCEPT efficacy.
Prevention or Management	Monitor patients for alterations in efficacy when PPIs are co-administered with CELLCEPT.
Examples	Lansoprazole, pantoprazole

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Mycophenolic acid PI

Clinical Impact	Concomitant use with calcium free phosphate binders decrease MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may reduce CELLCEPT efficacy.
Prevention or Management	Administer calcium free phosphate binders at least 2 hours after CELLCEPT.
Examples	Sevelamer

Table 6. Drug Interactions with CELLCEPT that Affect Other Drugs

Drugs that Undergo Renal Tubular Secretion	
Clinical Impact	When concomitantly used with CELLCEPT, its metabolite MPAG, may compete with drugs eliminated by renal tubular secretion which may increase plasma concentrations and/or adverse reactions associated with these drugs.
Prevention or Management	Monitor for drug-related adverse reactions in patients with renal impairment.
Examples	Acyclovir, ganciclovir, probenecid, valacyclovir, valganciclovir
Combination Oral Contraceptives	
Clinical Impact	Concomitant use with CELLCEPT decreased the systemic exposure to levonorgestrel, but did not affect the systemic exposure to ethinylestradiol [see *Clinical Pharmacology (12.3)*], which may result in reduced combination oral contraceptive effectiveness.
Prevention or Management	Use additional barrier contraceptive methods.

Proton Pump Inhibitors (PPIs)	
Clinical Impact	Concomitant use with PPIs decreases MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may reduce CELLCEPT efficacy.
Prevention or Management	Monitor patients for alterations in efficacy when PPIs are co-administered with CELLCEPT.
Examples	Lansoprazole, pantoprazole
Drugs that Interfere with Enterohepatic Recirculation	
Clinical Impact	Concomitant use with drugs that directly interfere with enterohepatic recirculation, or indirectly interfere with enterohepatic recirculation by altering the gastrointestinal flora, can decrease MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may reduce CELLCEPT efficacy.
Prevention or Management	Monitor patients for alterations in efficacy or CELLCEPT related adverse reactions when these drugs are co-administered with CELLCEPT.
Examples	Trimethoprim/sulfamethoxazole, bile acid sequestrants (cholestyramine), rifampin as well as aminoglycoside, cephalosporin, fluoroquinolone and penicillin classes of antimicrobials.
Drugs Modulating Glucuronidation	
Clinical Impact	Concomitant use with drugs inducing glucuronidation decreases MPA systemic exposure, potentially reducing CELLCEPT efficacy, while use with drugs inhibiting glucuronidation increases MPA systemic exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of CELLCEPT related adverse reactions.
Prevention or Management	Monitor patients for alterations in efficacy or CELLCEPT related adverse reactions when these drugs are co-administered with CELLCEPT.
Examples	Telmisartan (induces glucuronidation); isavuconazole (inhibits glucuronidation)

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Metoprolol PI

- Warnings and Precautions
  - Bronchospastic Disease: Avoid beta blockers [use lowest dose, or consider concomitant beta2-agonists)
  - Pheochromocytoma: First initiate therapy with an alpha blocker [due to observed paradoxical increase in BP]
- Drug Interactions
  - Catecholamine-depleting drugs may have an additive effect when given with beta-blocking agents.
  - Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.
  - CYP2D6 Inhibitors are likely to increase metoprolol concentration.
  - Concomitant use of glycosides, clonidine, and diltiazem and verapamil with beta-blockers can increase the risk of bradycardia.
  - Beta-blockers including metoprolol, may exacerbate the rebound hypertension that can follow the withdrawal of clonidine.
  - Alcohol interferes with the extended release properties of this product.

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Case Studies

- F, 55, femoral blood
  - Benztropine - QUAL
  - Cyclobenzaprine – 58 ng/mL
  - Bupropion (w/ metabolite) – 75 ng/mL (670 ng/mL)
  - Tramadol (w/metabolite) – 830 ng/mL (ODM- 83 ng/mL)
  - Topiramate – 5400 ng/mL
  - Caffeine - QUAL
  - Cotinine - QUAL
  - Fentanyl (w/metabolite) – 1.1 ng/mL (NF 1.2 ng/mL)
  - Paroxetine – 63 ng/mL
  - Pregabalin – 7.7 mg/L
  - Ziprasidone – 13 ng/mL

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Case Studies

- F, 55, femoral blood
  - Diphenhydramine – 0.328 mg/L
  - Dextromethorphan – 0.686 mg/L
  - Chlorpromazine – 0.076 mg/L
  - Trazodone – 0.399 mg/L
  - Olanzapine – QUAL
  - Donepezil – QUAL

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Case Studies

- M, 56, femoral blood
  - Dextromethorphan – QUAL
  - Doxepin (w/metabolite) – 0.097 mg/L
  - Ketamine (w/metabolite) – 0.826 mg/L
  - Mirtazapine – QUAL
  - Cocaine (w/metabolites) – 38 ng/mL (heart blood, BE >800 ng/mL)
  - Nicotine and cotinine – QUAL
  - Caffeine – QUAL
  - Oxycodone – 23 ng/mL
  - THC (w/metabolites) – 1.9 ng/mL (heart blood)

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Case Studies

- M, 32, femoral blood
  - Methadone (w/EDDP) – 0.672 mg/L
  - Mirtazapine – 0.101 mg/L
  - Nicotine and cotinine – QUAL
  - Caffeine – QUAL
  - Gabapentin – 3.8 mg/L
  - Hydroxyzine – 42 ng/mL

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Case Studies

- F, 47, femoral blood
  - Gabapentin – 17 mg/L
  - Amitriptyline (w/ NT) – QUAL (0.342 mg/L)
  - Sertraline (w/ metabolite) – QUAL
  - Diphenhydramine – 0.520 mg/L
  - Lidocaine (w/ metabolite) – QUAL
  - Cotinine – QUAL
  - Cocaine (w/ metabolites) – 103 ng/mL (BE 128 ng/mL)
  - *Urine: Also promethazine, dextromethorphan, doxylamine*

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Case Studies

- F, 79, femoral blood
  - Amitriptyline (w/ NT) – 0.402 mg/L (0.415 mg/L)
  - Bupropion (with metabolite) – QUAL
  - Citalopram (w/ metabolite) – 0.466 mg/L
  - Diphenhydramine – 0.162 mg/L
  - Cotinine – QUAL
  - Oxycodone – 112 ng/mL
  - 7-aminoclonazepam – QUAL
  - Memantine - QUAL

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Case Studies

- M, 38, femoral blood
  - Clonazepam (w/ metabolite) – 2.7 ng/mL (44 ng/mL)
  - Clomipramine (w/metabolite) – 900 mg/L
  - Fluoxetine (w/metabolite) – 410 ng/mL (270 ng/mL)
  - Trazodone (w/metabolite) – 32 mcg/mL (0.059 mcg/mL)
  - Dextromethorphan (w/ metabolite) – 110 ng/mL (15 ng/mL)
  - Caffeine – QUAL
  - Cotinine – QUAL

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Final thoughts

- Polypharmacy may be necessary – but needs to be managed well
- Contraindicated, serious and significant risks of DIs may contribute to, but not be obvious in, fatal outcomes
- Patients and HCPs both share responsibility for appropriate polytherapy
- Regulatory references are living documents that reflect key DI information
- Prescribed, licit, and illicit drug combinations are the norm in death investigations – toxicologists can help wade through the information ☺

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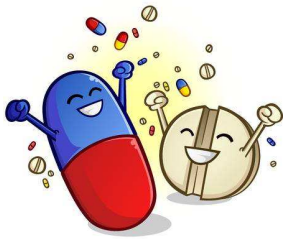
Questions



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Thank you!

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Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010–2014

by Margaret Warner, Ph.D., National Center for Health Statistics; James P. Trinidad, M.P.H., M.S., U.S. Food and Drug Administration; Brigham A. Bastian, B.S., Arialdi M. Miniño, M.P.H., and Holly Hedegaard, M.D., M.S.P.H., National Center for Health Statistics

By Year

2012			2013			2014		
Referent drug	Number of deaths	Percent	Referent drug	Number of deaths	Percent	Referent drug	Number of deaths	Percent
	(*n* = 41,502)			(*n* = 43,982)			(*n* = 47,055)	
Heroin	6,151	14.8	Heroin	8,412	19.1	Heroin	10,863	23.1
Oxycodone	5,169	12.5	Cocaine	5,289	12.0	Cocaine	5,856	12.4
Cocaine	4,759	11.5	Oxycodone	4,954	11.3	Oxycodone	5,417	11.5
Methadone	4,081	9.8	Morphine	3,771	8.6	Alprazolam	4,217	9.0
Alprazolam	3,785	9.1	Alprazolam	3,696	8.4	Fentanyl	4,200	8.9
Morphine	3,508	8.5	Methadone	3,693	8.4	Morphine	4,022	8.5
Hydrocodone	3,023	7.3	Methamphetamine	3,185	7.2	Methamphetamine	3,728	7.9
Methamphetamine	2,262	5.5	Hydrocodone	3,105	7.1	Methadone	3,495	7.4
Fentanyl	1,605	3.9	Fentanyl	1,905	4.3	Hydrocodone	3,274	7.0
Diazepam	1,567	3.8	Diazepam	1,601	3.6	Diazepam	1,729	3.7

All Years

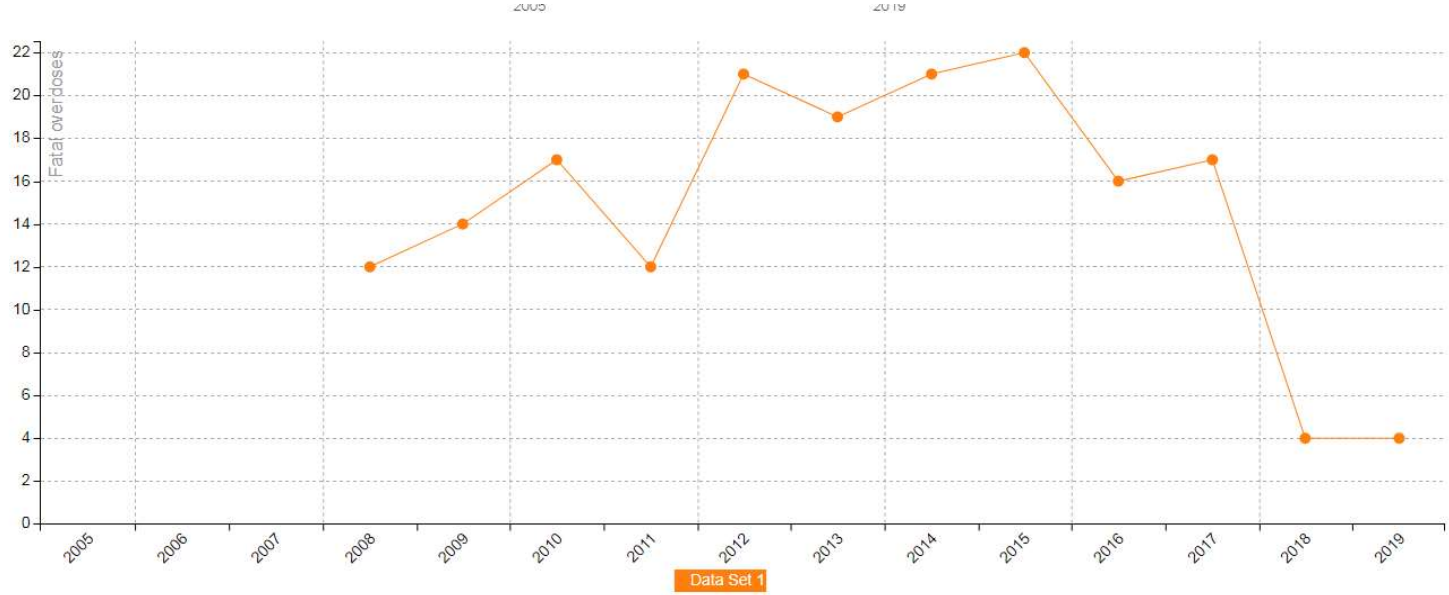
Referent drug	Number of deaths involving referent drug	Concomitant drug
Opioids		
Fentanyl	4,200	Heroin
Heroin	10,863	Cocaine
Hydrocodone	3,274	Alprazolam
Methadone	3,495	Alprazolam
Morphine	4,022	Oxycodone
Oxycodone	5,417	Alprazolam
Benzodiazepines		
Alprazolam	4,217	Oxycodone
Diazepam	1,729	Oxycodone
Stimulants		
Cocaine	5,856	Heroin
Methamphetamine	3,728	Heroin

Florida Data - 2016

Summary of Drug Occurrences in Decedents (continued)

	Drug Present in Body	Cause	Present	Total Occurrences
Inhalants	Halogenated	46	4	50
	Helium	13	0	13
	Hydrocarbon	1	0	1
	Nitrous Oxide	1	0	1
Opioids	Buprenorphine	32	103	135
	Codeine	87	420	507
	Fentanyl	1,390	254	1,644
	Fentanyl Analogs	965	61	1,026
	Heroin	952	71	1,023
	Hydrocodone	245	447	692
	Hydromorphone	196	399	595
	Meperidine	3	3	6
	Methadone	330	169	499
	Morphine	1,338	702	2,040
	Oxycodone	723	659	1,382
	Oxymorphone	153	409	562
	Tramadol	144	366	510

Query Results – Average ≈ 4.2%



Query	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
county=Allegheny OR Westmoreland, drugs=Morphine OR Morphine (Free)	-	-	-	12	14	17	12	21	19	21	22	16	17	4	4

THE CENTER FOR FORENSIC SCIENCE RESEARCH & EDUCATION

Identification and Quantification of Exogenous Insulin Analogs in Postmortem Specimens

Presenter: Laura Labay, PhD.
Kevin Legg, Ph.D., Sally Aiken, M.D., and Barry Logan, PhD.

INSULIN DEATHS

NEWS

Germany: Care worker charged with 6 murders by insulin injection

The alleged murders took place across Germany between April 2017 and February 2018. Police accuse the man of murdering his diabetic victims by injecting them with lethal doses of insulin.

NATIONAL

Second Death At West Virginia VA Hospital Ruled As Homicide

August 28, 2019 · 11:15 PM ET

ITV REPORT 23 November 2018 at 3:46pm

Deleted 'insulin overdose ' search found on Middlesbrough murder accused's phone, court told

Mitesh Patel. Credit: Gazette Media Syndiction

Inquiry: Nurse's colleagues called her 'angel of death'

By Jonathan Sher
More from By Jonathan Sher

Published on: June 13, 2018 | Last Updated: June 13, 2018 2:17 PM EDT

INSULIN ANALYSIS CHALLENGES

- Current techniques
  - Antibody-based (ELISA)
    - Cross reactivity & analog differentiation
- Analytical issues via LC/MS
  - Laborious sample prep
    - SPE/SPE + 2D-LC + nLC
    - Manual immunoaffinity purification
  - Analog co-elution via LC/MS
    - Isotope distribution
  - Poor fragmentation
  - Low-specificity transitions

Review — Drug Testing and Analysis

Received: 25 March 2009 Revised: 29 April 2009 Accepted: 6 May 2009 Published online in Wiley Interscience:

Murder by insulin: suspected, purported and proven – a review

Vincent Marks*

Murder by insulin – whether attempted, suspected or proven – is rare. Only 66 cases worldwide could be found for this review. A conviction was secured in 31 cases and additional weapon was employed in 11. Differentiation of attempted homicide from Munchausen syndrome by proxy in the young and from 'mercy killing' in the elderly was not attempted. Most perpetrators were close relatives and most victims were alive when discovered and responded to treatment. Hypoglycaemia is the first clue to homicidal insulin use in living subjects and requires the demonstration of a plasma insulin concentration of generally more than 1000 pmol/L and undetectable plasma C-peptide concentration to establish the diagnosis. Serum glucose measurements are valueless in victims found dead. The presence near the body of insulin vials, syringes or needles, loose talk by the suspected perpetrator or their ready access to insulin may be the only clue. The demonstration of insulin in tissue around an injection site by immunohistopathology or by measuring it in an extract clinches the diagnosis. Immunoassays suitable for clinical use to detect and measure insulin and C-peptide are subject to random errors and cannot be relied upon unless special precautions including separation by gel filtration or HPLC are undertaken prior to analysis. They do not detect or measure accurately a new generation of synthetic insulin analogues. Mass spectrometry will be required to do this and to validate clinical immunoassays, upon which convictions have always had to rely in the past. Copyright © 2009 John Wiley & Sons, Ltd.

"Immunoassays suitable for clinical use to detect and measure insulin and C-peptide are subject to random errors and cannot be relied upon [....] They do not detect or measure accurately a new generation of **synthetic insulin analogues**. **Mass spectrometry** will be required to do this [....]"

HUMAN & SYNTHETIC SEQUENCES

Most variability occurs at the c-terminal of the beta-chain

Human & Humulin® — **Native**

GIVEQCCTSICSLYQLENYCN
FVNQHLCGSHLVEALYLVCGERGFFYTPKT

Lispro (Humalog®) — **Fast Acting**

GIVEQCCTSICSLYQLENYCN
FVNQHLCGSHLVEALYLVCGERGFFYTKPT

Glargine (Lantus®) — **Long Acting**

GIVEQCCTSICSLYQLENYCG
FVNQHLCGSHLVEALYLVCGERGFFYTPKTRR

Aspart (Novolog®)

GIVEQCCTSICSLYQLENYCN
FVNQHLCGSHLVEALYLVCGERGFFYTDKT

Detemir (Levemir®)

GIVEQCCTSICSLYQLENYCN
FVNQHLCGSHLVEALYLVCGERGFFYTPK
Myristic acid

Glulisine (Aprida®)

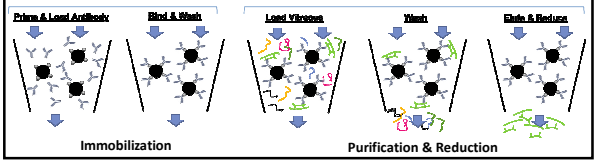
GIVEQCCTSICSLYQLENYCN
FVKQHLCGSHLVEALYLVCGERGFFYTPET

SAMPLE PREPARATION: IMMUNOAFFINITY MASS SPECTROMETRY

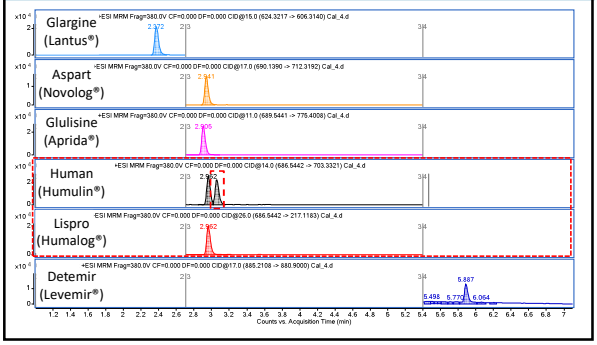
- Hands-free Immunoaffinity Purification
  - Agilent AssayMap Bravo
    - Reproducibility
    - Accuracy
    - Throughput
- Initial Preparations
  - 250 µL vitreous humor. Centrifuge 12,000 x g 5 min.
  - Dilute 200 µL vitreous with 100 µL Phosphate Buffer
  - Add ITSD (Porcine Insulin)
  - **Corning Non Binding Surface/NBS microplate**

SAMPLE PREPARATION: IMMUNOAFFINITY MASS SPECTROMETRY

- Immobilization
  - Prime Protein G cartridges with 50 µl PBS buffer
  - Load 1 µg each antibody
  - Wash 50 µl PBS buffer with 0.02% sodium azide. Store 4°C until use
- Purification
  - Equilibrate 50 µl PBS buffer
  - Load 250 µL dilute vitreous at 3 µL/min. Wash with 4x PBS followed by 20% ACN in 50 mM ABC
  - Elute with 15 µL 2% Acetic Acid into existing volume of 40 mM TCEP-HCL in 30% ACN
  - Eppendorf LoBind PCR plate. Seal, incubate 45°C 15 min, run on 6495 QQQ

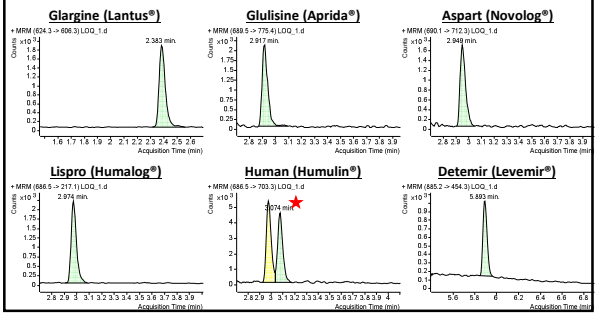


BETA-CHAIN CHROMATOGRAPHY



METHOD VALIDATION: LIMIT OF QUANTITATION (500 PG/ML)

Response and concentration (%CV) assessed with 10 replicates/day over 3 days



CASE SAMPLES 2017-2019

- Tested 58 vitreous humor samples where insulin was suspected to be involved with death
  - 19 (32%) yielded positive results
  - Aspart (Novolog®) & Lispro (Humalog®) most commonly found
  - No Glargine Identified
  - Sensitivity remains a challenge
    - <LOQ results
  - Positive results are corroborating with case history

STABILITY

- Standard glass vials vs. Protein low bind plastics
  - 10 to 50% loss in target concentration in standard glassware

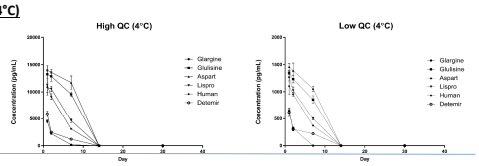
	Glargine (Lantus®)	Glulisine (Aprida®)	Aspart (Novolog®)	Lispro (Humalog®)	Human (Humulin®)	Detemir (Levemir®)
Glass HQC (pg/mL)	14,470	16,590	17,834	16,339	17,064	9,620
Plastic HQC (pg/mL)	19,696	20,133	19,387	19,443	20,004	18,406

20,000 pg/mL target concentration

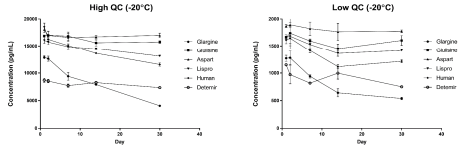
LONG-TERM STABILITY

Loss of all insulin analogs by Day 14 at 4°C

Refrigeration (4°C)

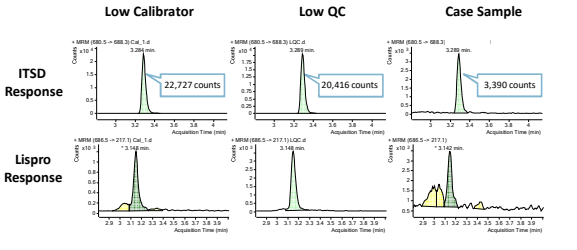


Frozen (-20°C)

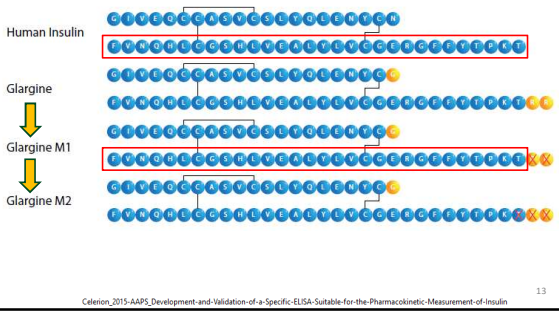


SAMPLE CONDITION IS CRITICAL!
HEMOLYZED VITREOUS

- Hemolyzed case sample
  - Bench notes state "Debris in sample. Mild hemolysis, light pink color"
  - ≈10x loss in internal standard response.
  - Lispro response ratios out of bounds



GLARGINE M1 & M2 METABOLITES



Celerion_2015-AAPS_Development-and-Validation-of-a-Specific-ELISA-Suitable-for-the-Pharmacokinetic-Measurement-of-Insulin

CASE - PRESENTATION

- 38 year old female was found deceased in bed
  - No obvious signs of trauma
  - Needle with bottle of insulin next to bed
- One of her primary physicians stated that the decedent had been mildly suicidal
- Comment from husband (insulin user)
  - "An insulin overdose would be a peaceful way to die."

CASE – TOXICOLOGY FINDINGS

- Toxicological Findings
  - Bupropion: 140 ng/mL
  - Fluoxetine: 1500 ng/mL
  - Norfluoxetine: 1300 ng/mL
  - Insulin Lispro (Humalog®): 2.37 ng/mL
  - Human insulin was not detected
- Husband verified as Humalog® user
- Cause of death documented as "Hypoglycemia due to intentional injection of insulin" and the manner of death was suicide

INSULIN 2.0: R & D for 2019/2020

- Scope Additions
  - Postmortem Blood
  - Deludec (Tresiba®), C-Peptide, Glargine metabolites
- Tissues
  - Injection sites as well as Brain/Liver
  - 1 gram tissue + 5 mL DI water, 1:10 dilution in blank vitreous

	2 ng/mL Target		20 ng/mL Target	
	Brain	Liver	Brain	Liver
Glargine	1.68	1.83	19.82	19.20
Glulisine	2.22	1.68	23.70	18.79
Aspart	2.04	1.68	21.00	19.41
Lispro	2.26	2.14	22.61	20.07
Human	2.29	1.80	24.10	20.41
Detemir	0.78	0.65	8.04	5.47

CONCLUSIONS

- Therapeutic insulin (vitreous) levels unknown
- Stability is a major concern!
  - Freeze following sample collection
- Hemolyzed samples have lowered analytical response
- Injection sites, blood, tissues

Involvement of Synthetic Cannabinoids as Cause or Contributing Cause of Death

Barry K Logan PhD
Chief Scientist, NMS Labs

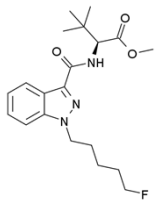
Disclosure

- Barry Logan is a salaried employee of NMS Labs, a commercial laboratory providing forensic testing services.

Synthetic Cannabinoids

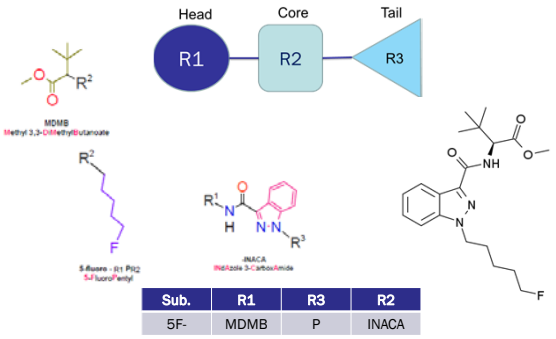
- 1982 – Chemists at Pfizer discovered cannabinoid activity of a new structural class.
- 1988 – Raphael Mechoulam at the Hebrew University synthesized benzopyran derivatives with cannabinoid activity.
- 1995 – John W Huffman synthesized a series of novel cannabinoid agonists at Clemson University.
- 2004 – These compounds began appearing in illicit drug products in Europe.
- 2009 – First SC seizure in the United States

What's in a Name?



methyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate

What's in Name?



Sub.	R1	R3	R2
5F-	MDMB	P	INACA

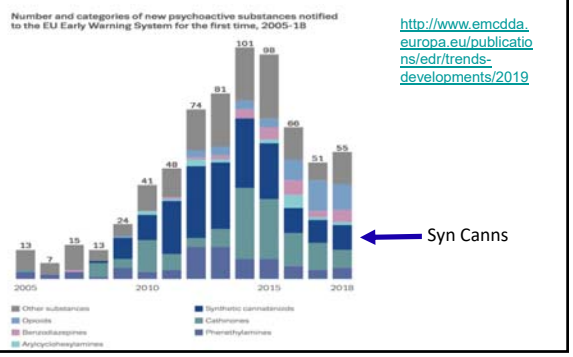
Naming the New Substances…

- EMCDDA provides tool to visualize compounds

Over 620 new psychoactive substances are currently monitored by the EMCDDA through the EU Early Warning System, **169** of which are synthetic cannabinoid receptor agonists.

http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids#panel2

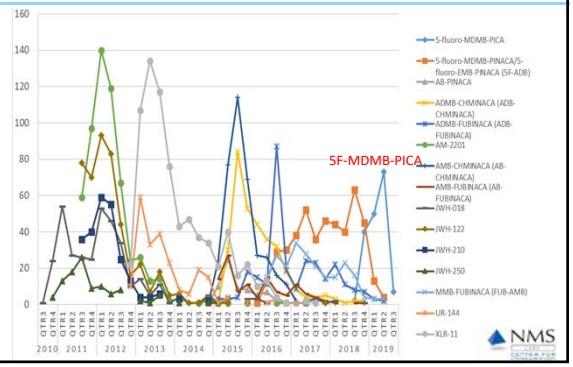
Synthetic Cannabinoid Evolution



http://www.emcdda.europa.eu/publications/edr/trends-developments/2019

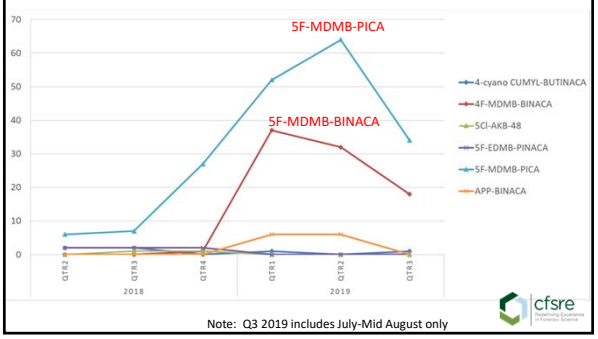
Syn Canns

Synthetic Cannabinoid Evolution



5F-MDMB-PICA

Emerging Synthetic Cannabinoids

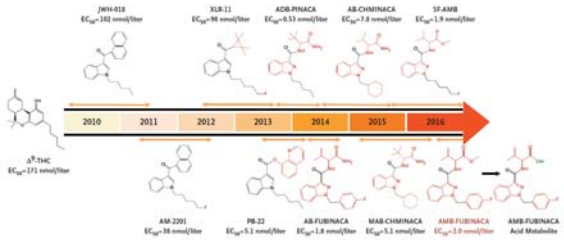


Note: Q3 2019 includes July-Mid August only

Synthetic Cannabinoid Evolution

Date Range	Major SC's
2010 - 2012	JWH-018, JWH-250, JWH-210, AM-2201
2013 - 2014	XLR-11, UR-144
2015 - 2016	AMB-CHMINACA, ADB-CHMINACA, ADB-FUBINACA
2017 - 2018	5F-ADB, FUB-AMB
2019	5F-MDMB-PICA, 5F-MDMB-BINACA

Synthetic Cannabinoid Evolution



Adams AJ, Banister SD, Irizarry L, Trecki J, Schwartz M, Gerona R. "Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York. N Engl J Med. 2017 Jan 19;376(3):235-242

Synthetic Cannabinoid Toxicity

Organ system affected	Symptoms and signs
Central nervous system	Agitation, psychosis, irritability, seizures, sedation, coma, delirium, hallucinations, paranoia, anxiety, self-harm, psychomotor impairment
Cardiovascular	Tachycardia, hypertension, acute coronary syndrome, arrhythmia, chest pain, myocardial infarction
Pulmonary	Tachypnea, diffuse alveolar hemorrhages
Other	Nausea, vomiting, fevers, mydriasis, lack of convergence of gaze, acute kidney injury, hyperglycemia, hypokalemia, apoptotic cell death

Logan BK, Mohr ALA, Friscia M, Krotulski AJ, Papsun DM, Kacinko SL, Ropero-Miller JD, Huestis MA. Reports of Adverse Events Associated with Use of Novel Psychoactive Substances, 2013-2016: A Review. J Anal Toxicol. 2017 Sep 1;41(7):573-610.

Cognitive Impairment

Blood Synthetic Cannabinoid Concentrations in Cases of Suspected Impaired Driving.

Yeakel JK, Logan BK. J Anal Toxicol. 2013 Oct;37(8):547-51.

- *12 cases of Suspected impaired driving involving synthetic cannabinoids.*
- *Attitude of the drivers was cooperative and relaxed, speech was slow and slurred, coordination was poor.*
- *Pulse and blood pressure were generally elevated.*
- *The most consistent sign noted was a marked lack of convergence in all cases where it was assessed.*
- *JWH-018 (n=4), 0.1-1.1ng/mL; JWH-081 (n=2) qualitative only; JWH-122 (n=3) 2.5ng/mL; JWH-210 (n=4) 0.1ng/mL; JWH-250 (n=1) 0.38ng/mL; AM-2201 (n=6) 0.43 – 4.0ng/mL.*

Cognitive Impairment

Differential physiological and behavioral cues observed in individuals smoking botanical marijuana versus synthetic cannabinoid drugs.

Chase PB, Hawkins J, Mosier J, Jimenez E, Boesen K, Logan BK, Walter FG.

- *16 synthetic cannabinoid and 25 marijuana cases.*
- *AM-2201, JWH-022, JWH-122, JWH-018 detected.*
- *Drivers under the influence of synthetic cannabinoids were more frequently impaired with confusion, disorientation, and incoherent, slurred speech than drivers under the influence of marijuana in this population evaluated by DREs.*

Cognitive Impairment

Select Other SC Driving Impairment Case Series:

- Kraemer M, Fels H, Dame T, Musshoff F, Halter S, Mogler L, Hess C, Madea B, Maas A. Mono-/polyintoxication with 5F-ADB: A case series. Forensic Sci Int. 2019 Aug;301:e29-e37.
- McCain KR, Jones JO, Chilbert KT, Patton AL, James LP, Moran JH. Impaired Driving Associated with the Synthetic Cannabinoid 5f-Adb. J Forensic Sci Criminol. 2018 Aug;6(1).
- Kaneko S. Motor vehicle collisions caused by the 'super-strength' synthetic cannabinoids, MAM-2201, 5F-PB-22, 5F-AB-PINACA, 5F-AMB and 5F-ADB in Japan experienced from 2012 to 2014. Forensic Toxicol. 2017;35(2):244-251.
- Peterson BL, Couper FJ. Concentrations of AB-CHMINACA and AB-PINACA and Driving Behavior in Suspected Impaired Driving Cases. J Anal Toxicol. 2015 Oct;39(8):642-7.
- Louis A, Peterson BL, Couper FJ. XLR-11 and UR-144 in Washington state and state of Alaska driving cases. J Anal Toxicol. 2014 Oct;38(8):563-8.

Synthetic Cannabinoid Toxicity

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Logan BK, Mohr ALA, Friscia M, Krotulski AJ, Papsun DM, Kacinko SL, Ropero-Miller JD, Huestis MA. Reports of Adverse Events Associated with Use of Novel Psychoactive Substances, 2013-2016: A Review. J Anal Toxicol. 2017 Sep 1;41(7):573-610.

Syn Cann Deaths

Synthetic Cannabinoid-Related Illnesses and Deaths.

Trecki J, Gerona RR, Schwartz MD. N Engl J Med. 2015 Jul 9;373(2):103-7.

- *Use of synthetic cannabinoids particularly by younger and inexperienced users, has led to multiple clusters of cases of adverse health effects and deaths.*
- *Effects include excited delirium, acute kidney injury, seizures, psychosis, hallucinations, cardiotoxic effects, coma, and death — with some users dying before they could reach an emergency department.*
- *ADB-FUBINACA, AB-CHMINACA, AB-PINACA, 5F-PB-22*
- *18 Deaths, and >600 cases of hospitalization.*

Syn Cann Deaths

Synthetic cannabinoid drug use as a cause or contributory cause of death.

Labay LM, Caruso JL, Gilson TP, Phipps RJ, Knight LD, Lemos NP, McIntyre IM, Stoppacher R, Tormos LM, Wiens AL, Williams E, Logan BK. Forensic Sci Int. 2016 Mar;260:31-39.

- *Deaths are being attributed to synthetic cannabinoids, with the highest risk areas being behavioral toxicity resulting in excited delirium, trauma or accidents and as contributing factors in subjects with pre-existing cardiopulmonary disease.*
- *Insufficient information exists to correlate blood synthetic cannabinoid concentrations to effect.*
- *In the absence of other reasonable causes, the drugs should be considered as a cause or contributory cause of death based on history and circumstances with supporting toxicological data.*

Syn Cann Deaths

Characteristics and circumstances of synthetic cannabinoid-related death.

Darke S, Duflou J, Farrell M, Peacock A, Lappin J. Clin Toxicol (Phila). 2019 Aug 7:1-7. [E-Pub ahead of print].

- *Retrospective study of cases in Australia in which synthetic cannabinoid use was a mechanism contributory to death (n = 55)*
- *Information was collected on cause of death, demographics, drug history, circumstances of death, toxicology and organ pathology.*
- *The most frequent synthetic cannabinoids were the indazolecarboxamides (61.8%), especially AB-CHMINACA (38.2%).*
- *While acute toxicity was the most common cause of death, cardiovascular disease was prominent.*

Syn Cann Deaths

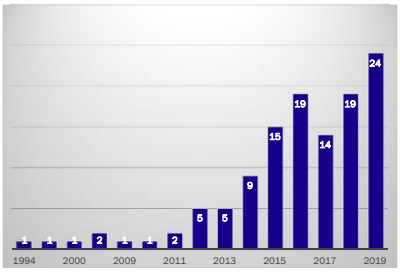
Select Other SC Related Death Case Series:

- Adams AJ, Banister SD, Irizarry L, Trecki J, Schwartz M, Gerona R. "Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York. N Engl J Med. 2017 Jan 19;376(3):235-242.
- Al-Matrouk A, Alqallaf M, AlShemmeri A, BoJbarah H. Identification of synthetic cannabinoids that were seized, consumed, or associated with deaths in Kuwait in 2018 using GC-MS and LC-MS-MS analysis. Forensic Sci Int. 2019 Sep 13;303:109960.
- Chan S, Wu J, Lee B. Fatalities related to new psychoactive substances in Singapore-A case series. Forensic Sci Int. 2019 Jul 26:109892.
- Boland DM, Reidy LJ, Seither JM, Radtke JM, Lew EO. Forty-Three Fatalities Involving the Synthetic Cannabinoid, 5-Fluoro-ADB: Forensic Pathology and Toxicology Implications. J Forensic Sci. 2019 Jun 18 [Epub ahead of print].
- Kraemer M, Fels H, Dame T, Musshoff F, Halter S, Mogler L, Hess C, Madea B, Maas A. Mono-/polyintoxication with 5F-ADB: A case series. Forensic Sci Int. 2019Aug;301:e29-e37.

Syn Cann Deaths

Publications in PubMed by year:

"Synthetic cannabinoids" and "Death"



Conclusions

- Synthetic cannabinoids continue to be popular.
- Novel, high potency compounds still appearing.
- Additional resources for testing available.
- Mounting evidence of synthetic cannabinoid involvement in deaths.
- Behavioral toxicity contributes to traumatic and traffic deaths.
- Cardiac compromise is a frequent contributing cause in these cases.

NMS

Looking Ahead to Toxicology in 2020

A Presentation from the NAME Toxicology Committee

Chair: Laura Labay, PhD; Vice-Chair: Charles Catanese, MD
Members: Luigino Apollonio, PhD; Gregory J. Davis, MD; Andrew Falzon, MD; Amanda Fisher-Hubbard, MD; Fintan Garavan, MD, PhD; Jirair Gevorkyan, PhD; Ami Jackson, DO; George Jackson, PhD; Karen Kelly, MD; Nikolas Lemos, PhD; Alison Miller, MA; Frank Miller, MD; D. Kimberley Molina, MD; Abraham Philip, MD; Megan Quinn, MD; Robert Stoppacher, MD; Linda Sullivan, BS

NAME 2019
TOX COMMITTEE

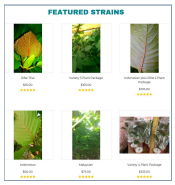
OBJECTIVES

1. To discuss drugs and chemicals that are important to the practice of toxicology in 2020
2. Mitragynine
   - Interpretation
3. Sodium Nitrate/Nitrite
   - No direct test for postmortem samples
4. Tianeptine
   - Antidepressant with an opioid high
5. Vaping
   - Emerging data about adverse effects and lethal outcomes
6. Delta-8 THC
   - Analytical impact to Delta-9 THC

NAME 2019
TOX COMMITTEE

KRATOM – Introduction

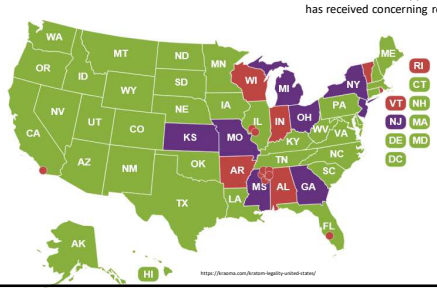
- KRATOM (*Mitragyna speciosa*) is a tropical tree found in southern Thailand and northern states of the Malay peninsula.
- In its native regions, leaves of the Kratom tree are typically consumed as a tea or chewed directly
- Purported to induce stimulant and opioid-like analgesic effects in a dose- and time-dependent manner
- Been reported to be useful in ameliorating withdrawal symptoms following cessation of opioid use



NAME 2019
TOX COMMITTEE

KRATOM – Legal Status

"There are no FDA-approved uses for kratom, and the agency has received concerning reports about the safety of kratom."



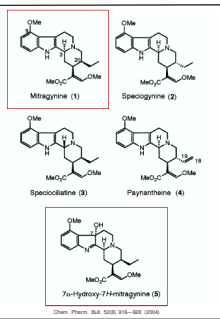
https://kratoma.com/kratom-legality-united-states/

Green – legal to purchase
Red – illegal
Red Dot – banned in city
Purple – pending legislation

NAME 2019
TOX COMMITTEE

KRATOM – Constituents

predominant indole alkaloids



Chem. Pharm. Bull. 52(8) 916—928 (2004)

NAME 2019
TOX COMMITTEE

KRATOM – Binding Affinities

JACS

Synthetic and Receptor Signaling Explorations of the *Mitragyna* Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators

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Table 2. Binding Affinities of *Mitragyna* Alkaloids at Human Opioid Receptors

	$K_i \pm$ SEM (μM)[a]		
compound	hMOR	hKOR	hDOR
mitragynine	0.233 ± 0.048	0.772 ± 0.207	>10
paynantheine	0.410 ± 0.152	2.56 ± 0.37	>10
speciogynine	0.728 ± 0.061	3.20 ± 0.36	>10
speciociliatine	0.560 ± 0.168	0.329 ± 0.112	>10
7-OH	0.047 ± 0.018	0.188 ± 0.038	0.219 ± 0.041

[a]All data points represent mean ± SEM (μM) of $n \geq 3$.

- Acts primarily via opioid receptors
- 7-hydroxymitragynine, which while present in the plant in much smaller quantities than mitragynine, is a much more potent opioid agonist.

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KRATOM – Human Performance Impairment and PM Concentrations

HUMAN PERFORMANCE IMPAIRMENT	POSTMORTEM
Order Date: 1/2018 - 8/2019	
N = 30	N = 1030
Range: 11 – 490 ng/mL*	Range: 6 – 4500 ng/mL*
Average: 106 ng/mL ± 117	Average: 282 ng/mL ± 484
Median: 66 ng/mL	Median: 110 ng/mL

* Other drugs may be present
NMS Labs Data

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KRATOM – Interpretation - Stability

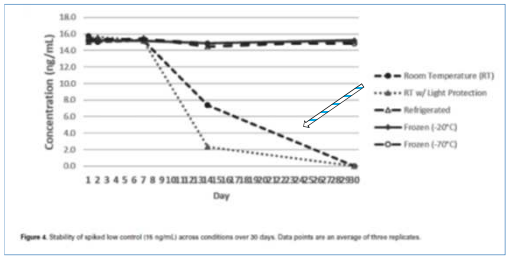

Figure 4. Stability of spiked low control (16 ng/mL) across conditions over 30 days. Data points are an average of three replicates.

Papsun DM, Chan-Hosokawa A, Friederich L, Brower J, Graf K, Logan B. The Trouble With Kratom: Analytical and Interpretative Issues Involving Mitragynine. J Anal Toxicol. 2019 Aug 19.

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SODIUM NITRATE/NITRITE – Suicides

Suicide Discussion

Aug 5, 2019 #1

Hi all, just wondering if we have any idea of how effective a stat dose is when attempting with SN. Do we know of any successful attempts using the stat dose? Thanks.

Response: "If you do a trial run of the regimen with Metoclopramide and experience adverse side effects you can use Domperidone instead."

EXIT INTERNATIONAL (https://exitinternational.net/docs/ExitActBC.pdf)

The two salts in question are sodium nitrite and sodium azide. Both are described in the Peaceful Pill *e*Handbook in the chapter on 'Lethal Inorganic Salts'. P.126 of Jan 2018 edition.

https://www.peacefulpillhandbook.com/preview-contents/

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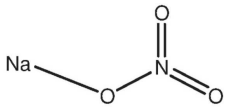
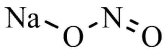
SODIUM NITRATE/NITRITE



Sodium nitrate



Sodium nitrite

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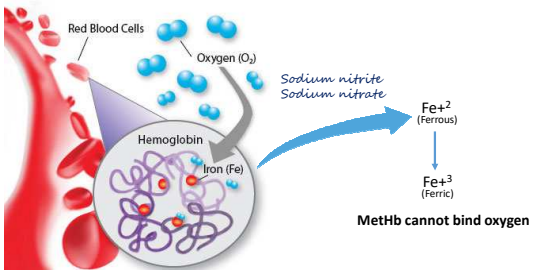
SODIUM NITRATE/NITRITE – MetHb



MetHb cannot bind oxygen

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SODIUM NITRATE/NITRITE – Levels

LEVEL	SYMPTOMS
1-2%	Normal Physiological State
10-20%	Cyanosis
20-50%	Respiratory distress, dizziness, headache, and fatigue
50-70%	Loss of consciousness and death
(>90%)	(Survival Reported)

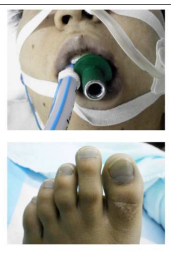

Figure 1: His face, lips, and toes were deeply cyanosed on admission.

Katabami K, Hayakawa M, Gando S. Severe Methemoglobinemia due to Sodium Nitrite Poisoning. Case Rep Emerg Med. 2016

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SODIUM NITRATE/NITRITE – MetHb in PM Blood

- Met-Hb formed is rapidly reduced to Hb when blood samples are stored without freezing
- MetHb formation can also occur by auto-oxidation or by putrefaction after sampling

Sato K, Tamaki K, Okajima H, Katsumata Y. Long-term storage of blood samples as whole blood at extremely low temperatures for methemoglobin determination. Forensic Sci Int. 1988 Apr;37(2):99-104

Introduction

Determination of methemoglobin (Met-Hb) in blood is important for the diagnosis of poisoning by oxidants such as nitrites and nitrates. Met-Hb itself, however, is very unstable and both formation and reduction of Met-Hb can occur even after sampling. Met-Hb formed is rapidly reduced to hemoglobin (Hb) by intraerythrocytic Met-Hb reductase when blood samples are stored as whole blood without freezing [1–3]. Met-Hb formation can also occur by autoxidation or by putrefaction after sampling [2–4]. Thus, care should be taken to prevent both formation and reduction of Met-Hb during storage of blood samples. For this purpose, blood samples are immediately hemolyzed with large volumes of a chilled buffer, and Met-Hb concentrations are determined as soon as possible [2,4].

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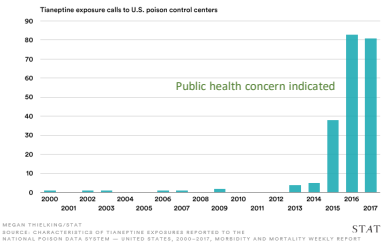
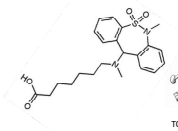
TIANEPTINE – Introduction



- Atypical tricyclic drug used as an antidepressant in Europe, Asia, and Latin America
- Not approved for use by the FDA in the United States
- Animal and human studies show that tianeptine is an opioid receptor agonist



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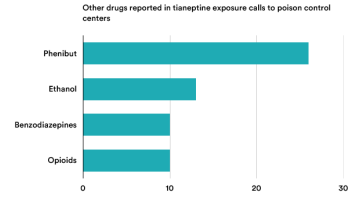
TIANEPTINE – Symptoms & Co-exposures



- SYMPTOMS:
  - Neurologic,
  - Cardiovascular
  - Gastrointestinal signs and symptoms
  - Some effects mimicking opioid toxicity
  - 83 tianeptine exposures with noted co-exposures

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VAPING – Introduction

VAPING DEVICES
- E-cigarettes
- Vape pens
- Advanced personal vaporizers

CONTENTS
- Propylene glycol or vegetable glycerin-based liquid with nicotine
- Flavoring (e.g., gummy bear, tobacco, coffee, cotton candy)
- Other chemicals and metals

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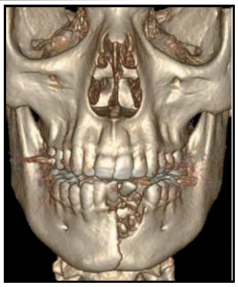
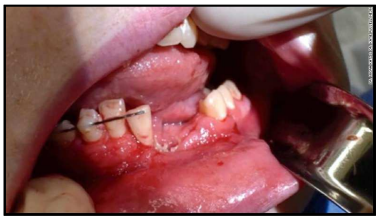
VAPING – Explosion Injuries





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VAPING – Reports of Injury & Death

Illinois patient's death from lung disease may be first vaping-related fatality in U.S.

AUGUST 24, 2019 / 6:35 PM / CBS/AP

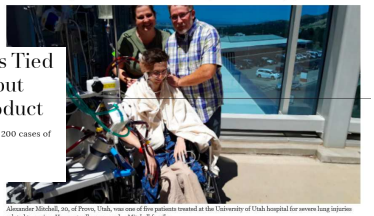
Juul CEO Says Lung Illnesses Tied to Vaping Are 'Worrisome' but Has No Plans to Remove Product

The Centers for Disease Control is currently investigating nearly 200 cases of severe respiratory illness linked to vaping

By Julie Mazziotta | August 28, 2019 11:33 AM

One man's brush with death after vaping-related lung failure

He went from hiking enthusiast to 'on death's door' within days. Doctors blamed vaping.



Alexander Mitchell, 20, of Provo, Utah, was one of five patients treated at the University of Utah hospital for severe lung injuries related to vaping. He eventually recovered. –Mitchell family

VAPING – CDC Communication

Clinical Action
CDC Clinician Outreach and Communication Activity

CDC Urges Clinicians to Report Possible Cases of Unexplained Vaping-associated Pulmonary Illness to their State/Local Health Department

- As of 8/14/19, 30 cases of severe pulmonary disease have been reported to the WI Department of Health Services
  - 15 cases are confirmed (ages 16-34 years)
  - 15 cases are still under investigation (ages 16-53 years)
- SYMPTOMS:
  - Patients presented with respiratory symptoms including cough, shortness of breath, and fatigue.
  - Symptoms worsened over a period of days or weeks before admission to the hospital.
  - Other symptoms reported by some patients included fever, chest pain, weight loss, nausea, and diarrhea.
  - Chest radiographs showed bilateral opacities, and CT imaging of the chest demonstrated diffuse ground-glass opacities, often with sub-pleural sparing.

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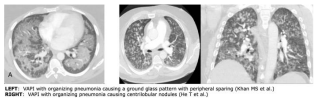
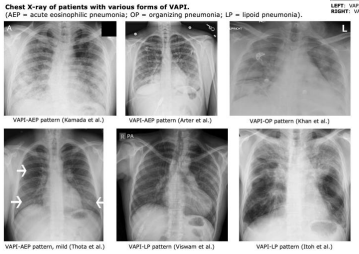
VAPING – Radiology



LEFT. VAPI with organizing pneumonia causing a ground glass pattern with peripheral sparing (Khan MS et al.)
RIGHT. VAPI with organizing pneumonia causing centrilobular nodules (He T et al.)

Chest X-ray of patients with various forms of VAPI.
(AEP = acute eosinophilic pneumonia; OP = organizing pneumonia; LP = lipoid pneumonia).



VAPI-AEP pattern (Kamada et al.) | VAPI-AEP pattern (Arter et al.) | VAPI-OP pattern (Khan et al.)

VAPI-AEP pattern, mild (Thota et al.) | VAPI-LP pattern (Viswam et al.) | VAPI-LP pattern (Itoh et al.)

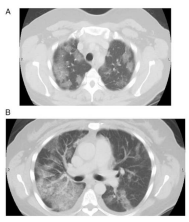


FIGURE 1. Representative CT images show the "crazy paving" pattern of patchy ground glass superimposed on interlobular septal thickening. A, Bilateral upper lobes. B, Bilateral lower lobes.

VAPI with lipoid pneumonia causing a crazy paving pattern, from McGuinty et al.

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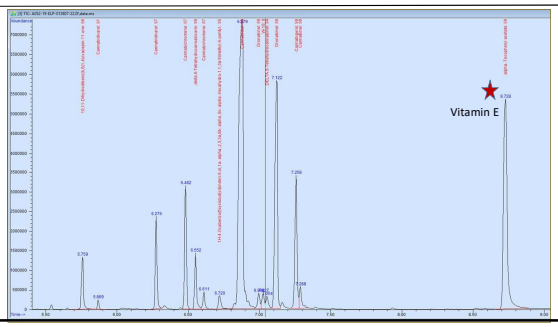
VAPING – Vaping Pen Extract



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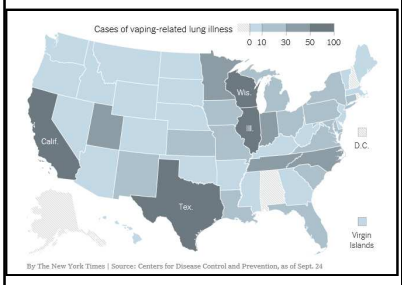
VAPING INJURIES BY LOCALE & BRAND



https://www.nytimes.com/2019/09/27/health/vaping-illness-thc.html

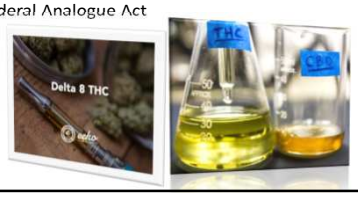
Dank Vapes, TKO and Other THC Vaping Brands Are Linked to Illnesses, C.D.C. Says

Health officials released the names of several products identified by patients who have been sickened in Illinois and Wisconsin.

Empty Dank Vapes packaging.

Delta-8 THC – Introduction

- A naturally occurring cannabinoid found in most cannabis plants
- Has been identified in botanicals, vape oils, and edibles
- Legal Status - Since the compound shares such a close molecular design with delta-9 THC, it currently falls under the same legal status per the Federal Analogue Act



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Delta-8 THC – Manufacturing

Delta-8 THC:
Not present in enough quantity to prepare a distillate

Delta-9 THC → Delta-8 THC

The reaction
Mix in 4% acidic alumina silicate with your extracted and winterized crude cannabis oil. Distill the cannabis oil and collect the THC distillate as you normally would. The combination of the acidic alumina silicate and boiling flask heat will catalyze the rearrangement of the THC molecule from delta-9 to delta-8-THC. The conversion rate should be at least 90 – 95%.

https://brinstrument.com/blog/cannabis-distillation/how-to-convert-thc-delta-9-to-thc-delta-8/

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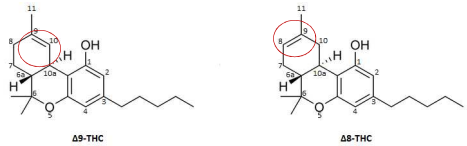
Delta-8 THC – Structure



Delta-9 THC and Delta-8 THC are isomers as are their metabolites.

In samples where Delta-8 THC and Delta-9 THC are present, the chromatography of the Delta-9 THC and the Delta-9 THCC metabolite may be adversely affected.

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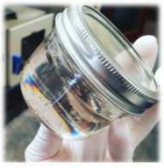
Delta-8 THC – Effects

- Properties:
  - antiemetic
  - anxiolytic
  - appetite-stimulating
  - analgesic



- Binds to the cannabinoid CB1 and CB2 receptors
- Exhibits a lower psychotropic potency than Delta-9 THC

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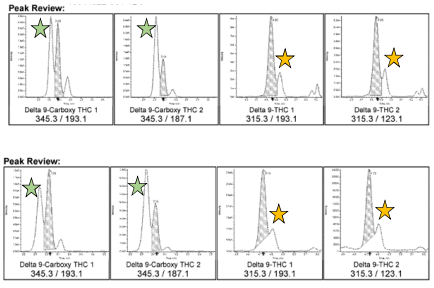
Delta-8 THC – Chromatographic Challenge



★ Delta-8 THC

★ Delta-8 THCC

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Delta-8 THC – Impact

Delta-8 THC INTERFERENCE IMPACT:

- Qualitative Identification
- Quantitation

To obtain baseline separation, a longer column may be needed. This results in a longer run-time, which may affect instrument capacity.

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SUMMARY

1. Mitragynine
   - Interpretation – Stability
2. Sodium Nitrate/Nitrite
   - No direct test for postmortem samples – MetHb is the clinical marker, but not a good marker for PM blood. Clinical correlation is a must!
3. Tianeptine
   - Antidepressant with an opioid high – Not *available* in U.S., but *used* in the U.S.
4. Vaping
   - Emerging data about adverse effects and lethal outcomes – Data is still emerging
5. Delta-8 THC
   - Analytical impact to Delta-9 THC – Identification and Quantitative Challenges

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Gross and Histologic Comparison of Acute and Chronic Skull Fractures to Typical and Accessory Sutures of the Infant Skull

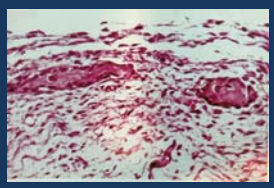
Agnieszka Rogalska, MD
Vincent Tranchida, MD

Objectives

- Review normal and variant sutures of the infant skull
- Review gross and radiographic features of normal and variant sutures of the infant skull
- Compare histology of sutures and bone fractures with typical and atypical sutures of the infant skull
- Discuss the value of identifying aberrant sutures in cases of infant death

Formation of the Skull

- Membranous ossification
  - Fuse
  - form sutures
- Atypical or incomplete *fusion* results in the formation of atypical sutures[2]
- Aberrant ossification centers form islands of bone with surrounding sutures ("Wormian bones")[1]

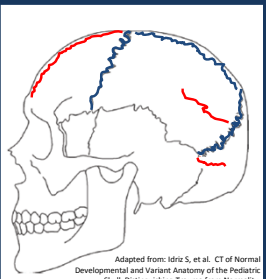


Bullough, PG. Orthopaedic Pathology. 5th Ed. Missouri. 38; 2010

1 Bellary SS, Steinberg A, et al. Wormian Bones; A Revie. Clinical Anatomy 2013; 26: 922-927
2. Brogdon BG, Shwayder T. Elifritz J. Child Abuse and Its Mimics in Skin and Bone. Boca Raton: CRC Press Taylor & Francis Group, 2013. 127-127

Suture of the Infant Skull

- Typical sutures:
  - Coronal
  - Sagittal
  - Lambdoid
- Three most commonly confused with fractures[2] :
  - Metopic suture
  - Intraparietal suture
  - Mendosal suture

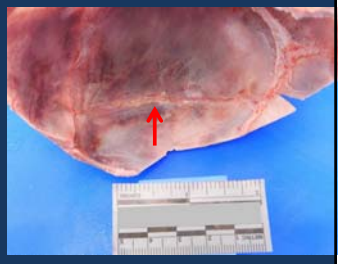


Adapted from: Idriz S, et al. CT of Normal Developmental and Variant Anatomy of the Pediatric Skull: Distinguishing Trauma from Normality. RadioGraphics 2015; 35:1585-1601

2. Brogdon BG, Shwayder T. Elifritz J. Child Abuse and Its Mimics in Skin and Bone. Boca Raton: CRC Press Taylor & Francis Group, 2013. 127-127

Gross Features of Atypical Sutures

- Feature similar to adjacent sutures
- Bilateral or asymmetrical
- Dural connection; interdigitations



Radiographic Features

Fractures

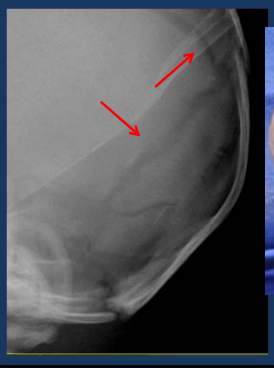
- Sharp, lucent edges
- Absence of sclerosis
- Displacement

Sutures

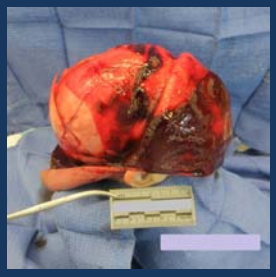
- Scalloped borders
- Sclerosis of the margins

Sanchez T, Stewart D, Walvick M. Skull fracture vs. accessory sutures: how can we tell the difference? Emergency Radiology 2010; 17: 413-418

Radiographic Features of Skull Sutures

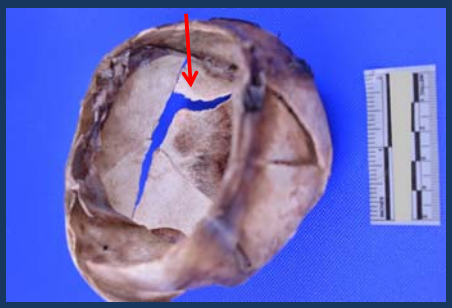


Acute Fracture

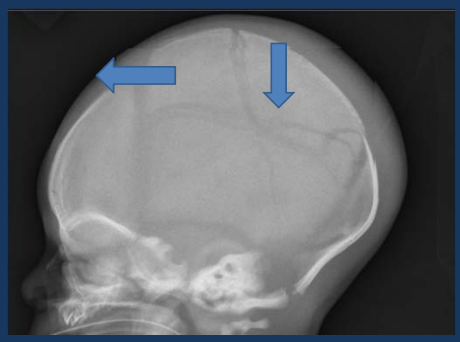


Acute Fracture vs Atypical Parietal Suture

Absence of Interdigitations

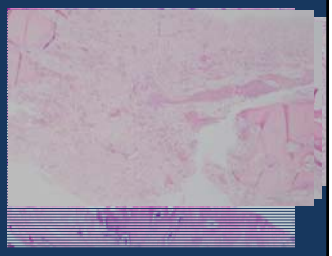


Radiographic Features



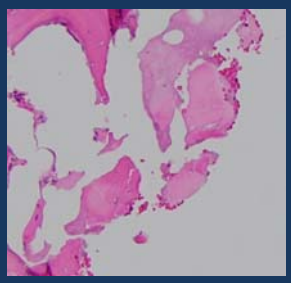
Histologic Feature of Sutures

- Fibrovascular core
- Smooth edges of ossified bone
- Rim of osteoblasts in periostium
- Small foci of woven bone formation



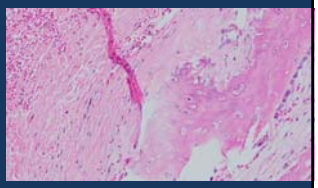
3. Tharp AM, Jason DR. Anomalous Parietal Suture Mimicking Skull Fracture. The American Journal of Forensic Medicine and Pathology 2009; 30 (1): 49-51
4. Furuya Y, Edwards MSB, Alpers CE, et al. Computed Tomography of Cranial Sutures Part I: Comparison of suture anatomy in

Histologic Examination-Fracture



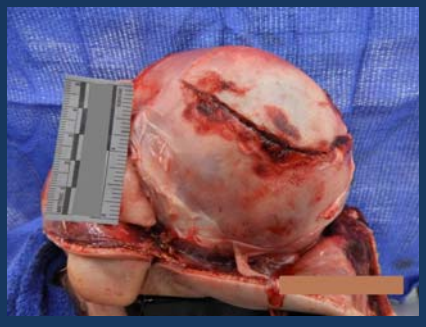
Histologic Feature of Sutures

- Free of inflammation, hemorrhage
- Free of hemosiderin-laden macrophages
- However, diastatic fractures and healing fractures may share histologic feature

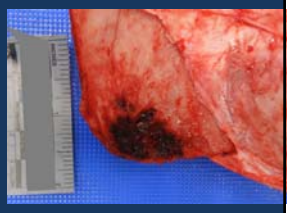


3. Tharp AM, Jason DR. Anomalous Parietal Suture Mimicking Skull Fracture. The American Journal of Forensic Medicine and Pathology 2009; 30 (1): 49-51
4. Furuya Y, Edwards MSB, Alpers CE, et al. Computed Tomography of Cranial Sutures Part I: Cmparison of suture anatomy in children and adults. Journal of Neurosurgery 1984; 61: 53-58

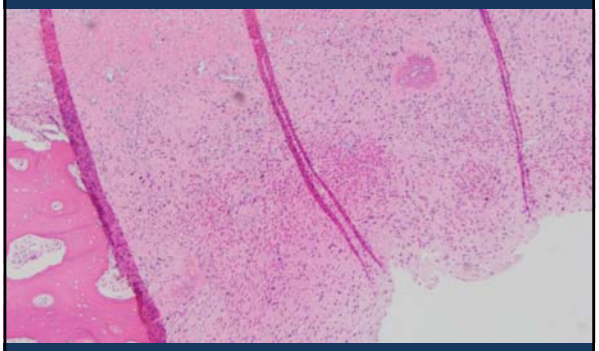
5 Week Old Infant Female



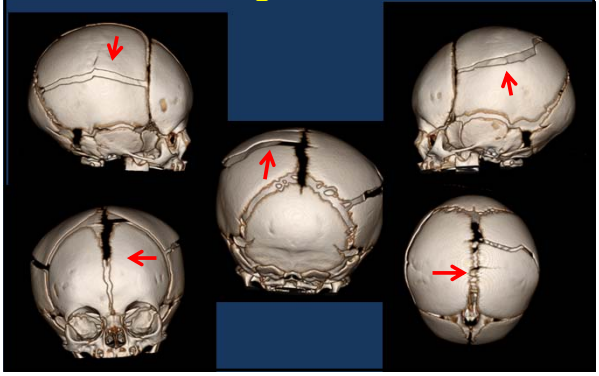
Internal Examination



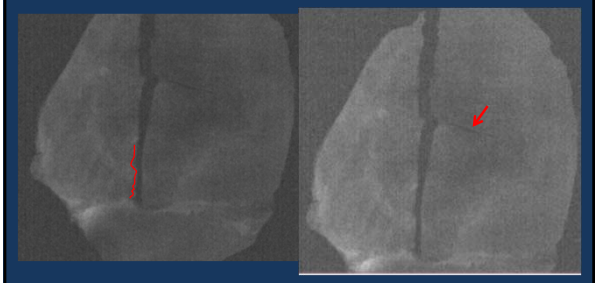
Parietal Fracture



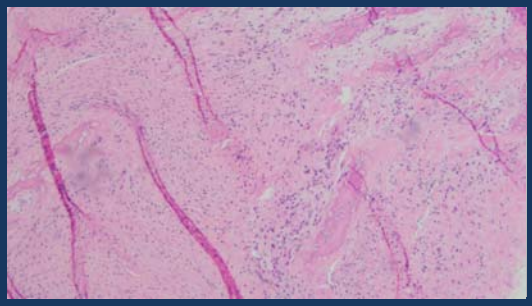
Radiologic Evaluation



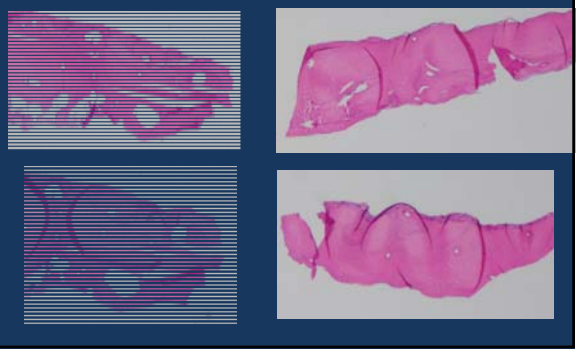
Postmortem Radiographs



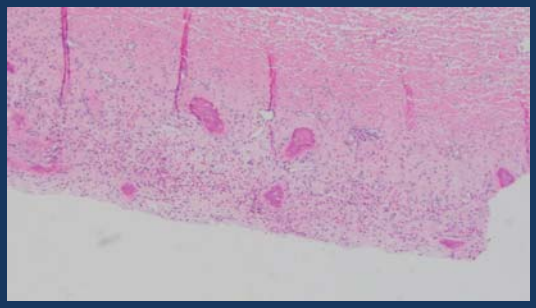
Coronal Suture



Parietal Fracture



Diastatic Parietal Suture Fracture



In Conclusion

- It is important to be familiar with the normal anatomic variants of the infant skull
- Normal variants and trauma can overlap, and may be missed for lack of examination
- Combining features of radiology, gross examination and histology can help differentiate acute and remote fractures from atypical sutures
- This presentation includes a small number of cases; further examination and documentation is warranted

Thank You

Tackling the Challenges of Fetal Autopsies in the Setting of Maternal Trauma

BY DR. DAGGETT, DR. ATHERTON, DR. DYE, DR. MCCLESKEY

Financial Disclosures

I have no financial disclosures to announce

Case 1

14 week stillborn fetus

Mother was shot in the LUQ of the abdomen

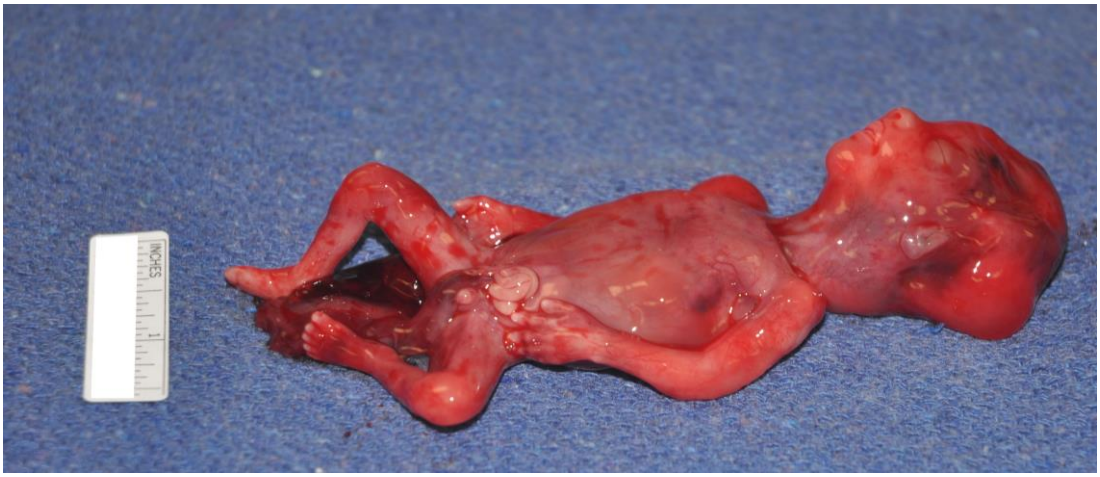
Fetal heart tones noted in ED prior to surgery

Autopsy findings

Stillborn fetus consistent with 14 wks gestation

Gastroschesis identified

Fetus and uterus not struck by the bullet based on ultrasound preformed in the ER



Cause of Death

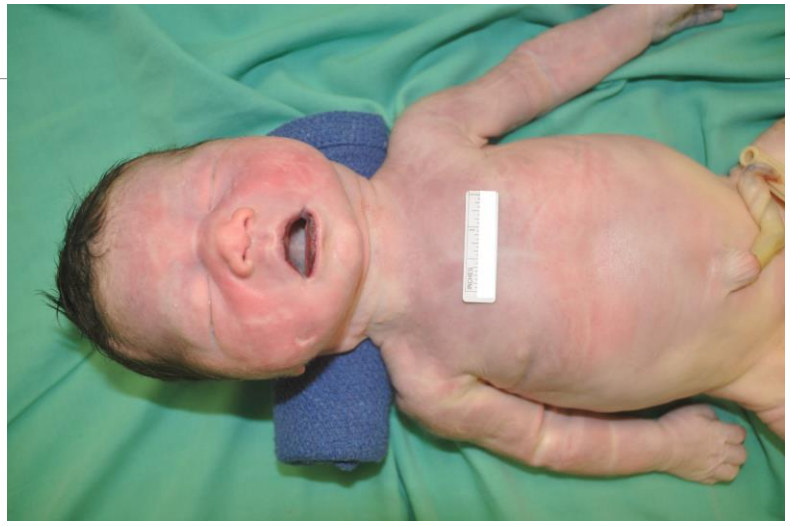
Intrauterine fetal demise following maternal trauma

- No physical findings to contribute to cause of death
- Cause of death determined by maternal history
- Gastroshisis noncontributory to cause of death

Case 2

36 week gestational age male fetus

Maternal history of drug abuse



Autopsy findings

Petechial hemorrhages
- Thymus
- Lungs

Placenta
- Acute hemorrhage at the edge of the placental disk

Toxicology

Meconium
- Morphine 153 ng/g
- Codeine 33ng/g

Samples taken
- Blood: ascending aorta, pulmonary trunk
- Other fluids: urine, vitreous humor, bile

Fetal metabolism of morphine

Metabolized by glucuronidation

Drugs begin accumulating in meconium around 12 weeks of gestation

Metabolized by liver and kidneys

- Bile excreted into the meconium
- Excreted urine swallowed to begin accumulating in meconium

Meconium drug testing

Effective sample for drug screening for:

- Amphetamines
- Opiates
- Cocaine
- Cannabinoids

Case 3

Male fetus 26 weeks gestational age

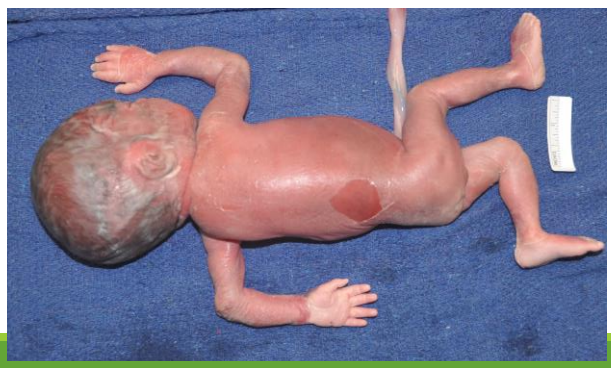
Delivered by caesarean section

Report of mother being assaulted 1 day prior to delivery

External examination

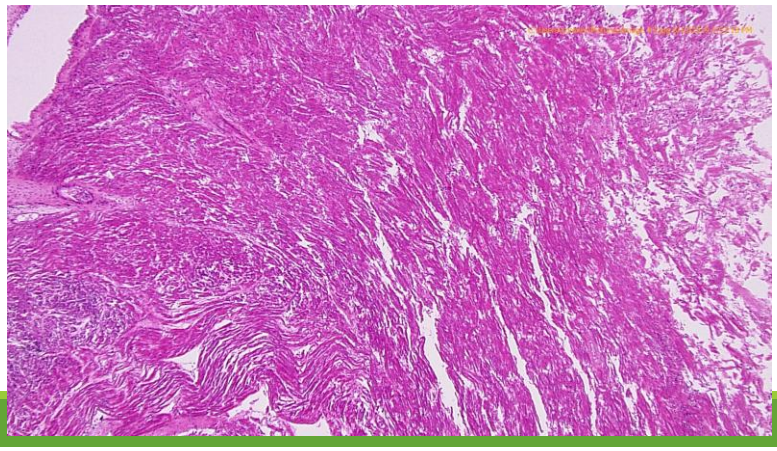
Maceration of ~5% of the body surface

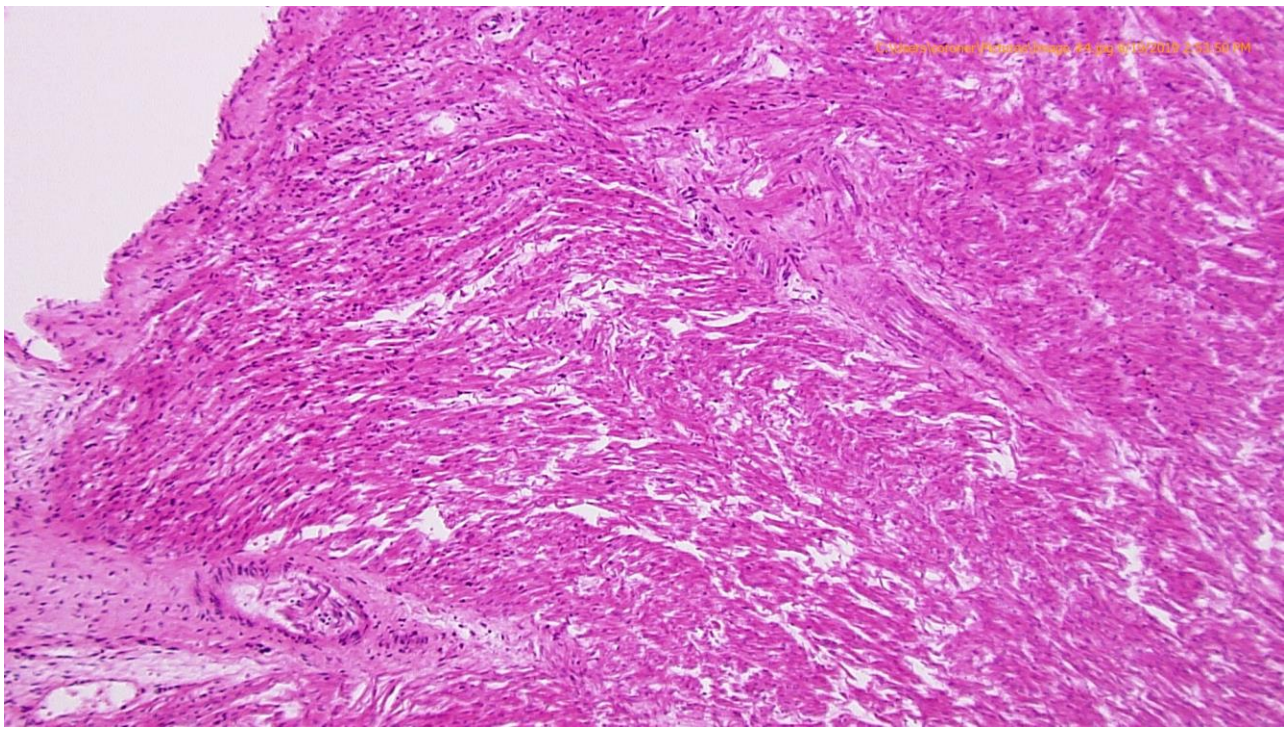
Red-brown discoloration of the umbilical cord

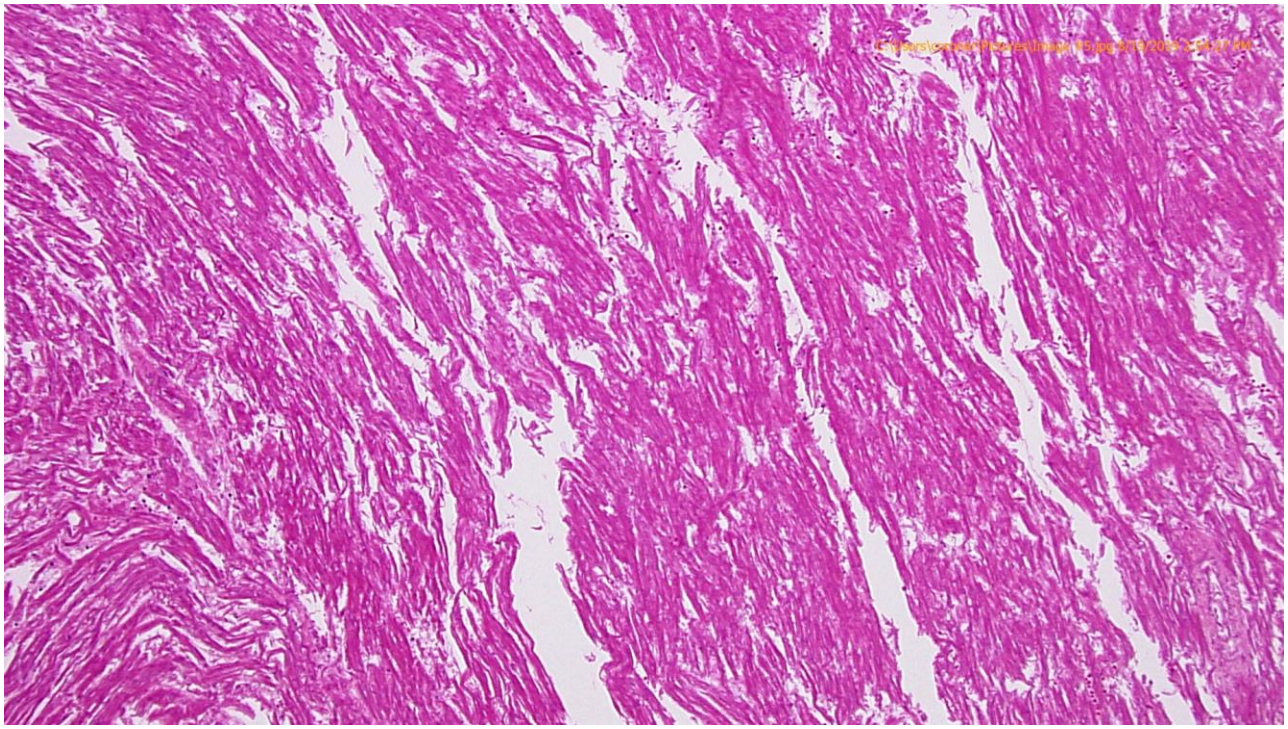


Internal examination

- Bilateral pleural petechia
- Loss nuclear basophilia of the inner half of the myocardium

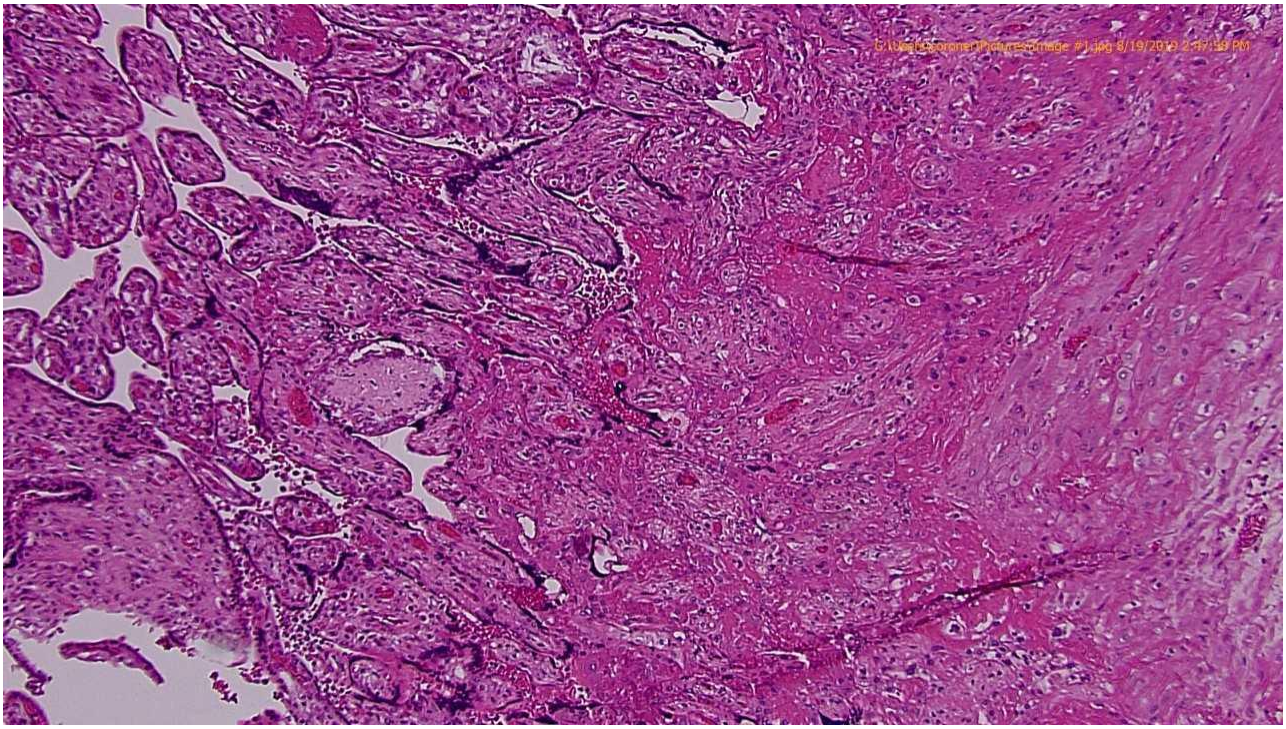






Placenta examination

- Necrotic villi
- Intervillious fibrinoid change
- Mildly increased nucleated red blood cells
- Focal intervillous hemorrhage



Intrauterine retention times

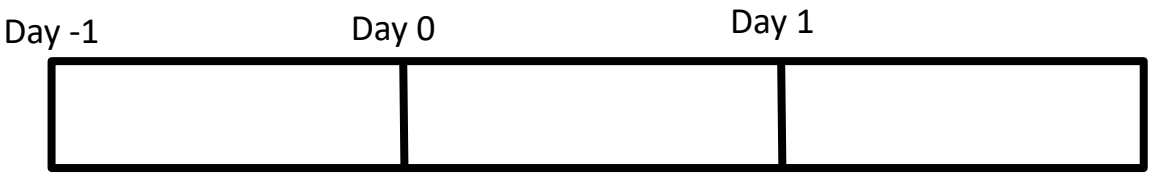
Placental Histology	Post-Demise Interval	Sensitivity	Specificity	PPV
Intravascular karyorrhexis in small villous vessels of several different regions	≥ 6 hrs	94%	100%	1.0
Multifocal (10-25%) vessel luminal abnormalities	≥ 48 hrs	94%	100%	1.0
Extensive (>25%) vessel luminal abnormalities	≥ 2 wks	78%	98%	0.875
Extensive (>25%) avascular villi	≥ 2 wks	100%	93%	0.75

Intrauterine retention times

External Fetal Examination	Post Demise Interval	Sensitivity	Specificity	PPV
Desquamation <1 cm	≥ 6hrs	86%	100%	1.0
Desquamation of face, back, or abdomen	≥ 12hrs	80%	100%	1.0
Desquamation of ≥ 5% of body surface	≥18hrs	80%	100%	1.0
Desquamation ≥ 2 of 11 body zones	≥18hrs	90%	92%	0.9
Mummification	≥2 weeks	100%	100%	1.0

Intrauterine retention times

External Fetal Examination	Post Demise Interval	Sensitivity	Specificity	PPV
Kidney: Loss of tubular nuclear basophilia	≥ 4 hrs	97%	89%	0.97
Liver: Loss of hepatocyte nuclear basophilia	≥ 24 hrs	100%	92%	0.89
Myocardium: Inner ½ loss of nuclear basophilia	≥ 24 hrs	94%	100%	1.0
Myocardium: Outer ½ loss of nuclear basophilia	≥ 48 hrs	100%	96%	0.91
Bronchus: Loss of epithelial nuclear basophilia ≥ 1% of cells	≥ 96hrs	100%	97%	0.91
Liver: Loss of nuclear basophilia 100% of cells	≥ 96hrs	91%	100%	1.0
GI tract: Loss of nuclear basophilia 100% of cells	≥ 1 week	90%	100%	1.0
Adrenal: Loss of nuclear basophilia 100% of cells	≥1 week	100%	100%	1.0
Trachea: Loss of chondrocyte nuclear basophilia ≥1% of cells	≥1 week	89%	100%	1.0
Kidney: loss of nuclear basophilia 100%	≥4 weeks	100%	98%	0.88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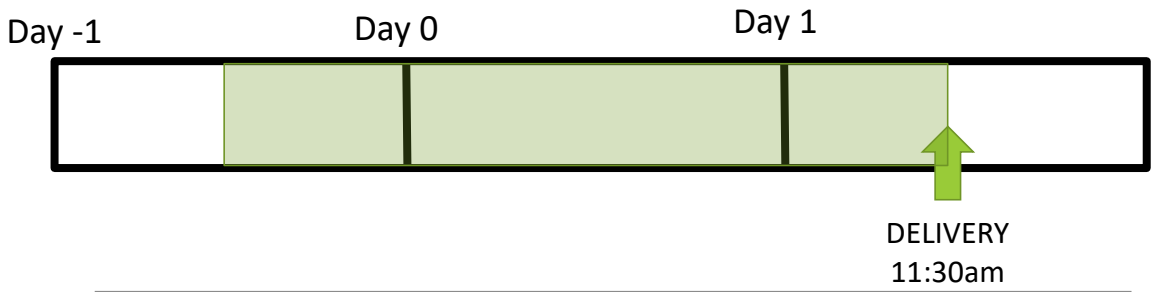
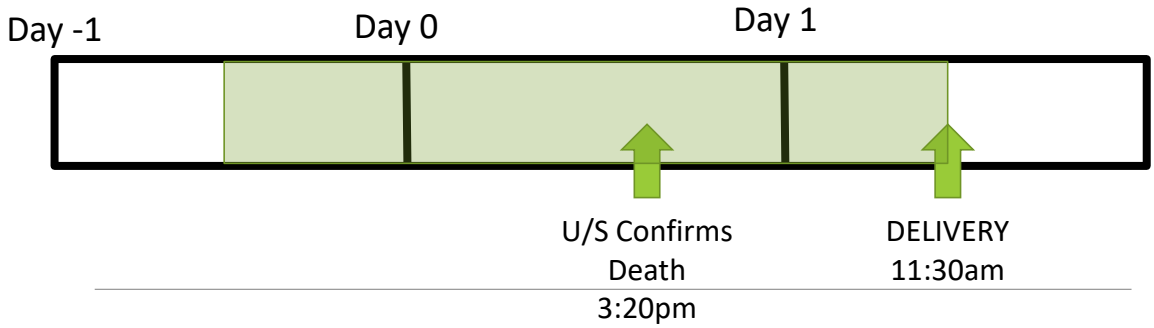
Day 0
Day 1


Day -1
Day 0
Day 1
DELIVERY
11:30am


Day -1
Day 0
Day 1
DELIVERY
11:30am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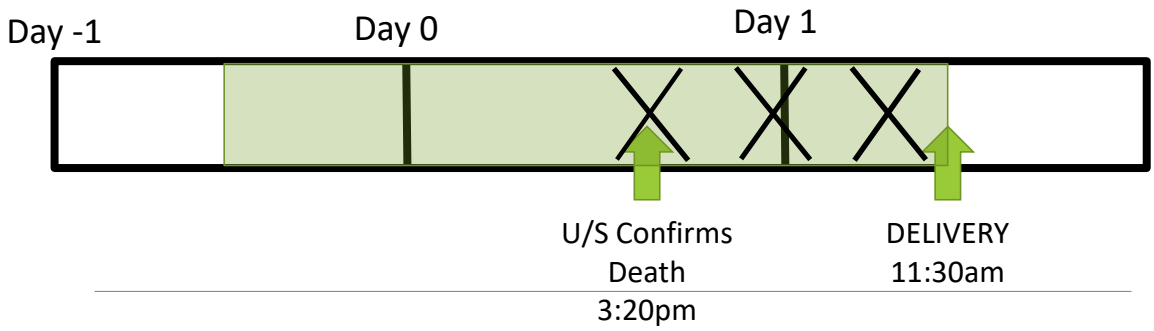
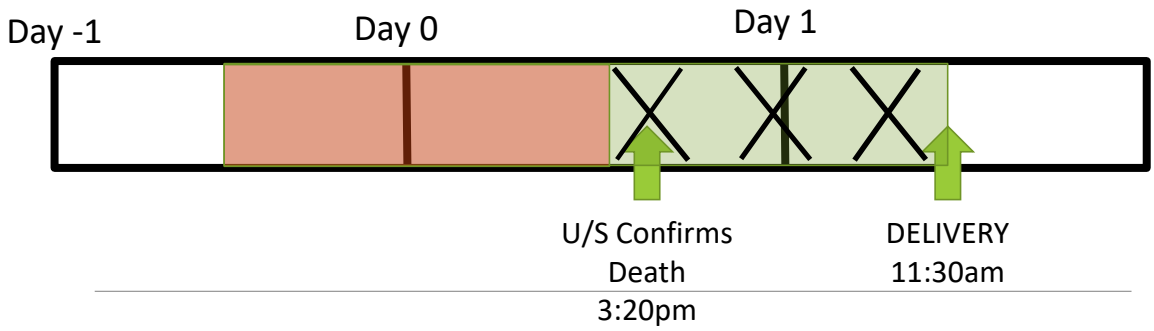
Day 1
U/S Confirms
Death
3:20pm
DELIVERY
11:30am


Day -1
Day 0
Day 1
U/S Confirms Death 3:20pm
DELIVERY 11:30am


Day -1
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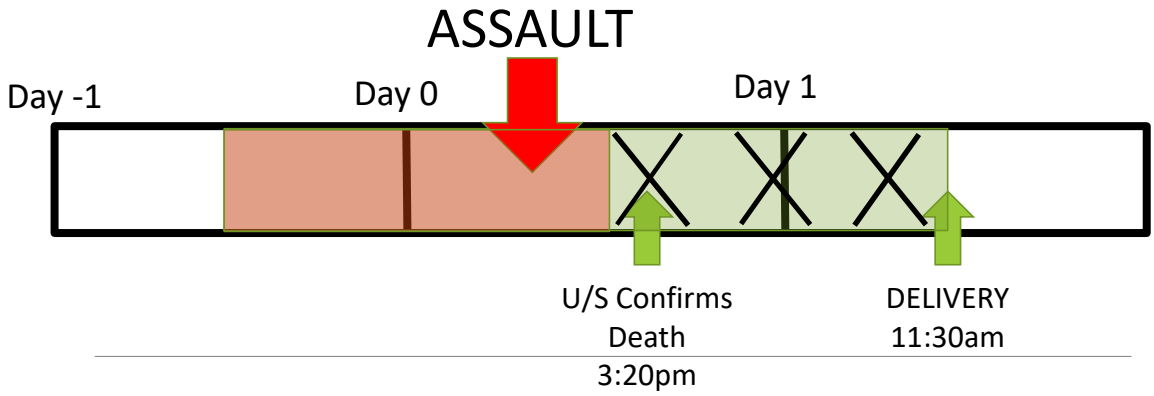
Day 1
U/S Confirms Death 3:20pm
DELIVERY 11:30am



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Gareri J, Klein J, and Koren G. *Drugs of Abuse Testing in Meconium.* **Clinica Chimica Acta** (2006) 101-111.

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Mechanisms of cerebral edema in abusive head trauma

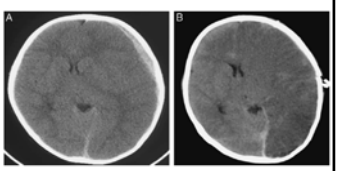
Rudy J Castellani, Ashley Rose Scholl, Carl J. Schmidt

Disclosures

- The speaker has no conflicts of interest to disclose

Introduction

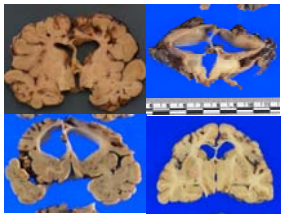
- Brain swelling in the acute phase of SBS/AHT is often pronounced and proceeds rapidly
- Asymmetrical hemispheric hypodensities ("Big Black Brain") suggests a level of complexity
- "The pathophysiological mechanisms…remain unknown."
  - Costine-Bartell et al, *J Neurotrauma* 2019;36:815-833

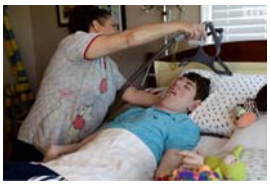


Duhaime and Durham. Progress in Brain Research 2007;161:293-302

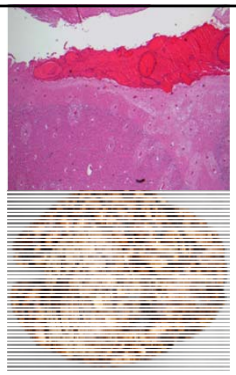
Introduction

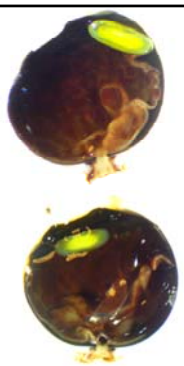
- Long term sequelae are often extensive among survivors of SBS/AHT, with widespread ischemic brain injury

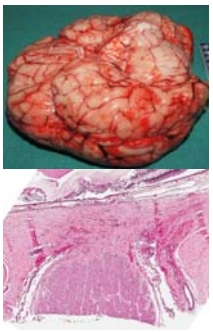


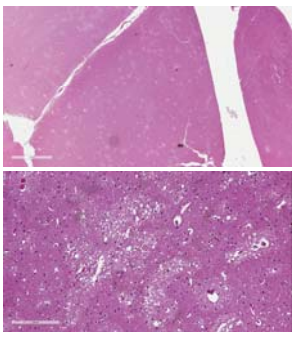


From: *The Daily Times*, Blount County, Tennessee









Methods

- Case material
  - 16 decedents
    - 9 deaths due to homicidal blunt force trauma
      - Age range 2.5 months to 16 months
      - Survival from 0 to 38 hours
    - 7 deaths due to asphyxia
      - Age range 0.5 months to 6 months
      - All decedents found dead
  - Autopsies including brain examination (gross and microscopic) performed in all cases

Methods

- Formalin-fixed, paraffin embedded sections with H&E staining
- Immunohistochemistry
  - IgG
  - Albumin
  - SUR1
  - Trpm4
  - Aquaporin 4
- Rationale
  - IgG and albumin - microvascular injury
  - SUR1 and Trpm4 work in concert to form a nonselective cation channel that upregulates in hypoxia, ischemic stroke, traumatic brain injury – contributing to oncotic edema
  - Aquaporin 4 is expressed in terminal astrocytic processes and facilitates water transport into and out of the central nervous system

HHS Public Access

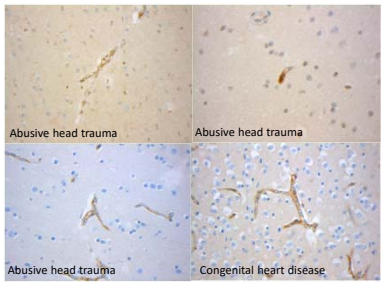
Author manuscript

Sur1-Trpm4 Cation Channel Expression in Human Cerebral Infarcts

Age (months)	Cause of death	Duration of survival	SDH
12	Blunt force trauma	12	Y
12	Blunt force trauma	0	Y
4	Blunt force trauma	?	N
12	Blunt force trauma	0	Y
1	Asphyxia	0	N
16	Blunt force trauma	0	N
6	Asphyxia	0	N
4	Blunt force trauma	48	Y
2.5	Blunt force trauma	0	Y
11	Blunt force trauma	36	N
1	Asphyxia	0	N
0.5	Asphyxia	0	N
0.7	Unknown	0	N
1	Blunt force trauma	24	Y
1	Asphyxia	0	N
5	Asphyxia	0	N
10	Complications of prematurity	0	N
3	Unknown	0	N
3	Asphyxia	0	N
0	Congenital heart disease	2	N

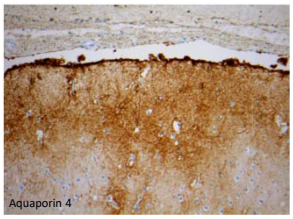
Results

- SUR1 – equivocal
- Trmp-4 - no differences

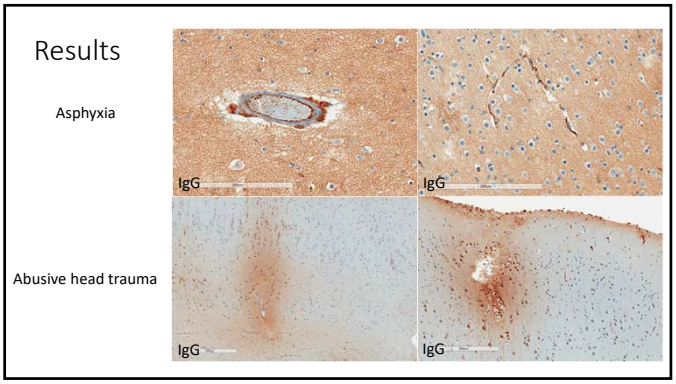


Results

- Aquaporin 4 – no differences

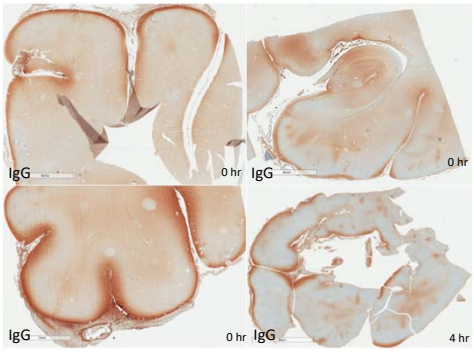


Results



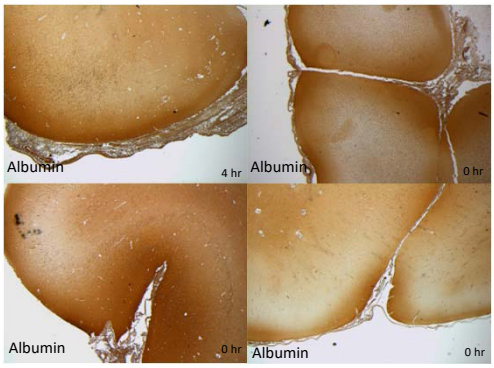
Results

Abusive head trauma



Results

Abusive head trauma



	Subpial, perivascular IgG	Subpial, perivascular albumin	SUR-1-Trpm4 up regulation
Blunt force trauma with subdural hematoma	+++	+++	+/-
Blunt force trauma without subdural hematoma	+	+	+/-
Asphyxia	+/-	+/-	+/-

(Breach of the blood brain barrier appears to precede channelopathy)

Conclusions

- Pathophysiology of brain injury in AHT/SBS is unknown, and not adequately explained by transient global ischemia, increased intracranial pressure, or traumatic axonal injury
- Evidence of SUR1-Trmp4 ion channel up regulation was equivocal; no evidence of aquaporin-4 involvement.
  - Process likely too rapid for channelopathy as a primary process
- Subpial and perivascular IgG, albumin suggest microvascular injury or dysfunction beyond bridging vein rupture
  - Structural damage?
  - Vasospasm?

The Autopsy Pathologist and the Extra Corporeal Membrane Oxygenation (ECMO) Related Autopsy

ABRAHAM T. PHILIP M.D., CASSIE BOGGS M.D.
& CHRISTOPHER GULLEDGE M.D. M.S
(WITH ASSISTANCE FROM CARA ROLFE PH.D.)
COBB COUNTY MEDICAL EXAMINER'S OFFICE
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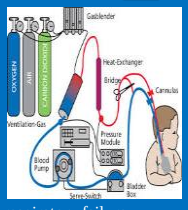
It Started with a Little Hope

- **Year:** 1974; **Place:** Orange County Medical Center, (OCMC) CA
- **Prologue:** A pregnant woman from Baja, Mexico, with aspirations to offer her offspring a better life, crossed the border & headed for L.A.
- She went into precipitate labor and delivered a baby.
- **Event:** Baby developed severe meconium aspiration pneumonia with very dismal prognostic chances.
- Robert Bartlett, a thoracic surgeon at OCMC, wheeled an ECMO machine from his lab and hooked the baby to the machine.
- **Outcome:** The baby survived and was named Esperanza or "Hope" in Spanish by the hospital nurses.

Wolfson PJ : The Development and Use of Extracorporeal Membranes in Neonates; Ann Thorac Sug 2003; 76:S 2224-9.

As always a successful event has many claimants, but failures have none



- Claimants to being progenitors of ECMO:
  - 1944 – Artificial kidney developers
  - 1953 – Gibbon – first open heart surgery
  - 1965 – Raskind bubble oxygenator – to support a neonate dying of respiratory failure
  - 1969 – Dorson – cardiopulmonary bypass
  - 1970 – Baffles – support adult with post traumatic respiratory failure
  - In 1971, Donald Hill, a San Francisco Thoracic Surgeon, had used an ECMO on a patient with ARDS

Anecdotal Success to Evidence Based ECMO Use

- Report of NIH sponsored multi-institutional prospective randomized controlled study published in JAMA 1979
  - 90 patients – mostly respiratory conditions randomly assigned to conventional medical therapy or ECMO - Prematurely stopped because 90% mortality in both groups
- Robert Bartlett – 1984 and 1986 – Hosp. Practice & Ann. of Surgery
  - 100 cases of infant on ECMO – 90% predicted mortality, 75% recovered
  - Are baby lungs different, better at self repair, or early Rx start
- University of Michigan's 1992 " Randomized play the winner" technique –
  - 11 treated with ECMO all survived; 1 treated conventional died
- 1989 – Boston Children's study – Adaptive design
  - 19 of 20 (97%) on ECMO survival vs 6 of 10 (60%) on conventional Rx
  - Criticized by readers, NIH to World Medical Association, Helsinki

Ave, Cesar, morituri te salutant!*
(Hail, Cesar, those who are about to die salute you!)

- UK Collaborative ECMO Trial Group. UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation; Lancet; 1996; 348; 75-82.
- UK Collaborative ECMO Trial Group. The UK ECMO trial follow –up to 1 year of age. Pediatrics; 1998; 101; E1.
- Efficacy and Economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multi-centric randomized controlled trial. Peek GJ, Mugford M , TiruvoipatiR et al: Lancet; 2009; 374; 1351-63.
- *Wallace DJ, Millbradnt EB & Boujoukos A: Critical Care; 2010; 14; 308.

Extracorporeal Membrane Oxygenation for 2009 Influenza A (H1N1) Acute Respiratory Distress Syndrome; JAMA; 2009; 302 (17); 1888-1895.

- Use of Bi-caval dual lumen catheter for adult veno-venous extracorporeal membrane oxygenation. Javidhar J, Brodie D, Wang D, Ann Thorac Surg; 2011; 91; 1763-9.

ECMO Indications for Cardiac Support

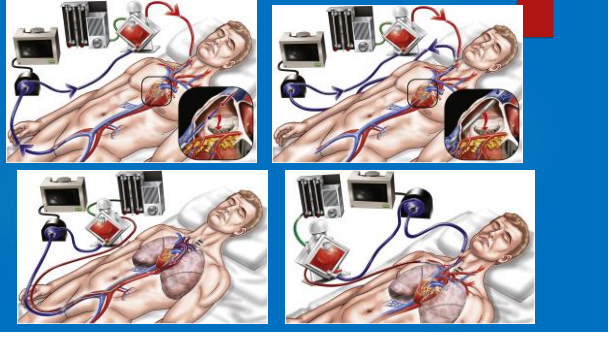
- Cardiogenic shock/ Sev. cardiac failure
  - Acute coronary syndrome
  - Cardiac arrhythmic storm refractory to other measures
  - Sepsis with prolonged cardiac depression
  - Drug overdose / toxicity with profound cardiac depression
  - Myocarditis
  - Pulmonary embolism
  - Isolated cardiac trauma
  - Acute anaphylaxis
- Other related conditions:
  - Post cardiotomy – inability to wean from cardiopulmonary bypass
  - Post heart transplant: primary graft failure or after heart lung transplant
  - Chronic cardiomyopathy
    - Bridge to longer term ventricular assist device support
    - Bridge to decision
  - Periprocedural support for high risk percutaneous cardiac intervention
  - Bridge to transplant

Makdisi G, Wang I-w: Extra corporeal Membrane Oxygenation (ECMO) a review of a life saving technology; J Thorac Dis; 2015; 7 (7); E 166 – E176.

ECMO Indications for Respiratory Support

- Acute respiratory distress syn.
  - Severe bacterial or viral pneumonia
  - Aspiration syndromes
  - Alveolar proteinosis
- Extra corporeal assistance to provide rest to lungs
  - Airway obstruction
  - Pulmonary contusion
  - Smoke inhalation
  - **Vaping Related Lung Injury***
- Lung transplant
  - Maintenance of patients after lung resection or failure of lung transplant
  - Bridge to lung transplant
  - Intraoperative ECMO
- Lung hyperinflation
- Pulmonary hemorrhage or massive hemoptysis
- Congenital diaphragmatic hernia
- Meconium aspiration

Makdisi G, Wang I-w: Extra Corporeal Membrane Oxygenation (ECMO) a review of a life saving technology; J Thorac Dis; 2015; 7 (7); E 166 – E176.



Differences between VA and VV ECMO

VA ECMO	VV ECMO
Provides cardiac support to assist systemic circulation	Does not provide cardiac support to assist systemic circulation
Requires arterial and venous cannulation	Requires venous cannulation
Bypasses pulmonary circulation	Maintains pulmonary blood flow
Decreases pulmonary artery pressures	
Could be used in Rt. V. failure	
Lower perfusion rates needed	Higher perfusion rates are needed
Higher PaO2 is achieved	Lower PaO2 is achieved
ECMO circuit in parallel to H & L	ECMO circuit in series to H & L

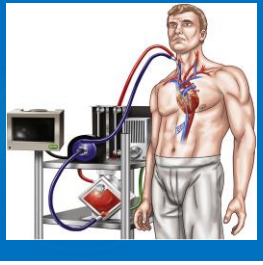
Makdisi G, Wang I-w: Extra Corporeal Membrane Oxygenation (ECMO) a review of a life saving technology.

COMING SOON TO AN AUTOPSY ★★ROOM NEAR YOU★★

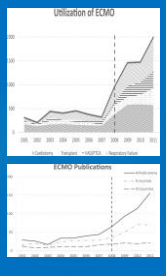
Nouveau Indications for ECMO use

- **Aeromedical evacuation of cases with acute lung injury**
  - Allan PF, Osborn EC, Bloom BB et al: The introduction of ECMO to Aeromedical evacuation; Military Med; 2011; Vol 176; p 932 – 937.
- **Awake ECMO as bridge to lung transplantation**
  - Fuehner T, Kuehn C, Hadem J et al: Extracorporeal Membrane oxygenation in awake patients as bridge to lung transplantation; Am J Respir Crit. Care Med; 2012; 185; 7; 763-768.
- **To facilitate organ recovery**
  - Shapiry IM & Muiesan P: Regional perfusion by extracorporeal membrane oxygenation of abdominal organs from donors after circulatory death: a systematic review; Liver trans; 2013; 19; 1292 - 1303.
- **Support in trauma cases**
  - Mokire JM, Kelsey M , Rut Y et al: ECMO for critically ill adults in emergency department: history current applications and future directions; Crit Care; 2015; 19; 431 – 439.

Nouveau Indications for ECMO Use



The ECMO market expected to reach US $346 m by 2024; US domination of current ECMO market 40% in 2015



- Improvements in biocompatible materials used in the devices
- "Tip to Tip" heparin coated circuit
- Heat exchanger built in to circuit or hypothermia inducer if brain trauma is suspected
- Smaller, more compatible and portable machines
- Use of software programs and feedback loops to monitor, predict and correct: anticoagulation, acid base balance and circuit issues like recirculation; pump pressures and training about safe operation and trouble shooting of all equipment

ECMO Use – Past, Present And Future

ECMO 1 (1990 -2008)	ECMO 2 (2009 – 2017)	ECMO 3 (2018 – 20??)
Sedation, paralysis	Awake Spontaneous breathing	Awake, Ambulatory
Intubated	Tracheostomy, extubate	Extubated
Resting ventilation settings	CPAP	Off Ventilator
Specialist care 24 hours -7 days a week	ICU Nurse, ECMO Support Group	Conventional care, weeks or home care for months
Lung recruitment	Watch and wait	Spontaneous breathing
Bleeding complication major	Bleeding complication minor	No anticoagulation

Bartlett R.H.: ECMO: The next ten years; Egyptian Jnl Crit Care Med; 2016; 4; 7-10

A limited glossary of ECMO acronyms

- **ALIRT**- Acute Lung Injury Rescue Team
- In the same cohort: Lung protective ventilation
- E**CCO2R** – **(ECCO2R)** Extracorporeal carbon dioxide removal
- **ECLA** – Extracorporeal Lung assist system
- **ECLS** –Extracorporeal Life Support Systems
- **ECPR or E-CPR** – Extracorporeal cardiopulmonary resuscitation
- **ELSO Registry** – Extracorporeal Life Support Organization
- **Hybrid ECMO circuit** - Double lumen cannula for VA & VA ECMO
- **VV and VA ECMO** – Veno-Venous and Veno-Arterial ECMO
- **LVAD & VAD** – Left ventricular assist device & Ventricular assist device

Continuing Training for ECMO Staff

- Training, education & certification of a broad based inter professional team including practice drills of the entire team of:
  - Registered Respiratory Therapists (RRTs) and Registered Nurses (RNs)
  - Cardiovascular perfusionists
  - Critical Care Unit (CCU) Staff physicians, Residents and Fellows
  - Cardiovascular Surgery (CVS) Staff physicians, Residents and Fellows
- ECLS/ Advances Technologies Education subcommittee
  - Continuing education by subject matter experts on a variety of topics
- Critical care interprofessional ECMO – Performance Improvement Process – Monthly meetings/ discussions

Kotani Y, Honjo O, Davey L, et al: Evolution …, estab.. of program……; Artificial Organs; 2013; 37 (1); 21 – 28.

ECMO RELATED AUTOPSIES ON HOSPITAL CASES AT CCMEO

Age / Sex Autopsy	Indication for ECMO	Type - Duration	Clinical question to be answered at autopsy	Significant ECMO related finding
75 - W Limited	Pulmonary fibrosis	VV 17 days	Appropriate location of catheter Severity of lung disease Remaining infection	Coagulopathy, not excessive
38 - M Limited	Reccurent pulmonary thomboemboli, unknown etiology	VA + V 20 days	Cause and origin of P E Pulmonary vascular disease? Pulmonary infarcts?	Partial occlusion of 2/3 SVC ports with thrombi
50 - W Complete	Pulmonary failure after gastric bypass surgery	VV 2 days	Any intracranial hemorrhage? Source of abdominal hemorrhage Lung condition Was there endocarditis?	Focal thrombosis within femoral catheter tip extending into hepatic vein with liver necrosis Multifocal cerebral white matter Abdominal hemorrhages
47 - M Limited	Acute respiratory failure with hypoxia and hypercapnia	VV 13 days	Why he decompensated rapidly while waiting for lung transplant	None
40 - W Complete	Aspirated food during intubation Developed hypoxia & hypercapnia Developed intracranial hemorrhage	VV 1 day	What cause? Unclear whether about IC He or need for intubation	Rt. Atrial mural thrombus, probably unrelated to ECMO

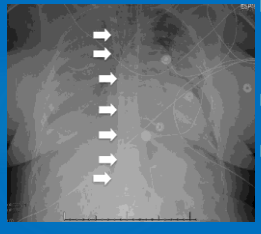
Our recommendations for developing a protocol for requesting autopsies on ECMO cases:

- Renal failure and renal injury occur in about 55% of cases. Work up of medical renal conditions involves extensive immunohistochemistry, something that is not frequently done in the usual variety Medical Examiner case work.
- Hemorrhagic complications occur in 40% of cases and evaluation of coagulopathy is in the domain of specialized Clinical Pathologist. Heparin induced thrombocytopenia leaves no organic lesion that can be identified.
- Infection is a complication in about 30% of cases and hospital bed side is the ideal place for obtaining cultures to identify organism.
- Gastrointestinal bleed is also known to occur due to stress, ischemia and secondary to the bleeding disorders. Again, an organic lesion may not be identified at autopsy.

Our approach for autopsies on ECMO cases:

- A complete autopsy should be advocated. Considering 5 to 10% of causes of death in ECMO cases could be intracranial hemorrhage, a torso only autopsy is inappropriate. Reassurance of the next of kin that all funeral options are possible after the autopsy as is routine in forensic autopsy cases.
- The ECMO cannula and lines should be left in place at the hospital. The cannula should be evaluated in situ at the start of the autopsy to identify appropriate placement and patency and rule out injuries to right ventricle.
- Signs of hemorrhage, thrombosis, ischemia and/or stroke should be sought at the immediate end organs but also peripherally including extremities and brain.
- The migration of the catheter tip to hepatic vein and secondary hepatic necrosis or infarct is a known complication and in situ dissection is the only way to document the condition.
- Malpositioning of the cannula in relation to tricuspid valve should be noted.

NOT EVERYTHING IS CLEAR CUT DESPITE THE ADVANCES IN THE TECHNOLOGY



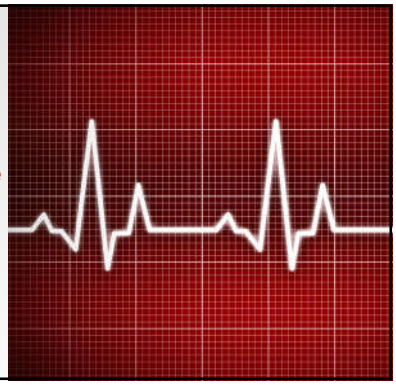
- Radiological opinions are at best the interpretations of black, white and gray scale images and have their own limitations.
- Reinforces the need for pathological / autopsy evaluation
- Co-training of pathologist with the ECMO team will help communication, formulating the proper questions and modulate the expectations from the autopsy results.

Sorry! We Cannot Connect your Vaping device to the Mechanical Ventilator Yet!

If you have any questions regarding this presentation or need additional information or want copies of the articles cited - Please feel free to contact me at 770-528-2200 or by e-mail at: abraham.Philip@Cobbcounty.org

The "Molecular Autopsy": Real Life Experience in a Medical Examiner's Office

MICHAEL BELL, M.D.
RETIRED CHIEF MEDICAL EXAMINER
PALM BEACH COUNTY, FLORIDA



1

Learning Objectives

- List the types of deaths that blood should be retained for postmortem genetic testing
- List the most common inherited cardiac channelopathies that cause sudden death
- List the most common inherited cardiomyopathies and the genes affected
- Define a genetic variant of uncertain significance (VUS) and its clinicopathologic implications

2

Disclaimer

- I have NO financial interests or conflicts of interest in any genetic testing company discussed in this presentation

3

Methods and Materials

- Decedent selection based on criteria established by NAME for postmortem genetic testing
- Expanded the selection to cases involving cardiomyopathies and aortic dissection
- Used a commercial genetic testing laboratory (Invitae)
- 2017-2019
- 37 cases tested (EDTA blood collected at autopsy)
- 5 additional cases tested from 2008-2016 (blood frozen at -85°F)

4

Postmortem Genetic Testing (Molecular Autopsy)

	Phone	Cost	TAT	URL
Invitae	800-436-3037	$475	2-3 weeks	invitae.com
Northwestern Sudden Death Collaboration	312-227-2525	free	varies	labs.Feinberg.northwestern.edu/webster
Ambry Genetics	949-900-5500	$249	4-6 weeks	ambrygen.com/clinician/postmortem
GeneDx	301-519-2100	$4580	4 weeks	genedx.com
Prevention Genetics	715-387-0484	??	??	preventiongenetics.com
Blueprint Genetics	650-452-9340	$990	3-4 weeks	blueprintgenetics.com

5

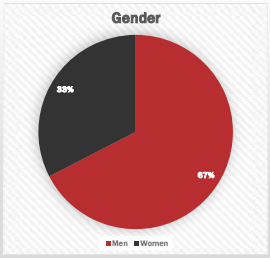
Retaining postmortem samples for genetic testing

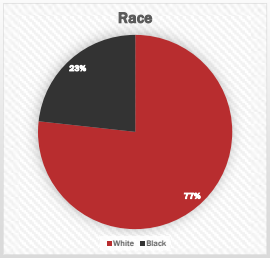
- When to retain a specimen for future testing:
  - Drowning in sober or experienced swimmer
  - Single motor vehicle accidents without mitigating factors (toxicology negative, not suicide, etc)
  - Unexplained seizure in a young person
  - Cardiomyopathy or aneurysm identified at autopsy
  - Unexplained death of a person with known family history of sudden death or inherited cardiovascular disease
  - Sudden death in a person 40 years or younger that is unexplained after a complete autopsy

Middleton O, Baxter S, Demo E, Honeywell C, Jentzen J, Miller F, Pinckard JK, et al. National Association of Medical Examiners position paper: Retaining postmortem samples for genetic testing. *Acad Forensic Pathol*, 3(2):191-194, 2013.

6

The Decedents: Gender and Race





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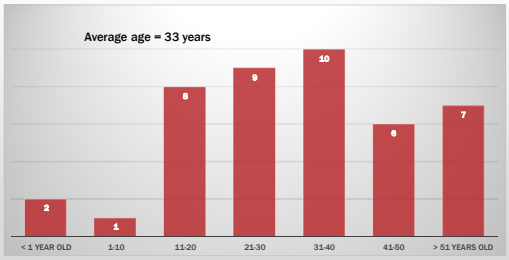
The Decedents: Age



8

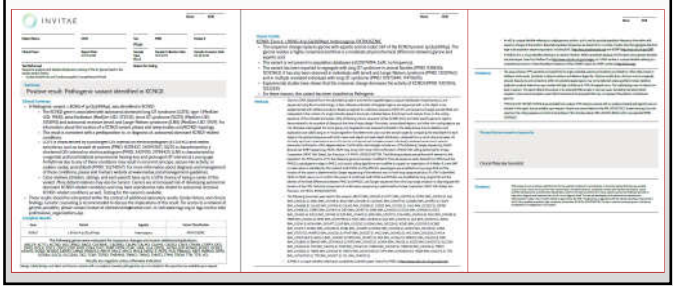
Case #1

- 29-year-old man, former heroin addict
- Sudden witnessed collapse at his desk after eating
- Unable to be resuscitated, pronounced dead at ER
- Slight cardiomegaly, 417 g
- Blood venlafaxine = 906 ng/ml (100-500 ng/ml)
- No drugs of abuse in blood or urine
- No previous known medical conditions

Pathogenic variant in KCNQ1 gene

9

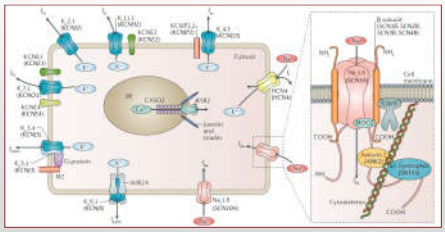
Genetic report



10

Cardiac Ion Channelopathies

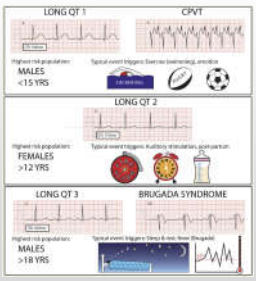
- Inherited cardiac ion channelopathies are disorders caused by mutations in ion channel genes that result in disturbances to normal heart rhythm
  - Long QT syndrome
  - Catecholamine Polymorphic Ventricular Tachycardia (CPVT)
  - Brugada syndrome
  - Short QT-syndrome



11

Congenital Long QT Syndrome

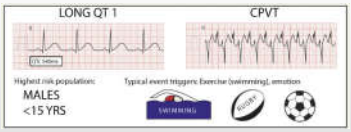
- Delayed repolarization of myocardium
- Usually autosomal dominant
- QT prolongation (QTc > 470 ms)
- Syncope, seizures, sudden death
- Triggers include exertion, swimming, emotion, sudden auditory stimuli, postpartum
- Up to 5-10% die suddenly as a sentinel event



12

Catecholamine Polymorphic Ventricular Tachycardia (CPVT)

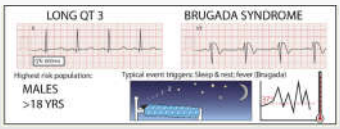
- Autosomal dominant
- Structurally normal heart
- Young men
- Normal resting ECG
- Exercise or catecholamine stress produces ventricular ectopy, syncope, SCD
- Mortality rate 30-50% by age 35
- Cardiac ryanodine receptor gene (RyR2)



13

Brugada Syndrome

- Ventricular arrhythmia
  - Syncope, aborted cardiac arrest, SCD
- Usually men
  - Common cause of sudden death in Thailand, Philippines, Japan in men under 50 years
- Can occur at any age
  - Average age is 41 years
- Autosomal dominant in 50% of cases
- Structurally normal heart



14

Autopsy Negative Sudden Cardiac Death (SCD)

- A negative autopsy is NOT a phenotype
- Postmortem genetic testing of individuals who die suddenly and have a phenotypically normal heart will be positive in 25-30% of cases
  - 15% Long-QT syndrome
  - 10% Catecholamine Polymorphic Ventricular Tachycardia (CPVT)
  - 3% Brugada syndrome

15

Case #2

- 44-year-old woman
- Found dead, seated at home by her daughter
- Active lifestyle, no alcohol or drugs
- Heart = 416 grams
- Blood toxicology negative

Pathogenic variant in DSP gene

16

Case #2

- DSP gene
  - Autosomal dominant arrhythmogenic right ventricular cardiomyopathy
  - Dilated cardiomyopathy with wooly hair, keratoderma, and tooth agenesis
  - Autosomal dilated cardiomyopathy with wooly hair and keratoderma (Carvajal syndrome)
- Other genes associated with Arrhythmogenic right ventricular cardiomyopathy
  - RYR2
  - DSC2
  - DSG2

17

Case #3

- 14-year-old girl
- Witnessed collapse while walking in school hallway'
- PEA, taken to ER where she died
  - Chest radiography showed cardiomegaly
  - Chest CT showed dilated RA, slightly dilated LA,LV
- Complained of dyspnea during competitive cheerleading
- Heart = 390 grams
- Toxicology was negative
- 15-year-old brother

18

Case #3

Pathogenic variant in TNNI3 gene

19

Case #4

- 88-year-old woman
- Seen in the ER complaining of hip pain after she fell at home and discharged with Tramadol
- History of atrial fibrillation, mitral insufficiency, congestive heart failure with automatic cardioverter/defibrillator (AICD), previous AV node ablation
- History COPD, Type 2 diabetes mellitus, CVA, macular degeneration
- Returned to hospital with altered mental status, diagnosed with hip fracture, ?tramadol overdose
- Deteriorated clinically, transferred to hospice where she died

20

Variant of Uncertain Significance (VUS) in GLA gene

21

Variant of Uncertain Significance (VUS)

- A variant that cannot be classified as pathogenic nor benign
- A variant of uncertain significance should not be used in clinical decision making

22

Results

- Of the 32 cases tested,
  - 8 (25%) had recognized pathogenic variants
  - 17 (53%) had genetic variants of uncertain significance
  - 7 (22%) showed no genetic mutations
- In 17 cases (53%), there was a correlation between the clinical and/or pathological findings found in the decedent and that expected based on the affected gene found during the molecular autopsy.

23

Summary

- We find postmortem genetic testing is affordable and helps to corroborate the clinical and pathological findings in individuals who die from heritable cardiovascular disease.

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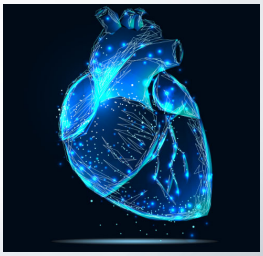
USE OF MOLECULAR AUTOPSY IN CASES OF SUSPECTED ARVC

KENNETH SNELL, MD
KRISTEN DE BERG, MS MS CGC

SANFORD HEALTH

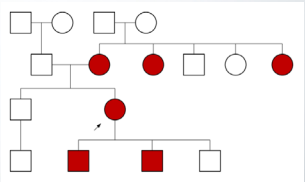
OBJECTIVES

- Case examples
- Background
  - ARVC
  - Molecular autopsy
- Molecular autopsy screen



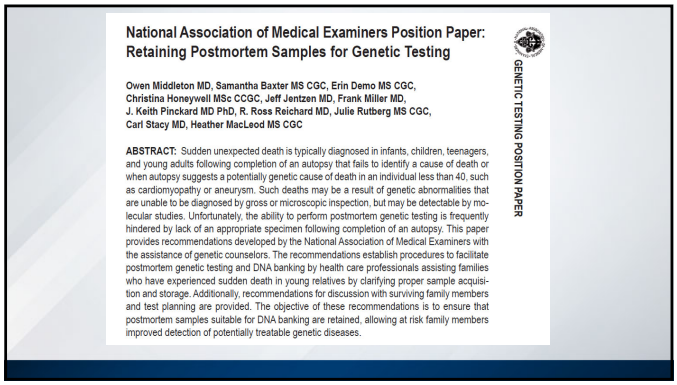
ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

- ARVC is an inherited cardiac disease
- Fibrofatty replacement of the myocardium that predisposes to ventricular tachycardia and sudden death in young individuals and athletes
- Autosomal dominant inheritance



MOLECULAR AUTOPSY

- The use of genetic testing to help determine a decedent's cause of death
- NAME Position Paper (2013): Retaining Postmortem Samples for Genetic Testing
  - Good sources for testing include:
    - Blood in EDTA***
    - Cardiac tissue
    - Skin tissue
    - Formalin-fixed tissue***



National Association of Medical Examiners Position Paper: Retaining Postmortem Samples for Genetic Testing

GENETIC TESTING POSITION PAPER

Owen Middleton MD, Samantha Baxter MS CGC, Erin Demo MS CGC, Christina Honeywell MSc CCGC, Jeff Jentzen MD, Frank Miller MD, J. Keith Pinckard MD PhD, R. Ross Reichard MD, Julie Rutberg MS CGC, Carl Stacy MD, Heather MacLeod MS CGC

ABSTRACT: Sudden unexpected death is typically diagnosed in infants, children, teenagers, and young adults following completion of an autopsy that fails to identify a cause of death or when autopsy suggests a potentially genetic cause of death in an individual less than 40, such as cardiomyopathy or aneurysm. Such deaths may be a result of genetic abnormalities that are unable to be diagnosed by gross or microscopic inspection, but may be detectable by molecular studies. Unfortunately, the ability to perform postmortem genetic testing is frequently hindered by lack of an appropriate specimen following completion of an autopsy. This paper provides recommendations developed by the National Association of Medical Examiners with the assistance of genetic counselors. The recommendations establish procedures to facilitate postmortem genetic testing and DNA banking by health care professionals assisting families who have experienced sudden death in young relatives by clarifying proper sample acquisition and storage. Additionally, recommendations for discussion with surviving family members and test planning are provided. The objective of these recommendations is to ensure that postmortem samples suitable for DNA banking are retained, allowing at risk family members improved detection of potentially treatable genetic diseases.

WHEN TO COLLECT:

- At a minimum, samples should be saved from individuals 40 years of age and younger who die suddenly and unexpectedly and whose deaths remain unexplained at the completion of the autopsy.

1) Drowning, particularly in the case of a sober or experienced swimmer;
2) Single motor vehicle accidents when no mitigating factors are present (e.g., toxicology negative, favorable road conditions);
3) An unexplained seizure in a young person;
4) Cardiomyopathy or aneurysm identified on autopsy;
5) An unexplained death of an individual with a family history of sudden death or inherited heart disease, such as a cardiomyopathy, thoracic aneurysm or known genetic cardiac diagnosis;
6) All deaths that are sudden and unexplained where cause of death is not clear at autopsy.

SANFORD CHIP

The Sanford CHIP is a laboratory developed test which is clinically validated by the Sanford Medical Genetics Laboratory to return two main classes of results:

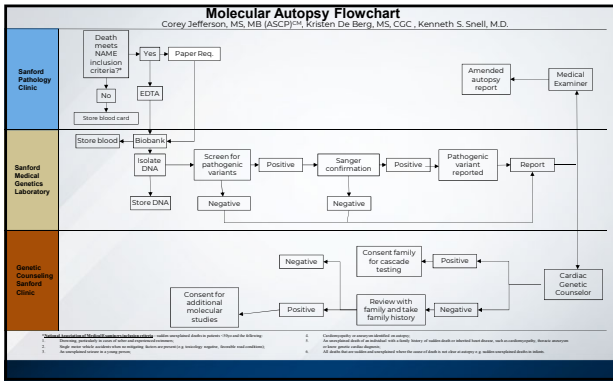
SANFORD CHIP CLINICAL RESULTS

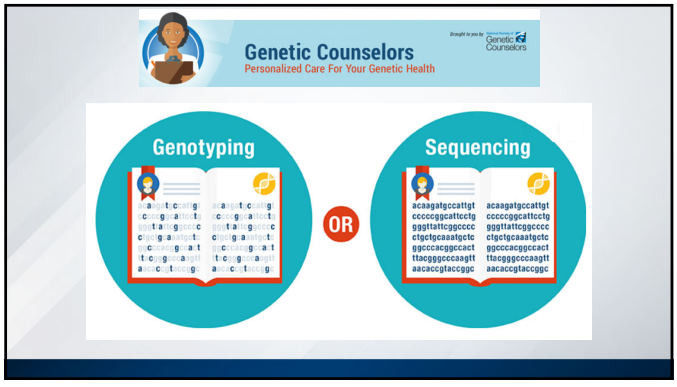
1. **PHARMACOGENETICS:** Returns genetic variants known to impact an individual's ability to metabolize certain medications.
2. **DISEASE PREDISPOSITION:** Returns genetic variants from a set of genes defined by the ACMG known to increase risk for conditions known to have medical actionability.

All positive results are confirmed with an alternate method.

Molecular Autopsy Flowchart

Corey Jefferson, MS, MB (ASCP)^{CM}, Kristen De Berg, MS, CGC , Kenneth S. Snell, M.D.

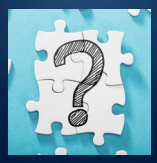




CONCLUSIONS

- Presented two cases that had appeared to have an underlying cardiac death
- Genetic testing revealed etiology and provided management guidelines for family
- Sanford has helped develop a genetic screen to help diagnose underlying hereditary cardiac conditions

QUESTIONS?



SANFORD HEALTH

2019 Salary Survey Results

William R Oliver, MD
Regional Forensic Center
Knoxville, TN

Disclaimer

This is my own stuff.

I do not speak for Knox County, TN, the Regional Forensic Center, the Mayor, or my boss.

Any opinions expressed are my own and reflect no one else's.

Methods

- Survey of the medicolegal death investigation community
- Active from 6/1/2019 – 8/3/2019
- Solicited participation from NAME membership, NAME mailinglist, and IACME broadcast, as well as mention by Path/Bio AAFS newsletter.
- 303 responses, 209 completions

- 110 questions in 16 groups
  - Some questions were respondent-specific, e.g. some for Fps, some for MDIs, etc. so nobody saw all 110 questions
- Responses were anonymized, but tokens were sent to allow stop and restart

- Survey software: Limesurvey v 3.16.1+190314
- Hardware:
  - Survey deployment: Virtual computer hosted by Bluehost, CentOS 6.4 operating system
  - Data analysis:
    - HP laptop, KDE neon OS/QubesOS,
- Statistics using R (x86_64-pc-linux-gnu, v 3.4.4)

Survey covered primary areas

- Income
- Workload
- Duties
- Satisfaction

Results posted to NAME-L

- Available for download from: www.forensicpath.biz/2019survey
- Will just hit the highlights in this short presentation

Responses

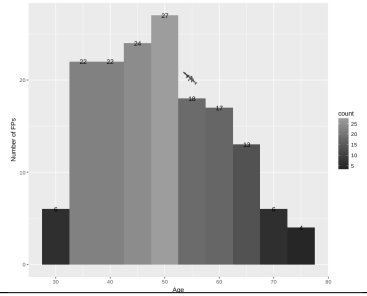
- FP n= 161
- MDI n= 70
- AA n= 12
- Admin n= 12
- Biologist n=2
- Non-MD medical (e.g. DDS) n=2
- General Pathologist n=1
- Non-pathologist MD n=1
- "Other" n=1
- ***This basically meant that only FP and MDI (and to a much smaller extent, AA and Admin) were evaluable***

Age

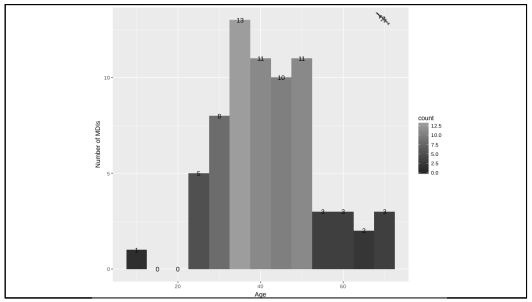
- FP Mean: 49.3, Median 49
- MDI Mean:41.6, Median 41
- AA Mean 35.8, Median 37
- Admin Mean 51, Median 53.50

FP s

- Doesn't look like we are replacing as fast as we are losing, if the respondents are representative. Each younger age group is smaller...



MDIs



Race/Sex - FP

- White n=129, 71 male, 58 female, mean age 49.5 yrs
- Black n=5, 4 male, 1 female, mean 50 yrs
- Hispanic n=7, male 4, female 3, mean 48.6 yrs
- Asian n=10, male 4, female 6, mean 46 yrs
- Mixed n=1
- Native American n=1
- Other n=5, male 5, female 0, mean 55.6

MDI

- White n=62, male 23, female 38, mean 42.3 yrs
- Black n=3 male 0, female 3, man 36.7 yrs
- Hispanic n=4, male 1, female 3, mean 37.75 yrs
- Asian n=0
- Mixed n=0
- Native American n=1
- Other n=0

AA

- White n=8, male 1, female 7, 36 yrs
- Black n=4, male 3, female 4, mean 37.75
- Hispanic n=0
- Asian n=0
- Mixed n=0
- Native Americans n=0
- Other n=0

Admin

- White n=8 male 2, female 6, age 49.2
- Black n=1
- Hispanic n=1
- Asian n=0
- Mixed n=1
- Native American n=1
- Other n=0

International Respondents

- Canada 8
- Australia 3
- New Zealand 1

Years in practice

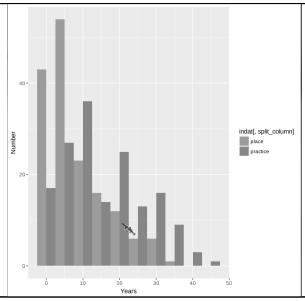
- FP
  - Mean 15.44
  - Median 13
- MDIs
  - Mean 12.6
  - Median 11.5
- AA
  - Mean 7.83
  - Median 7.5
- Admins
  - Mean 16.33
  - Median 11.5

Years in current job

- FP
  - Mean 8.53
  - Median 6
- MDI
  - Mean 9.3
  - Median 6.25
- AA
  - Mean 5.25
  - Median 3.0
- Admin
  - Mean 13.75
  - Median 10.0

But, that's a little misleading...

- For FPs, the mean years in place of 8.5 is a little misleading. If you look at the graph, the mode is **3** years, which means there's a fair amount of churning. Here's the graph, with each bar being one year…
- The red is years in place, the blue is years in practeice.



Work type - FP

- Owner of company or self employed No 131, Yes 30
- Employee of private company No 146, Yes 15
- Public employee No 32 Yes 129
- Retired - 1

Academics - FP

- Tenure track – 7
- Nontenure – 15
- Affiliate/adjunct faculty – 72
- Affiliate/adjunct non-faculty (e.g. affiliate physician) – 13
- Non-faculty employee – 1
- Academic other - 5

Income from primary job

- This is the income from the “primary” mdi-related job. It does not include side jobs, consults, etc.

FP – income from primary job

- I modified a number of entries in this group. Some folk entered 3 digits, e.g. 205 as their annual income. I assume they meant $205,000, etc.. Similarly, one person entered $221 billion. I changed that to $221,000, and another said he/she made around $3 million. I changed that to $300,000

FP

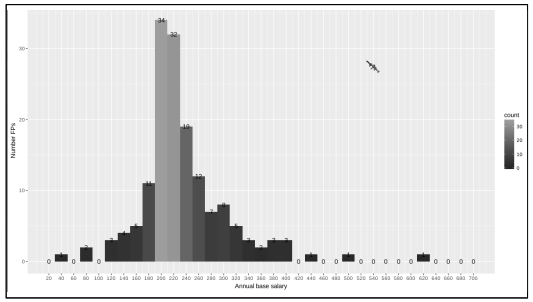
Mean $237K

Median $221K

Min $50K

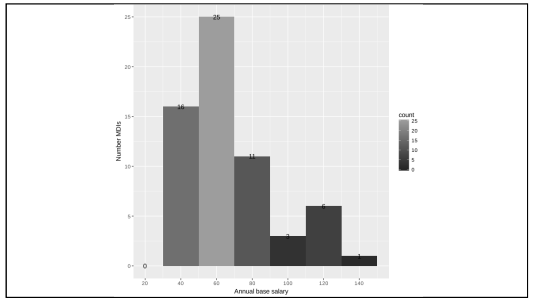
Max $630K

	vars	n	mean	sd	median	trimmed	mad	min	max	range	skew	kurtosis
X1		154	237.56	73.39	221	230.41	42.25	50	630	580	1.57	5.64



MDI

- Min $3000
- Median $58,500
- Mean $61,950
- Max $136,000



AA

- Min $30,000
- Median $42,000
- Mean $43,570
- Max $66,000

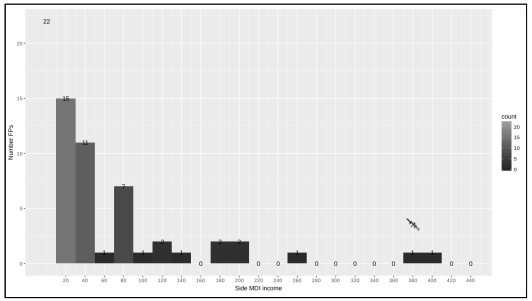
Admins

- Min $25,000
- Median $83,000
- Mean $89,970
- Max $150,000

Side income

FP

- Only people with side incomes greater than $0 are included. Since a minority of people have side income, including the zeros would be misleading.
- Min $1000, Median $25,000, Mean $58,470, Max $400,000
- n=67
- Most people, it seems, are like me – they do a occasional side consultation for a few large a year. Others seem to flip it, and do “real” jobs to maintain their bona fides, and make the big money on consults.



Total income – mdi+side+retirement+other (in thousands)

- FP

```
Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's  SD=116.9
  81.5   209.0   242.0   275.9   305.0   850.0       4
```

- MDIs

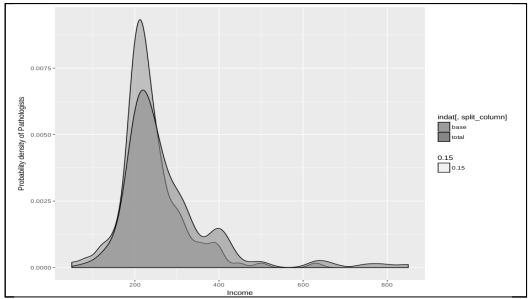
```
Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's  SD=123.3
   4.9    51.5    66.0    88.4    88.0  1062.0       1
```

- AAs

```
Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's  SD=68.8
  30.00   37.00   42.04   63.93   52.25  269.00       1
```

- Admins

```
Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's   SD=45.4
  25.00   66.75   83.00   93.14  120.00  186.00       1
```



Cost of living adjusted base income

base income, fp

- Raw:

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
   50.0   198.2   221.0   237.6   260.0   630.0       4 
```

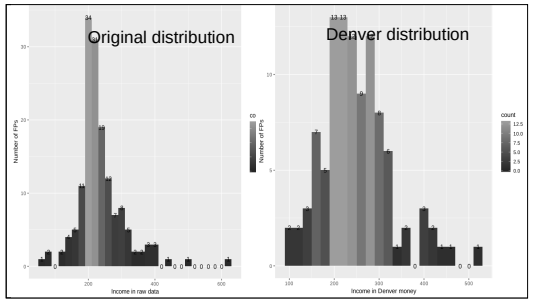
```
     vars   n   mean     sd median trimmed   mad min max range skew kurtosis
X1      1 154 237.56 73.39    221  230.41 42.25  50 630   580 1.57     5.64
```

- Denver dollars

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  94.95  198.97  239.12  249.46  289.29  524.15      55 
```

```
  vars   n   mean    sd median trimmed  mad   min    max range skew kurtosis
X1    1 103 249.46 78.17 239.12  243.51 64.38 94.95 524.15 429.21 0.78     0.97
```

- Note the difference in the number of NAs



Hours worked

FP – hours worked

- Main job – pretty homogeneous
  - Min 5
  - Median 45
  - Mean 45.8
  - Max 80
  - n=160

Type of office, primary job - FPs

- Public (governmental) nonacademic office headed by FP : 112
- University-affiliated, headed by FP 10
- Private company headed by FP: 19
- Elected lay Coroner: 7
- Appointed lay Coroner: 5
- Private consultant: 9
- Government employee that consults with offices: 1
- Multiple (move around): 1

Workload – autopsies

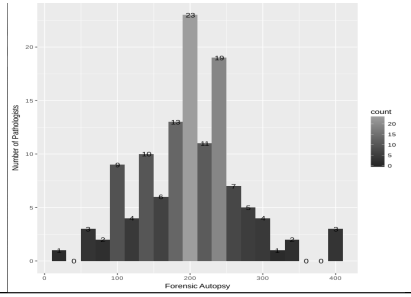
FP – primary job

- Asked about:
  - Full forensic autopsies
  - Forensic limited dissections
  - Forensic external exams
  - Private/hospital autopsies
  - Private/hospital limited dissections
  - Private/hospital externals

Forensic full autopsies per year

- Summary data

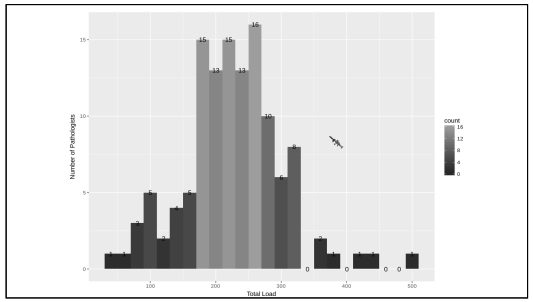
```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.  SD=69.9
   25.0   162.5   200.0   203.3   250.0   400.0
```



Total Load

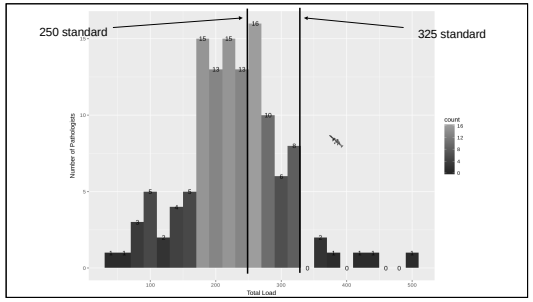
- Calculated as:
- Autopsies =1, limited dissection = 0.5, external = 0.2

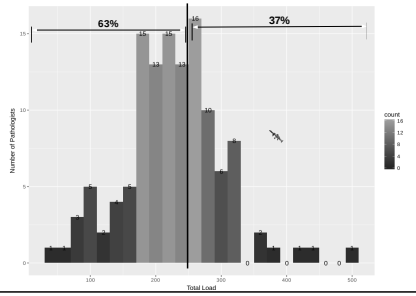
```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
   37.0   185.0   228.0   228.4   270.0   506.5
```



NAME accreditation standards

- Greater than 250, phase I
- Greater than 325, phase II
- The average is just below the 250 standard, at 228.4
- Approximately 63% of respondents were below the 250 limit, and 37% were above it.
- Approximately 5% were above the 325 limit





Pay per autopsy

Min. 1st Qu. Median Mean 3rd Qu. Max. SD= 464.81
554.5 829.2 978.7 1119.4 1242.3 2739.7
(Without outliers)

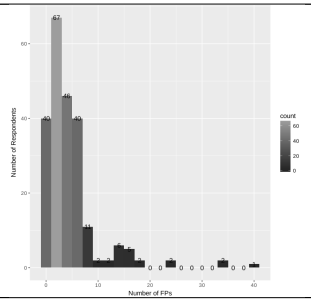
- In general, we are paid around a grand per autopsy. There are a couple of big outliers, primarily by people who do something else for most of their money. The outlier on the other side is someone who said they made $3000 per year, and performed 210 autopsies.
- For instance, here in Knoxville, I do about 330 autopsies per year, and get paid about $220K, for a payment per autopsy of $666 per autopsy (the job of the Beast!)

Number of FPs

FPs

- Most offices have 4-5 Fps. Same issue with the outliers - one person said there were 40.

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
  0.000   2.000   4.000   5.069   6.000  40.000      76
```



Do you do private consultations

- FP - Yes 36, No 2, NA 119 (presumed to be no/ skipped)
  - Last year, 67 said yes, so this number may be bogus
- No responses from MDI,AA,Admin

Private consultation structure

- Incorporated?
  - No 17
    - 1 in process of doing LLC but not there yet
  - Yes 24
    - S corp 6
    - LLC/PLLC 12
    - PA 1
    - PLC 1
    - PC 1
  - NA 119

Hourly charge, by case type, for cases that are **not** pro bono

- Criminal defense

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
0.0	350.0	450.0	427.1	512.5	750.0	134

- Indigent defense

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
0.0	200.0	350.0	317.5	450.0	700.0	138

- Criminal prosecution

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
0.0	350.0	400.0	415.9	450.0	700.0	136

- Civil defense

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1	400	450	518	550	2000	133

- Civil plaintiff

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
3.0	400.0	450.0	506.1	550.0	2000.0	133

- NGOs

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
0.0	0.0	350.0	244.4	400.0	700.0	140

Do you do locums?

- FP – Yes 16, No 25, NA 119
- NA all others

Ru happy?

- Asked a large series of questions about satisfaction.

RU happy with your life right now

- 10 point scale 1 = happy happy, 10 = sad sad
- FP

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.000	2.000	2.000	2.669	3.000	8.000	30

- MDI

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.000	2.000	3.000	3.712	5.000	10.000	18

- AA

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.00	1.75	2.00	2.00	2.25	3.00	4

- Admin

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.0	2.0	2.0	2.9	3.0	7.0	2

Ru happy with job?

- FP

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.0	2.0	3.0	3.4	4.0	10.0	30

- MDI

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.000	3.000	4.000	4.585	6.000	10.000	17

- AA

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.00	2.75	4.50	5.00	8.00	9.00	4

- Admin

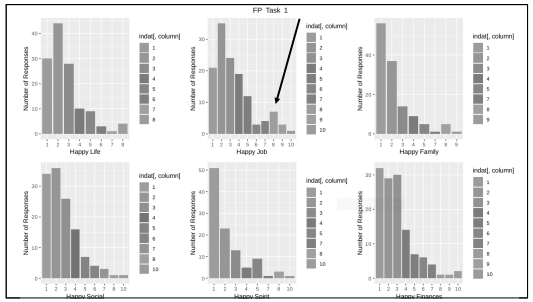
Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
1.00	2.00	3.00	3.00	3.75	6.00	2

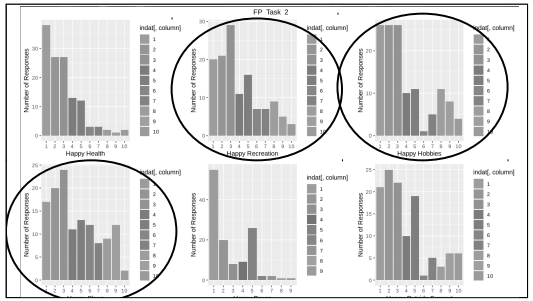
Asked a large number of specifics

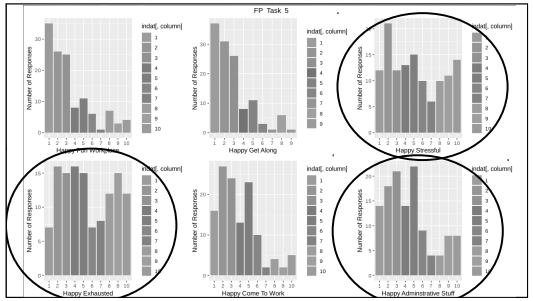
- Facilities, relationship with boss, etc. Please see URL for specifics

FP

- FP s are generally happy.
- The high scorers (more unhappy) are
  - Exhaustion, stress, sleep, time for hobbies and/or recreation
  - Support from outside agencies (e.g. Sheriff, DA s, etc)
  - Support from superior agency (e.g. DHHS)
- Interestingly, there a bimodal distribution for “happy with my job” with one peak at around 2.5 and the other (smaller peak) around 8.


FP Task 1
Number of Responses
index[, column]
Happy Life
Happy Job
Happy Family
Happy Social
Happy Spirit
Happy Finances


FP Task 2
Number of Responses
index[, column]
Happy Health
Happy Recreation
Happy Hobbies


FP Task 5
Number of Responses
index[, column]
Happy Get Along
Happy Stressful
Happy Exhausted
Happy Come To Work
Happy Administrative Stuff

The most important predictor of happiness was relationship with boss

- This is consistent with studies done in other places
  - Among physicians, key predictors are relationship with supervisor/command, professional growth, and feeling that what you are doing is appreciated.
  - Salary was 21st out of 22

Proportion of variance explained by model: 90.59%

Relative importance metrics:

Support from boss	0.103875065
Love coming to work	0.093116673
Workplace fun	0.070053044
Race	0.070618862
Support from superior agency	0.069174494
Regulation	0.062904455
Treated with respect at work	0.050291560
Marital	0.049213006
Time for hobbies	0.037106387
Get along at work	0.034360609
Academic affiliation	0.033901708
Time for recreation	0.033087347
Public vs Private employee	0.033576276
Coroner v ME v consultant	0.029282217
Facilities	0.027192269
Overworked v Bored	0.025017313
Personal office space	0.020542673
Enough sleep	0.018138664
Job Position (Chief v staff)	0.015555586
Religious	0.013503895
cost adjusted primary income	0.009276948
Admin v Pathologist in charge	0.006087704

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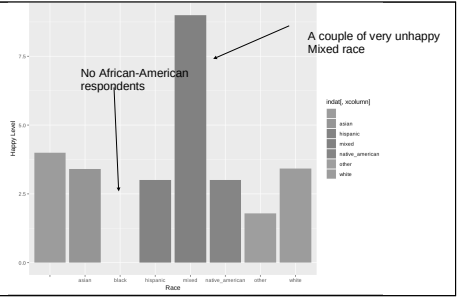
Religious	0.013503895
cost adjusted primary income	0.009276948
Admin v Pathologist in charge	0.006087704

Race - misleading result

- No respondents in the “black” classification answered the “are you happy at your job” question. Thus, the column is blank.
- The first column is people who didn’t answer the race question but answered the happy job question.
- The results are weighed by a very small number of very unhappy self-identified “mixed.”
- These results are not normalized by n. This would be different if it were



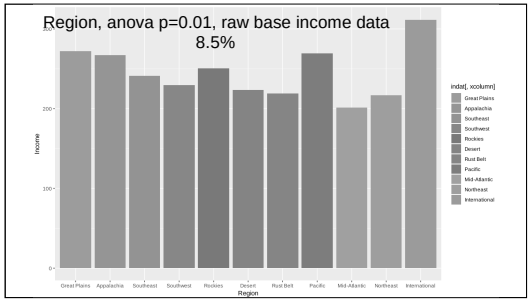
Similarly, asked a number of predictors for income

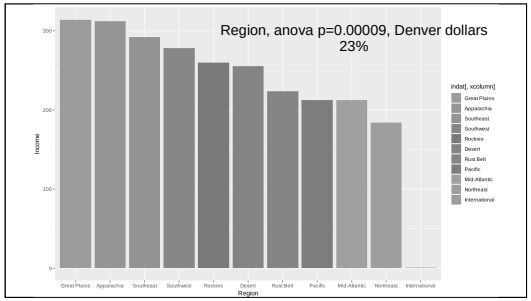
- Type of office (Coroner, ME)
- Region of country
- Population served
- Etc
- Again, please see URL for details
- Region and title (e.g. Chief, Deputy, Staff) were the most important

2018 multivariate results

Base Income

- Region: 15.0%
- Title 9.8%
- Does locums 5.5%
- Specialty certification (any) 5.49%
- Experience: 5.2%
- Employer type: 4.9%
- Office type:3.2%
- Does consults 3.1%
- FP certification 2.7%
- Office size 2.4%
- Race 2.4%
- Sex 2.3%
- System size 1.9%
- Age 1.6%





Once again, for the full data analysis...

- 22 installments
- Go to www.forensicpath.biz/2019survey

ISO 17020 ACCREDITATION & NAME ACCREDITATION

OUR EXPERIENCE AND REMOVING THE MISCONCEPTIONS

- Barbara C. Wolf, M.D., Districts 5 & 24 Medical Examiner's Office, FL
- Sally S. Aiken, M.D., Spokane County Medical Examiner's Office, WA
- Amy C. Gruszecki, D.O., American Forensics, Mesquite, TX
- Ponni Arunkumar, M.D., Cook County Medical Examiner's Office, IL
- Roger A. Mitchell, Jr., M.D., Office of the Chief Medical Examiner, Washington, DC

ISO 17020 ACCREDITATION & NAME ACCREDITATION

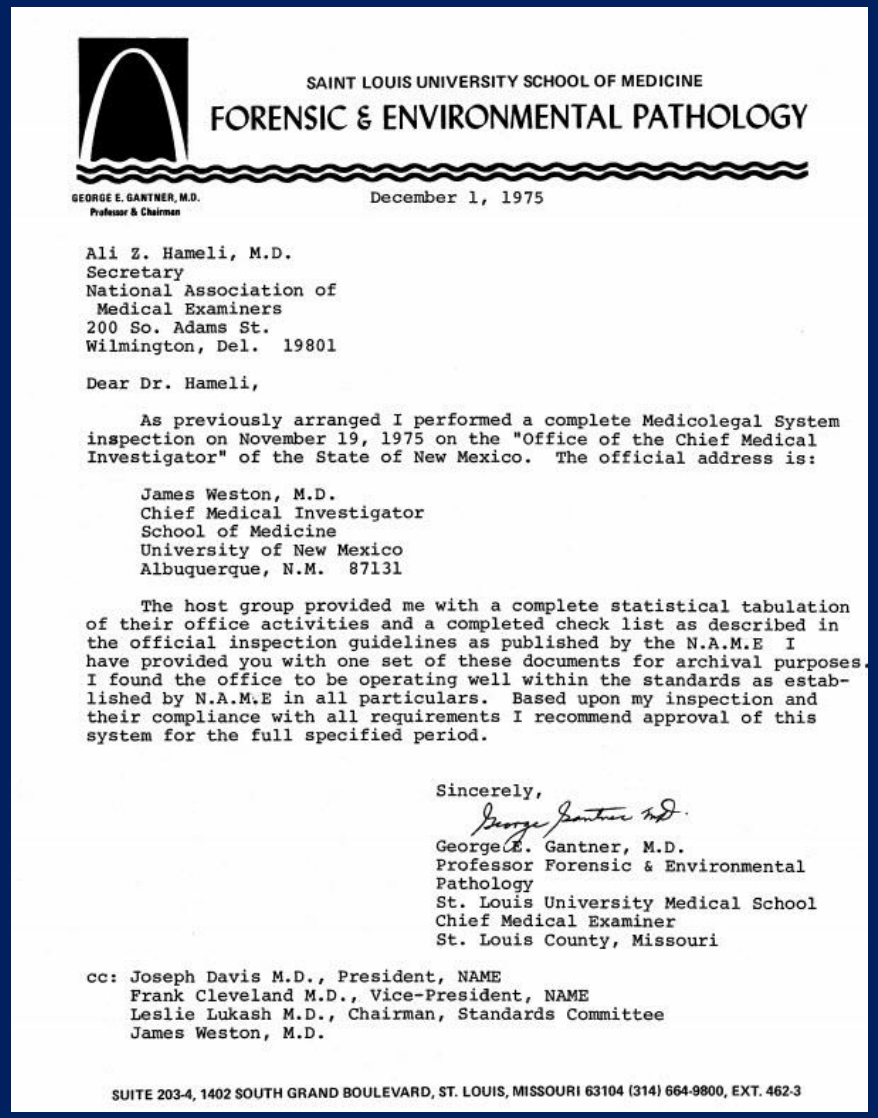
Where we are and how we got here

Barbara C. Wolf, M.D., Districts 5 & 24 Medical Examiner's Office, FL

THE EARLY DAYS

- 1976: First NAME Accreditation certificates awarded
- 1977: Inspection and Accreditation became a NAME program.
- 2009: Annual inspector training was instituted.

FIRST NAME CORE INSPECTION



SAINT LOUIS UNIVERSITY SCHOOL OF MEDICINE
FORENSIC & ENVIRONMENTAL PATHOLOGY

GEORGE E. GANTNER, M.D.
Professor & Chairman

December 1, 1975

Ali Z. Hameli, M.D.
Secretary
National Association of
Medical Examiners
200 So. Adams St.
Wilmington, Del. 19801

Dear Dr. Hameli,

As previously arranged I performed a complete Medicolegal System inspection on November 19, 1975 on the "Office of the Chief Medical Investigator" of the State of New Mexico. The official address is:

James Weston, M.D.
Chief Medical Investigator
School of Medicine
University of New Mexico
Albuquerque, N.M. 87131

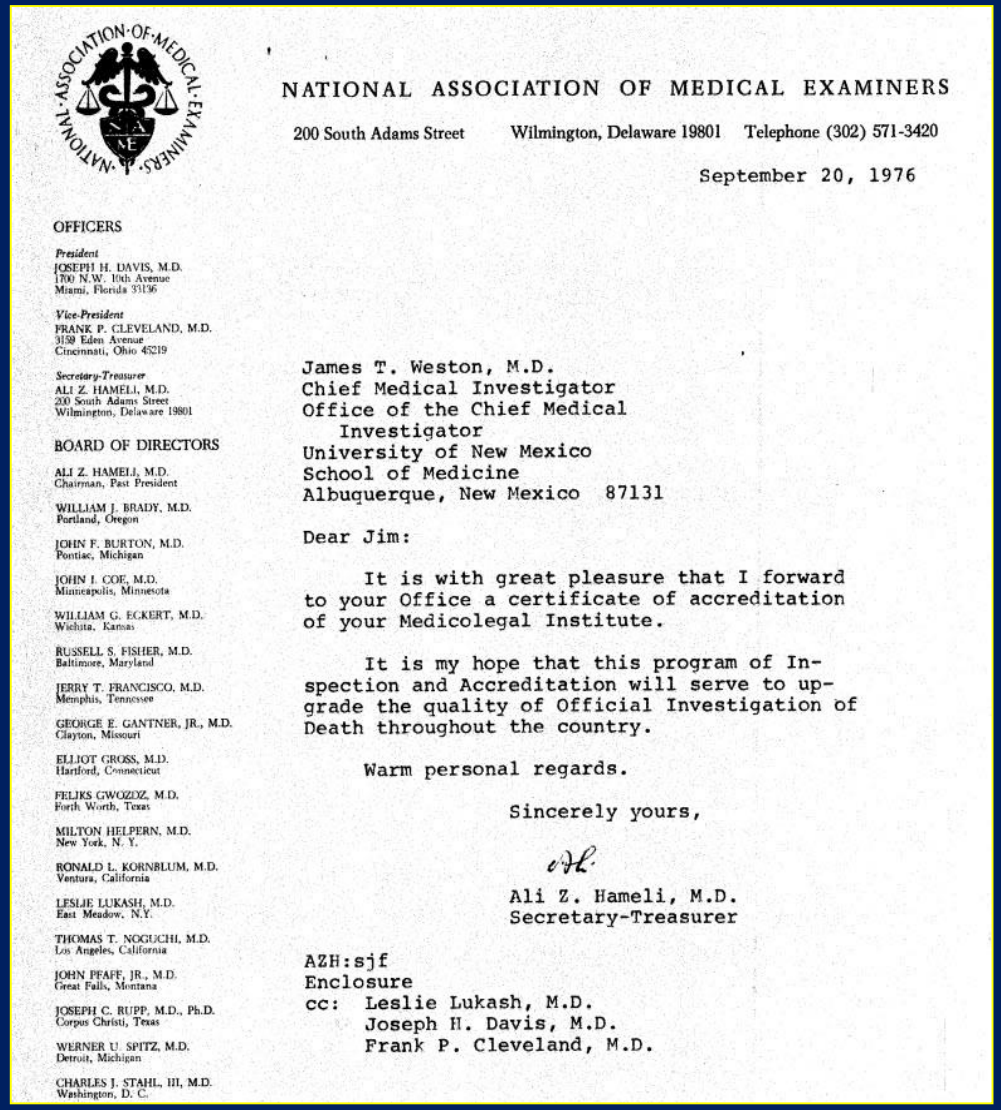
The host group provided me with a complete statistical tabulation of their office activities and a completed check list as described in the official inspection guidelines as published by the N.A.M.E I have provided you with one set of these documents for archival purposes. I found the office to be operating well within the standards as established by N.A.M.E in all particulars. Based upon my inspection and their compliance with all requirements I recommend approval of this system for the full specified period.

Sincerely,

George E. Gantner, M.D.
Professor Forensic & Environmental Pathology
St. Louis University Medical School
Chief Medical Examiner
St. Louis County, Missouri

cc: Joseph Davis M.D., President, NAME
Frank Cleveland M.D., Vice-President, NAME
Leslie Lukash M.D., Chairman, Standards Committee
James Weston, M.D.

SUITE 203-4, 1402 SOUTH GRAND BOULEVARD, ST. LOUIS, MISSOURI 63104 (314) 664-9800, EXT. 462-3



NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

200 South Adams Street Wilmington, Delaware 19801 Telephone (302) 571-3420

September 20, 1976

OFFICERS

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1700 N.W. 10th Avenue
Miami, Florida 33136

Vice-President
FRANK P. CLEVELAND, M.D.
3159 Eden Avenue
Cincinnati, Ohio 45219

Secretary-Treasurer
ALI Z. HAMELI, M.D.
200 South Adams Street
Wilmington, Delaware 19801

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Detroit, Michigan

CHARLES J. STAHL, III, M.D.
Washington, D. C.

James T. Weston, M.D.
Chief Medical Investigator
Office of the Chief Medical
Investigator
University of New Mexico
School of Medicine
Albuquerque, New Mexico 87131

Dear Jim:

It is with great pleasure that I forward to your Office a certificate of accreditation of your Medicolegal Institute.

It is my hope that this program of Inspection and Accreditation will serve to upgrade the quality of Official Investigation of Death throughout the country.

Warm personal regards.

Sincerely yours,

Ali Z. Hameli, M.D.
Secretary-Treasurer

AZH:sjf
Enclosure
cc: Leslie Lukash, M.D.
Joseph H. Davis, M.D.
Frank P. Cleveland, M.D.

PURCHASE ORDER

THE UNIVERSITY OF NEW MEXICO

ALBUQUERQUE, NEW MEXICO 87131
Area Code 505 Phone 277-2036

PURCHASE ORDER NUMBER .5 05039

TO:
National Association of Medical Examiners
200 South Adams Street
Wilmington, Delaware 19801

SHIP TO ADDRESS BELOW
THE UNIVERSITY OF NEW MEXICO
School of Medicine
Shipping & Receiving
915 Stanford N.E.
Mark for: Medical Investigator

ALBUQUERQUE, NEW MEXICO 87131

DATE	ACCOUNT NUMBER	DEPARTMENT	CHARGE FISCAL YEAR ENDING	REQUISITION NUMBER
4/22/75	087-530-020	Medical Investigator/Larrichio		M19033

PLEASE PROVIDE THE FOLLOWING:	PRICE	EXTENSION
Payment to the National Association of Medical Examiners for inspection accreditation of the medicolegal investigative system.		100.00

1/26/76
Gentlemen:
The inspection of the New Mexico system has been completed and we request now the remittance of $100.00 be submitted to this Office as soon as possible.
Thank you for your kind consideration.

Ali Z. Hameli, M.D.
Secretary-Treasurer

11

INSTRUCTIONS
1. ACKNOWLEDGE ORDER, ADVISE OF SHIPPING DATE, AND MAIL ALL INVOICES TO U.N.M. COMPTROLLER'S OFFICE.
2. PURCHASE ORDER NUMBER MUST BE ON ALL INVOICES.
3. SUBMIT ORIGINAL INVOICE.
4. SUBMIT SEPERATE INVOICE FOR EACH PURCHASE ORDER NUMBER.

THE UNIVERSITY OF NEW MEXICO

Frank Montoya
PURCHASING AGENT

13A PROFESSIONAL CREDENTIALS AND PRIVILEGES

13A.1 Is licensure of the medical staff verified at the time of initial employment?	II	✓	—	—
13A.2 Does the chief medical examiner evaluate the performance of each member of the professional staff at least once each year?	I	✓	—	—

13B TRAINING AND CONTINUING EDUCATION

13B.1 Are all new personnel provided information on the written policies of the office during orientation?	II	✓	—	—
13B.2 Is each licensed professional employee required to participate in continuing education? *	II	✓	—	—
13B.3 Is there continuing education available for all medical investigators?	I	✓	—	—
13B.4 Are operators of radiologic equipment properly trained?	I	—	—	✓

* Not required under NY State Law. Staff required to list 40 hours of CME every 2 years.

NAME ACCREDITED OFFICES

- Number of accredited offices as of August, 2019:
  - 83 Fully Accredited
  - 9 Provisionally Accredited
- The population now served by NAME accredited offices is approximately 149, 857, 097.

BLUE=FULL
RED=PROVISIONAL

INTERNATIONAL OUTREACH PROGRAM

- 2005: Forensic Medicine Division of the Health Sciences Authority in the Republic of Singapore becomes first international office to be accredited by NAME.
- The I & A Committee will continue partnering with the International Relations Committee to further the NAME accreditation process on the international level.

ISO/IEC 17020 PROGRAM

- 2016: NAME entered into an agreement with ANSI-ASQ National Accreditation Board (ANAB) to develop an ISO/IEC 17020 program for medical examiner/coroner offices that seek ISO (International Organization for Standardization) accreditation, either solely or in addition to accreditation under the NAME Core program
- Ad hoc ISO Transition Committee organized to develop sample policies aimed at ISO/IEC 17020 requirements to assist offices seeking to apply for ISO accreditation

ANAB/NAME JOINT ACCREDITATIONS

- January, 2019: American Forensics, Mesquite, TX becomes first office to undergo re-accreditation inspection under the NAME Autopsy Services program jointly with assessment under ISO/IEC Standard 17020

- March, 2019: Office of the Medical Examiner of Cook County, Chicago, IL underwent inspection for re-accreditation under the NAME core accreditation program jointly with assessment under ISO/IEC Standard 17020, as well as under Standard 17025 for forensic toxicology.

THE FUTURE:

Everything that's old is new again.

ISO 17020 ACCREDITATION AND NAME ACCREDITATION

Sally S. Aiken, MD

Spokane County Medical Examiner's Office

ISO (EQUALS)

- Founded 1947 (72 years)
- 21,740 standards to date

NAME RELEVANT STANDARDS

- 9001 Quality management
- 15189 Medical Laboratories—requirements for quality and competence
- 17020 Conformity Assessment Requirements for the operation of various types of bodies performing inspections
- 17025 General requirements for the competence of testing and calibration laboratories

ISO NUMBERS?

- 16982 Ergonomics of human-system interaction-usability methods supporting human-centered design
- 17020 Conformity assessment requirements for the operation of various types of bodies performing inspections
- 17025 General requirements for the competence of testing and calibration laboratories
- 17047 Application of Braille on signage, equipment, and appliances
- 17075 Leather-Chemical determination of chromium (VI) content in leather

OF 21,740 ISO CHOICES, WHY ISO17020?

- No ISO standard is specific to Medical Examiners/Coroners
- ISO standards tend to be general, large organizations don't want to develop quality management systems for each department/function
- Developing a new ISO standards takes years, and begins with demonstration of a "market need".

ISO Translated into Plain English

ISO STANDARDS IN PLAY

9000 Series

- Quality management for businesses 1987
- Many other ISOs use elements of quality management from 9000s
- In ISO 17020, you forego quality management sections if you already have a management system compliant with ISO 9001

ISO 17025

- For competence of testing and calibration laboratories-1999 For analytical testing laboratories
- Many toxicology laboratories
- Technical requirements for correctness and reliability of tests in a laboratory. Focus on uncertainty, and analytical validation
- 17025 and 17020 have “equal weight” in the world
- Management requirements similar in 17020 and 17025

MORE OF THOSE 21,740 ISOS

ISO 15189

- Came after 17025 (2003), based on 17025 and ISO 9001
- Designed for Medical Laboratories
- Emphasizes analytical tests
- Added patient samples, acceptable turnaround, testing in medical emergencies

ISO 17020!!!!!!

- No use of instrumentation for analytical testing
- RELIANCE ON PROFESSIONAL JUDGEMENT
- Focus on impartiality, independence, confidentiality
- Similar management system as 17025 (9001)

ISO Translated into Plain English

PESKY AND QUIRKY ISO TERMS

- Inspection: examine closely, to compare against established standards. Involves examination, measurements, testing.
- Inspection: the autopsy
- Inspector: investigator who uses professional judgement at a death scene, forensic pathologist who performs autopsy
- Inspection body: Medical Examiner or Coroner's Office
- Inspection system: rules, procedures, and management for carrying out office functions

ISO 17020

NAME Core Accreditation

ISO 17020 VERSUS NAME CORE ACCREDITATION

ISO 17020

- Broader, more generic—need to fit for "bodies performing inspections"
- Quality management, Quality management, Quality Management
- Ongoing internal audits for improvement, complaint management
- Technical competence and training emphasis
- Much more expensive
- More management, no medicine

Core Accreditation

- More specific requirements: 90% of reports in 60 days, Ground faults
- 5 items in checklist on QA (A8)
  4 items on performance evaluation (G8)
- Yearly checklist completion to maintain accreditation
- All facets of operation addressed: photography, histology, facility etc.
- Less expensive
- The practice of medicine

WHY CAN'T NAME ADMINISTER NAME ACCREDITATION AND ISO ACCREDITATION?

- NAME Core Accreditation belongs to us, we make the rules
- ISO Accreditation is International—we don't make the rules
- ISO Accreditation Services: There's an ISO for that
- Accreditation bodies are accredited to ISO 17011
- Accreditation bodies are signatories to ILAC—International Laboratory Accreditation Cooperation

EXAMPLES OF ACCREDITATION BODIES

- ANAB
- CAP
- Canada: Standards Council of Canada

Private companies that are accredited to perform ISO Accreditations have a limited number of ISOs in their repertoire.

ORDER OF OPERATIONS

- ISO 17020 does not supplant NAME Accreditation
- NAME Accreditation is the foundation
- It would be difficult to achieve 17020 without Core Accreditation first
- ISO 17020 is internationally recognized and for NAME Accredited offices that want robust quality management and continual improvement

4.1-4.2 Bias and Confidentiality
5.1 Administrative Requirements
5.2 Organization and Management
6.1 Personnel
Quality Assurance and Performance Improvement
6.21-6.25 Facilities
6.2.6-6.2.12 Measurement Traceability
6.2.13-6.2.15 Computers and Defective Equipment
6.3 Subcontracting
7.1-7.1.9 Inspection Methods
7.2-7.4 Handling Inspection Items, Inspection Records, Inspection Reports and Certificates
7.5-7.6 Complaints and Appeals
Complaints and Appeals Policy
Complaint Tracking Form
8.2-8.3 Management Documentation
8.4 Management System Documentation, Control of Records
ISO 8.5- 8.8
AF Chapter 22 Internal Audit
8.6-8.7 Campobosso
ISO 8.5- 8.8

A complete set of sample ISO 17020 policies is available on the NAME website, under the Inspection/ Accreditation Tab

NAME ISO 17020 TRANSITION SUBCOMMITTEE

Commercial: Part 2

TIME THE DEVOURER OF ALL THINGS.

Metamorphoses, IX, l. 500

Practical Aspects of ISO Accreditation

Amy C. Gruszecki, MSFS, DO

ISO Accreditation

- ISO is based on documentation and chain of custody procedures
- It is applicable to many organizations -manufacturing, health care, and forensics organizations.
- In my experience very similar to a CAP inspection.

ISO Accreditation

- ISO Accreditation goes hand in hand with NAME core accreditation.
- What NAME requires for accreditation - ISO requires proof that it is being done.
- Example policies are present on the NAME website.

ISO Accreditation

- Simplified - ISO is

- saying in a procedure that you do something

- and proving up that you do it

- keeping a chain of custody.

Must demonstrate

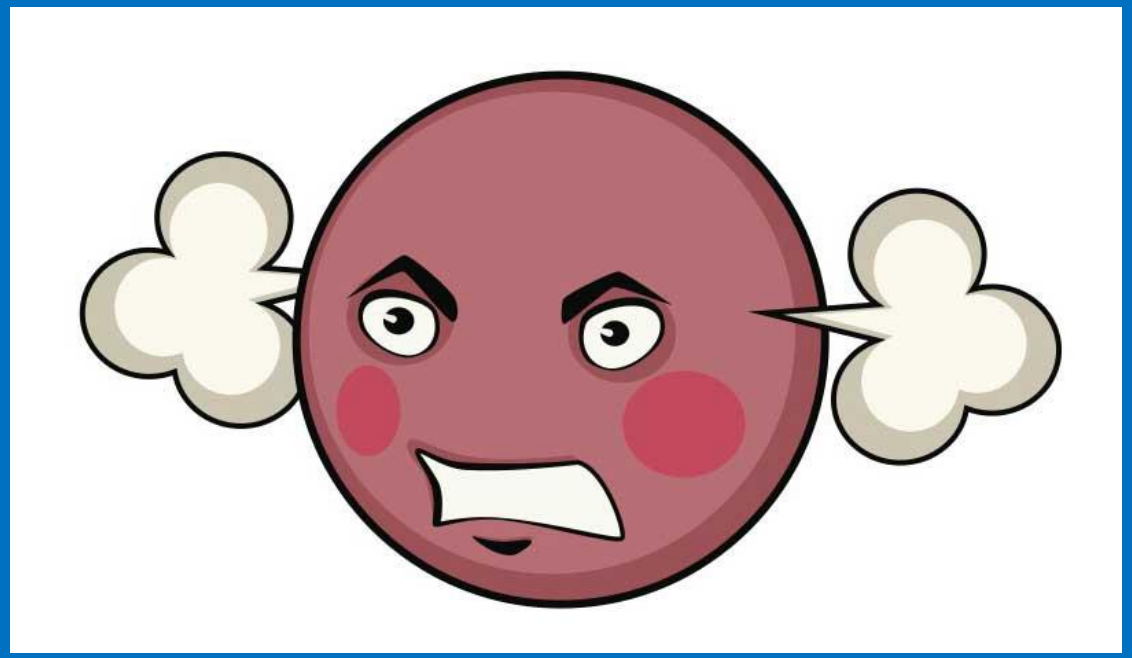
- Confidentiality
- No conflict of interest

Examples

- track the time an autopsy exam starts
- What time the body is removed from the cooler and by whom
- What time the exam ends
- when stock tissue is put away and by whom

- Easy for large organizations with a LIMS
- Smaller organizations can use paper documentation

Some points of contention



Proficiency testing

- ANAB has accepted the proficiency testing approved by NAME – The ASCP case studies (Check Samples)

Calibration

- Calibrate scales
- Rulers that are calibrated (these can be bought!)
- Calibration must be traceable (means there is a certificate).

Witnessing

- Need to observe another forensic pathologist performing an autopsy.

- Need to observe court testimony

No defined time intervals!

Resources involved

- Time
- Lots of office supplies!
- The application fees

- Can use a consultant – though not necessary.

ISO 17020 AND 17025

Cook County Medical Examiner's Office

BENEFITS OF ISO ACCREDITATION

- Uniformity of quality systems
- Internationally recognized standard of quality
- Process improvement
- Decreases mistakes
- Regulatory compliance
- Specific expectations

PROCESS TO ACCREDITATION

- In depth review of all current procedures and processes
- Compare current procedures and processes to ISO 17020 standard requirements
- Implementation of ISO 17020 requirements
- Quality Manual is essential
- Quality Manager to oversee process

PROCESS TO ACCREDITATION

- Document root cause analysis and corrective actions for non conformances
- Document management system to house SOPs, non conformances, and proficiency testing

ISO 17020 CHALLENGES

- Cost of Accreditation
- Determination of proper scope
- Extensive checklist requirements
- All requirements must be met prior to being granted accreditation. (0 deficiencies allowed)
- Requires a dedicated quality manager to oversee process
- Testing laboratories require ISO 17025 accreditation

PROCESS CHALLENGES

- NAME and ISO inspection concurrently requires extensive preparation
- ISO stresses on quality management and chain of custody
- NAME stresses on work environment and medicolegal functions of the office.

Government of the District of Columbia
OFFICE OF THE CHIEF MEDICAL EXAMINER

Preparing for Accreditation
ISO-017020:2012

Roger A. Mitchell Jr. MD

Chief Medical Examiner

District of Columbia
Office of the Chief Medical Examiner

Dual Accreditation

NATIONAL ACCREDITATION
(National Association of Medical Examiners)

TO

INTERNATIONAL ACCREDITATION
(ISO/IEC 17020:2012 Conformity assessment-Requirements for the operation of various types of bodies performing inspection)

TO

DUAL ACCREDITATION

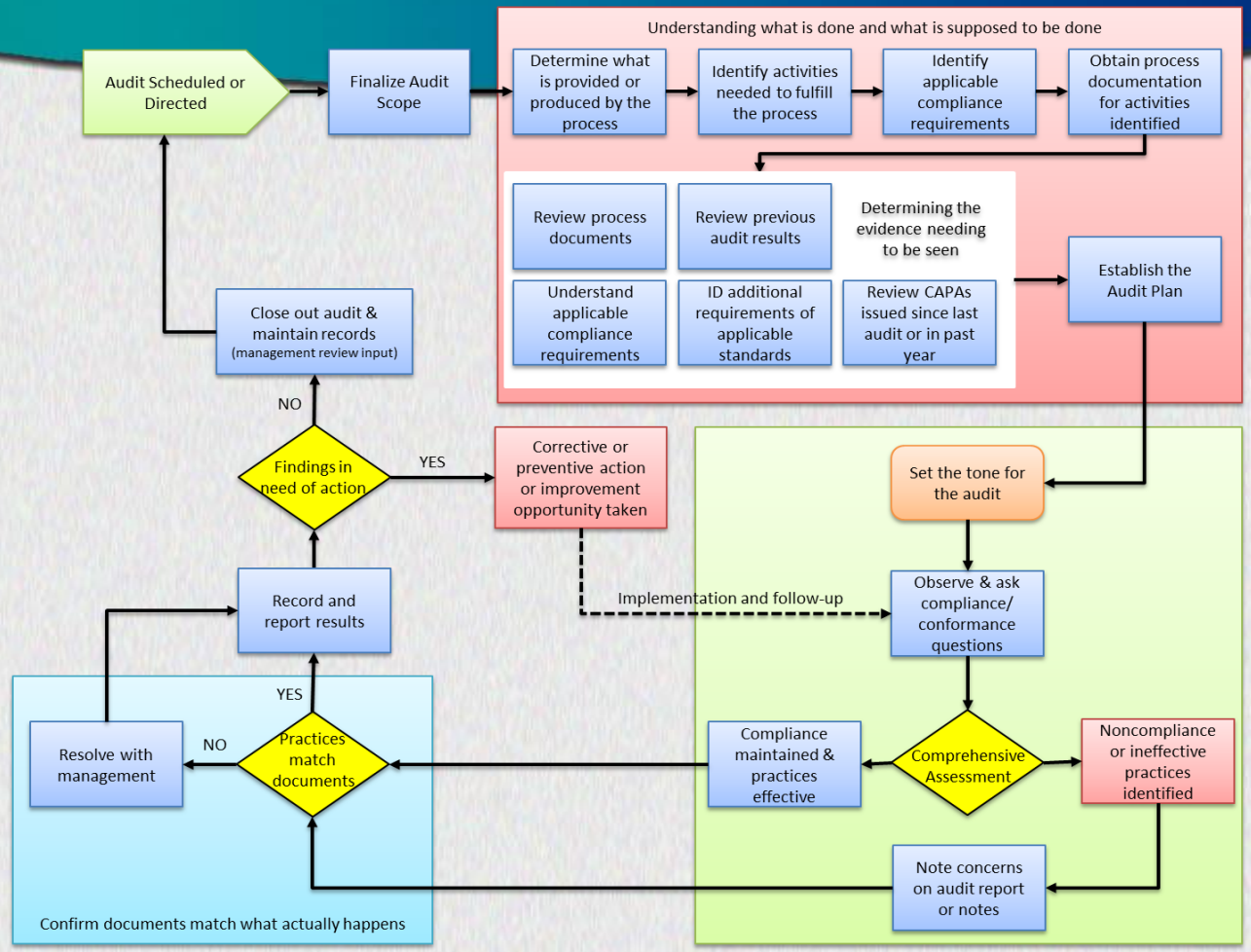
Investment in ISO Accreditation Process

- Investment is to ensure strong foundation and sustainability.
  - Reorganization of Records Division to Include Quality Management
  - Purchased/Maintained Quality Software
  - Identified and Trained Quality Manager in ISO process
  - Developed Internal Quality Committee
    - Select Managers meet monthly to discuss quality related issues
  - Development of Executive QCAR Review

Additional Investment

- Investment in an ISO Quality Consultant
  - Performed Gap Analysis to for ISO Compliance
  - Performed ISO 017020 – NAME Accreditation Checklist Crosswalk
  - Prepared Agency for Internal Audit
  - Performed Internal Audit
    - Established Standard Operating Procedure for the Internal Audit.

Internal Audit Flow Diagram



Non-Conformities Identified

- Health & Safety (3)
- Proficiency Testing (5)
- Personnel/Training (3)
- Expert Testimony (1)
- Calibration (1)
- Evidence Storage (2)
- Chemical Log (2)
- Labeling Reagents (1)

18 Total Non-Conformities

Continued Preparation

ISO 17020 ACCREDITATION PREPARATION

1. Written Procedures for Evidence (security/control/handling)
   - ✓ SOP Improvement - SOP # Mort 1.005 – Evidence Collection and Handling
2. Written Reports
   - ✓ Exam Reports (Autopsy and External)
   - ✓ Investigation Reports
   - ✓ Anthropology Reports
3. Technical and Administrative Review of Reports and Supporting Records
   - ✓ SOP Development - SOP # QC 1.001
4. Testimony Monitoring/Moot Court Training for Forensic Pathologists and Death Investigator
   - ➢ MOU Development with the Office of the Attorney General (OAG)
5. Technical Procedures
   - ✓ SOP Development - Death Investigations
6. Training program
   - ✓ Training Manual Draft completed
7. Proficiency testing
   - ➢ Death investigations, Pathology, and Anthropology
8. Corrective and Preventative Action Process
   - ✓ SOP # QC 1.001
   - ✓ SOP # QC1.003

Appropriation

- **Supervisory Records Management Specialist – Grade MS14 FY2015 - $8,333.52**
  - Move from IT Specialist ($101,860) to Supervisory Records Mgt Specialist ($110,193.52)
- **Training ($2000 per person for $12,000)**
  - **ISO Materials $2600**
- **Qualtrax Implementation and Training - $71,415**
  - **Qualtrax Maintenance $12,500**
- **Quality Assurance Specialist – Grade CS11, Step 7 FY2016 - $5765**
  - Move from Records Management Specialist ($59,049) to Quality Assurance Specialist ($64,814)
- **ISO Consultant - Precision Digital Forensics $50,000**
- **Quality Assurance Specialist – Grade CS12, Step 9 – FY2017 – New Position - $92,250**
- **ANAB ISO Inspection Cost – $18,600 Initial Year**

$189,548.52
Investment over ~3 years

CHECK PLEASE!

The Importance of The Pregnancy Check Box On Death Certificates in Identifying Pregnancy-Related Deaths

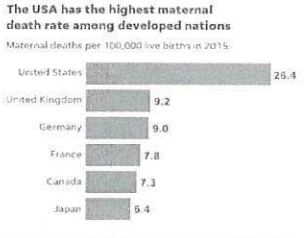
Jan M. Gorniak, DO, MHSA
Chief Medical Examiner
Fulton County Medical Examiner's Office
Atlanta, Georgia

TRENDS IN PREGNANCY-RELATED MORTALITY IN THE US 1987 - 2015

*Note: Number of pregnancy-related deaths per 100,000 live births per year.

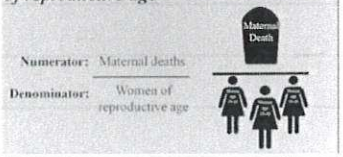
STATISTICS

- According to the CDC, about 700 women die each year from complications of pregnancy or delivery



DEFINIITIONS, DEFINITIONS, AND MORE DEFINITIONS!!!

Maternal mortality rate:
the number of maternal deaths in a given period per population of ***women who are of reproductive age***



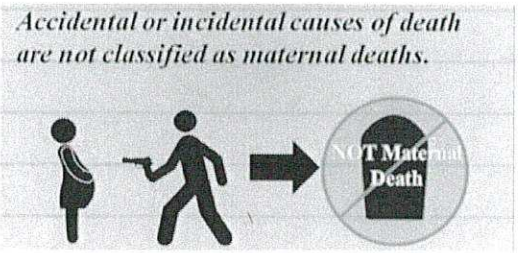
MATERNAL DEATH

- The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes

PREGNANCY-RELATED DEATH

- The death of a woman while pregnant or within 1 year of the end of a pregnancy –regardless of the outcome, duration or site of the pregnancy–from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

Accidental or incidental causes of death are not classified as maternal deaths.



DEATHS ASSOCIATED WITH PREGNANCY

- Deaths which occur during pregnancy, at the time of delivery, or within 1 year postpartum, regardless of the cause

PREGNANCY ASSOCIATED DEATH

- Deaths of women who were pregnant within the last year that are identified by death records, as well as other sources (obituaries, social media, news outlets, etc)

MATERNAL MORTALITY REVIEW COMMITTEE (MMRC)

- Multi-disciplinary groups that identify and review pregnancy-associated deaths, to identify which are causally related, and make recommendations for prevention of future deaths.

MORE DEFINITIONS!!!

PREGNANCY-RELATED

- Deaths related to or aggravated by pregnancy or its management

PREGNANCY-ASSOCIATED

- Deaths related to causes unrelated to pregnancy

PURPOSE OF THE DEATH CERTIFICATE

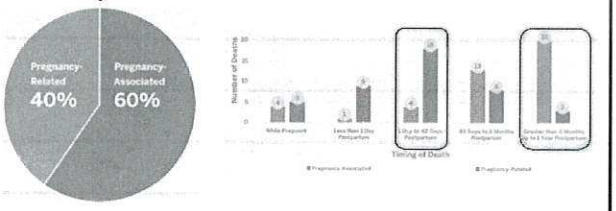
- Legal documentation that the named person is dead
- Information about the deceased
- Information that may be used to evaluate the cause, manner, and circumstances of death
- Information that may be used to settle the deceased's estate
- Information about disposition of the remains, such as where burial occurred
- Information that may be used by government, public health agencies, other state or federal agencies, or researchers to plan or fund programs designed to analyze, reduce, or prevent mortality

US STANDARD CERTIFICATE OF DEATH

36. IF FEMALE:

- ❑ Not pregnant within past year
- ❑ Pregnant at time of death
- ❑ Not pregnant, but pregnant within 42 days of death
- ❑ Not pregnant, but pregnant 43 days to 1 year before death
- ❑ Unknown if pregnant within the past year

GEORGIA MATERNAL MORTALITY REVIEW COMMITTEE



MATERNAL MORTALITY REFERENCE GUIDE

- Council of State and Territorial Epidemiologists (CSTE) Maternal Mortality Workgroup is currently developing a reference guide for certifying deaths associated with pregnancy.

MATERNAL MORTALITY REFERENCE GUIDE

PARTICIPANTS

- CDC Division of Reproductive Health
- West Virginia Office of Maternal Child and Family Health
- National Association of Public Health Statistics and Information Systems (NAPHSIS)
- Michigan Department of Health and Human Services
- Louisiana Office of Public Health
- Georgia Department of Public Health
- Ohio Department of Public Health
- Forensic Pathologists – Georgia, New York, Washington

TAKE HOME POINTS

- Pregnancy checkbox is important
- Medicolegal death investigators must ask about pregnancy status on all females of reproductive age
- Certifiers should be as clear, precise, and complete as possible

THANK YOU

10.4

Reclaiming the Autopsy as the Practice of Medicine:

A Pathway to Remediation of the Forensic Pathology Workforce Shortages?

Victor Weedn, M.D, J.D.
George Washington University
Washington, DC

M.J. Menendez, J.D.
National Medical Services
Horsham, PA

TUESDAY, OCTOBER 22, 2019
SESSION 10: ADMINISTRATIVE
9:30 AM – 9:50 AM

FORENSIC PATHOLOGY IS FACING A WORKFORCE CRISIS

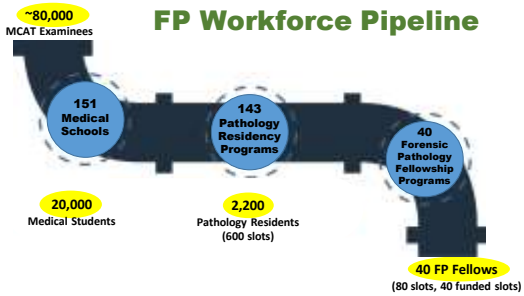
United States

500 Forensic Pathologists
Population: 327 M
Homicides: 17K

Brazil

>2,000 Forensic Pathologists
Population: 211 M
Homicides: 64K

FP Workforce Pipeline



2013 Pathology Workforce Summit

1. Academy of Clinical Laboratory Physicians and Scientists
2. Accreditation Council for Graduate Medical Education–Pathology Residency Review Committee
3. American Association of Neuropathologists
4. American Board of Oral and Maxillofacial Pathology
5. American Board of Pathology
6. American Society of Cytopathology
7. American Medical Association
8. American Pathology Foundation
9. American Society for Investigative Pathology
10. American Society of Dermatopathology
11. Association for Molecular Pathology
12. Association for Pathology Informatics
13. Association of American Medical Colleges
14. Association of Clinical Scientists
15. Association of Directors of Anatomic and Surgical Pathology
16. Canadian Association of Pathologists
17. National Association of Medical Examiners
18. Program Directors Section (PRODS) of APC
19. Society for Hematopathology
20. Society for Pediatric Pathology

No mention of the current 50% FP shortage in the final report

Stanley Robboy report

Through 2010 there were approximately 18,000 practicing pathologists in the U.S. … Our model projects that the absolute and per capita numbers of practicing pathologists will decrease to approximately 14,000 full-time equivalent (FTE) pathologists…in the coming 2 decades. …beginning in 2015, the numbers of pathologists retiring will increase precipitously, and is anticipated to peak by 2021. …this trend will continue at least through 2030.

Arch Pathol Lab Med. 2013;137:1723–1732; doi: 10.5858/arpa.2013-0200-OA

Recent Attention from George Lundberg

May 31, 2019

How Many Pathologists Does the United States Need?

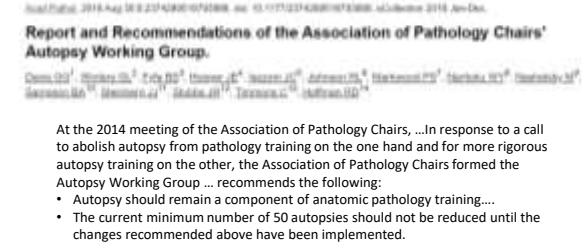
Is the decline of the U.S. pathology workforce 'a blip or a trend ...

https://www.captodayonline.com › CAP TODAY Recommends ▾

Jul 17, 2019 · George O. Lundberg, MD, addresses that question and more in a recent JAMA

PATHOLOGY RESIDENTS ARE EXPOSED TO FORENSIC PATHOLOGY THROUGH THE ACGME AUTOPSY REQUIREMENT,

BUT SUPPORT FOR THIS REQUIREMENT IS WEAK & DWINDLING



Acad Pathol. 2018 Aug 30;5:2374289518793898. doi: 10.1177/2374289518793898. eCollection 2018 Jan-Dec.

Report and Recommendations of the Association of Pathology Chairs' Autopsy Working Group.

Davis GG[1], Rinsky RL[2], Fyfe BS[3], Hoover JE[4], Iacono JT[5], Johnson RL[6], Markwood PS[7], Nartsky RY[8], Nadelsky M[9], Sampson BA[10], Silverstein JJ[11], Stubbs AR[12], Tavassoli A[13], Huffman HD[14].

At the 2014 meeting of the Association of Pathology Chairs, …In response to a call to abolish autopsy from pathology training on the one hand and for more rigorous autopsy training on the other, the Association of Pathology Chairs formed the Autopsy Working Group … recommends the following:

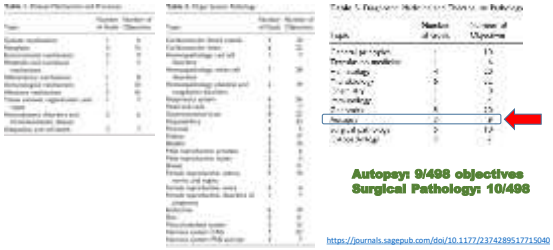
- Autopsy should remain a component of anatomic pathology training….
- The current minimum number of 50 autopsies should not be reduced until the changes recommended above have been implemented.

Pathology residents are exposed to Forensic Pathology through the ACGME autopsy requirement, but this requirement is not supported by many Pathology Department Chairs.

Frequently Asked Questions: Anatomic Pathology and Clinical Pathology Review Committee for Pathology ACGME
Effective: July 1, 2018

Pathology Competencies for Medical Education and Educational Cases

Association of Pathology Chairs

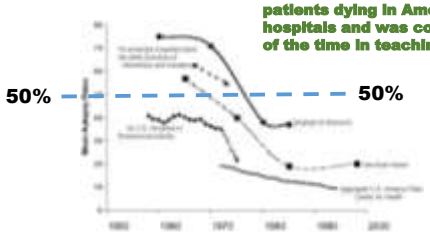


Autopsy: 9/498 objectives
Surgical Pathology: 10/498

https://journals.sagepub.com/doi/10.1177/2374289517715040

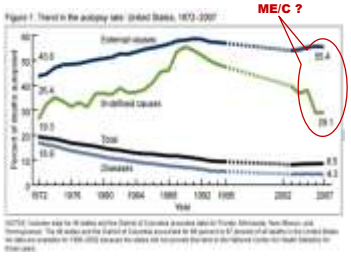
AUTOPSY RATES HAVE PLUMMETED

In 1950, an autopsy was conducted on one-half of the patients dying in American hospitals and was conducted 90% of the time in teaching hospitals.



How Common is Death with No Apparent Cause on an Autopsy?, Quora, 2011, https://www.quora.com/How-common-is-death-with-no-apparent-cause-on-an-autopsy

AUTOPSY DECLINE: WHAT ARE THE REASON? WHAT ARE THE LESSONS?



Autopsy rates declined >50% from 1972 to 2007

In 1972, almost 1 out of 5 deaths were autopsied. From 1972 through 2003, however, the autopsy rate dropped 58% from 19.3% to 8.1%. Although the autopsy rate has increased slightly since 2003, only 8.5%, or fewer than 1 out of 10 deaths, were autopsied in 2007.

Source: CDC / NCHS National Vital Statistics System

Autopsy rates declined precipitously after the 1971 decision by the Joint Commission on Accreditation of Hospitals (JCAH) (now JCAHO) to eliminate the 20% autopsy requirement for hospital accreditation.

The decline further accelerated in 1986, Health Care Financing Agency (HCFA) (now CMS) ruled that autopsies were not part of patient care and thus were not the practice of medicine to be funded by the federal government.

WHY THE DECLINE IN AUTOPSIES?

- ✓ Greater confidence in antemortem diagnostics
- ✓ Advanced imaging technologies & new laboratory tests
- ✓ Lack of interest of hospitals, physicians, regulators, & payors
- ✓ Perception that they will expose hospital liability
- ✓ Concerns over liability from NOK
- ✓ Lack of interest & expertise in hospital pathologists
- ✓ (time consuming, costly, engenders hostility with medical peers)
- ✓ No morgue facility
- ✓ They are unfunded

BENEFICIAL ATTRIBUTES OF AUTOPSY COMMON TO CLINICAL AND FORENSIC AUTOPSIES

- **Determine the cause of death of a patient**
- **Reveal familial conditions**
- **Reveal new and previously unknown conditions**
- **Quality assurance measure / Monitor for foul play**
- **Epidemiologic trending analysis**
- **Education**
- **Research**

2011

PROPUBLICA

https://www.propublica.org/article/without-autopsies-hospitals-bury-their-mistakes

THE CENTER FOR MEDICARE & MEDICAID SERVICES (CMS)

DOES NOT PAY FOR AUTOPSIES
BECAUSE
AUTOPSIES ARE NOT THE PRACTICE OF MEDICINE

THE AUTOPSY IS THE PRACTICE OF MEDICINE

Medical Interpretation
Medical Procedure

THE AUTOPSY HAS A LONG MEDICAL TRADITION

Herophilus and Erasistratus
The Butchers of Alexandria
3rd Century BCE
Alexandria, Greece

Julius Caesar
44 BCE
autopsied by Antistitius
giving rise to term "forensic"

Bartolomeo De Varignana
1302 performs 1st medicolegal
autopsy in Bologna, Italy

Paolo Zacchia (1584-1659)
"Father of Forensic Medicince"
Quaestiones Medico-Legales
(1621-1651)

Giovanni Battista Morgagni
(1682-1771)
"Father of Anatomic Pathology"
De Sedibus (1769)

John Hunter
(1728-1793)
"Father of Modern Surgery"

Rudolf Virchow
(1682-1771)
"Father of Cellular Pathology"
Vorlesungen über Cellularpathologie (1859)

William Osler
(1849-1919)
"Father of Modern Medicine
The Principles and Practices of Medicine (1892)

Practice of Medicine = Patient Care

What about diagnosis and prevention?

…hospital pathology is basically diagnostic,
CMS pays for it because it is patient care

AUTOPSIES:

- ❖ involve diagnosis of patients.
- ❖ are performed by physicians.
- ❖ are preventive medicine & public health.
- ❖ are a form of quality assurance.

Relevant Sources of Law

- Medical Practice Statutes
- Licensure Board Regulations
- Caselaw

Lexis-Nexis Search

- **No court failed to recognize the autopsy as the practice of medicine**
- **No case addressed the CMS ruling**

Who argues that it isn't the practice of medicine?

Pathologists who aren't licensed

Pathologists who are challenged by licensure boards

ME/C offices that hire an FP before licensed in the state

Funding agencies

1937

"Chiropracters advertise in telephone directories and elsewhere in the Commonwealth, and they tell their legislative committees that they will continue to practice without authorization. …how ridiculous are their claims that they do not practice medicine."

S Rushmore, A Definition of the Practice of Medicine, N Eng J Med 217:342-5, 1937
https://www.nejm.org/doi/full/10.1056/NEJM193708262170902

Sean Parcells

Prosecutors are reluctant to prosecute these cases!

Recent NAME Listserv case

- The MEO began a new procedure to look for cervical nerve root hemorrhage in infants suspected of possible shaken baby syndrome. An out-of-state lab was used to assist examining the cervical block. An out-of-state FP from the lab assisted in the dissection and removal of the cervical block.
- An autopsy assistant alleged that autopsies of infants were being performed by an unlicensed physician and body parts were being flown to a lab for research without consent of the NOK. The MEO responded that the out-of-state FP did not perform the autopsy, but assisted it, and that no research was being conducted. The autopsy assistant was terminated from the county MEO.

- **Employment lawsuit**: The assistant sued for tortious interference with her county employment contract, after she made her whistleblowing allegations.
  - The trial judge threw out the lawsuit against the unlicensed physician and the supervising physician because he found that she could not produce sufficient evidence to back up her allegations.
- **Criminal investigation**: The county district attorney has requested an investigation into the potentially illegal and suspicious activity within the office.
- **Personal Injury lawsuit**: A lawsuit was also brought by the family of the child for mental anguish for disassembly of the body for research.
- **Medical Licensure Action**: A complaint was filed with the licensure board.
  - The licensure board decided not to take action against the physician without an applicable state license, nor against the supervising physician.

California code 27522. (a)

A forensic autopsy shall only be conducted by a licensed physician and surgeon. The results of a forensic autopsy shall only be determined by a licensed physician and surgeon.

- **Intended:**
  Sheriff's can't perform or interpret autopsies
- **Unintended:**
  Creates uncertainty about use of assistants & students -- presumably, they can be used under the supervision of the forensic pathologist

"I checked the CDC public health law website on the ME/C state statutes and the following states: AZ, CO, CT, DE, FL, HI, IN, IA, KS, KY, MD, NH, NM, ND, OK, OR, UT, VA, WV, WI, DC specifically make reference to a FP performing autopsies (at least by our lawyers reading of the statute)."

Margaret Warner
Sep 13, 2019

Is an Autopsy a Medical Procedure?

A 'medical procedure' is merely a label that it is procedure performed in a healthcare facility and can be billed for under CMS codes. It does not mean that prosection must be physically performed by a physician.

Cut down for Tox?

Virtual Autopsy?

Molecular Autopsy?

2018 …

Medicare and Medicaid Programs: Regulatory Provisions To Promote Program Efficiency, Transparency, and Burden Reduction

83 FR 47686-01 2018 WL 4489885 September 28, 2018 (Approx. 144 pages)

3. Proposals That Are Obsolete, Duplicative, or That Contain Unnecessary Requirements

a. Medical Staff: Autopsies

We propose to remove the requirement for hospitals at § 482.22(d), which states that a hospital's medical staff should attempt to secure autopsies in all cases of unusual deaths and of medical-legal and educational interest. We propose to instead defer to State law regarding such medical-legal requirements.

10/1/2019

Medicare's Elimination of Autopsy Standard for Hospitals Firmly Opposed by CAP

The CAP strongly opposed the Centers for Medicare & Medicaid Services (CMS) decision to remove the autopsy standards for hospitals. As a condition for Medicare reimbursement, hospitals were required to have an autopsy program. With this regulation change, hospitals are no longer required to have autopsy programs to qualify for Medicare reimbursement.

In September 2018, the CMS released a proposed regulation to reform Medicare regulations that are identified as unnecessary, obsolete, or excessively burdensome on health care providers and suppliers. Within this proposal, the CMS had recommended removal of the autopsy standard that requires autopsies in all cases of unusual deaths, medical-legal, and educational interests. The CAP strongly opposed the removal of this provision as it would open the door to not performing or offering autopsies at hospitals. This would, in turn, have a detrimental impact on public health, patient care, organ donations, and potential health or genetic predispositions to diseases and disorders, creating even more burdens within the health system, the CAP said.

On September 26, the CMS went ahead and released the final regulation which alarmingly removed the autopsy standards for hospitals by justifying this change as a means to reduce regulatory burdens on physicians and the health care system. In the final regulation, the CMS changed its Medicare reimbursement policy where hospitals are no longer required to have autopsy programs to qualify for Medicare reimbursement. The agency clarified that the removal of this standard does not prohibit hospitals from performing autopsies and encouraged hospitals to implement policies for autopsy, where appropriate.

The CAP continues to oppose this change and will keep its membership updated on any new actions concerning this policy.

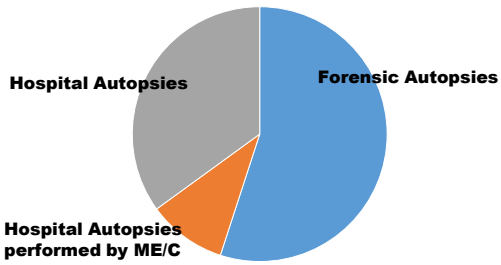
IF CMS CAN BE FORCED TO RECOGNIZE AUTOPSIES AS THE PRACTICE OF MEDICINE, THEN THEY MAY BE FORCED TO PAY $$ FOR THEM

PAYING FOR AUTOPSIES WOULD RESULT IN:

- **MORE HOSPITAL AUTOPSIES**
- **GREATER SUPPORT FROM DEPTS OF PATHOLOGY**
- **GREATER EXPOSURE OF PATH RESIDENTS**
- **MORE FPS IN THE PIPELINE**

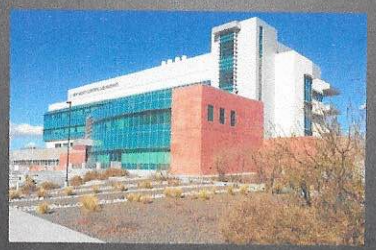
- **POSSIBLY, FINANCIAL SUPPORT FOR ME/C**

Theoretical Distribution of Autopsies



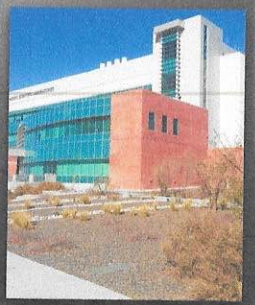
Should ME/C be funded as public health entities?

In fiscal year 2018, state spending on **public health** increased by 2% to a total of $11.8 billion. ... Both state and local **health** departments receive the majority of their **funding** from grants provided by the Prevention and **Public Health Fund** established under the Affordable Care Act. Apr 24, 2019

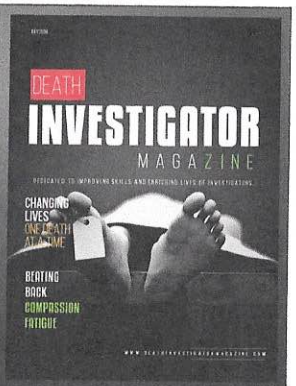


ECHO: Medicolegal Death Investigation
Ian Paul, MD
Office of the Medical Investigator
University of New Mexico

- Office of the Medical Investigator is NM's sole ME office located on the University of NM campus
- We investigate 7000 deaths/year
- Perform approximately 2000 autopsies/year; 1000 external examinations
- All bodies transported to OMI if an examination is required
- Widely distributed medical examiner system



- Medicolegal Death Investigators
  - Who are they
  - What do they do
  - Training challenges
  - Training solutions



Medicolegal Death Investigators

- They are the eyes, ears, and noses of a forensic pathologist at death scenes
- Make critical scene observations
- Determine whether a death is potentially natural or unnatural
- Document evidence
- Photograph the scene and body
- Make critical case triage decisions

SCHOOL OF MEDICINE

- 14 Central Office Medicolegal Death Investigators
  - 7 ABMDI certified
  - Must be certified within 1 year of hire
  - Many have death investigation background
- Approximately 110 Field Medicolegal Investigators
  - Minimum qualifications are high school diploma and valid drivers license
  - 17 of these investigators are at least ABMDI registry certified
  - Cover all New Mexico counties outside of Bernalillo

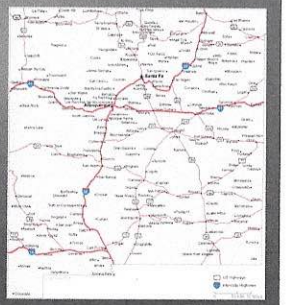
Training Challenges

*Geographically distributed system

*Travel distances

*Limited resources

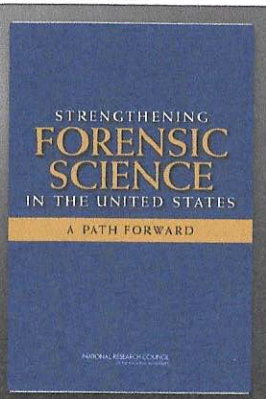
*Professional isolation



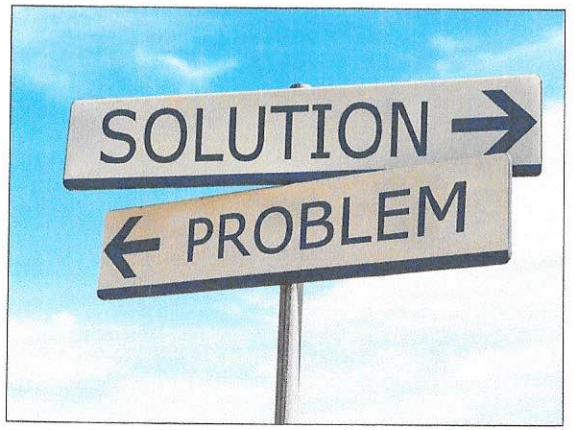
Historical Training Model

- *2-3 day introductory training course for medicolegal death investigators
- *Annual central office training sessions
- *Cover essentials of MDI training
- *Limited in depth and breadth

National Research Council of the National Academies 2009



- *Certification of MDI's is a national priority
- **No person (public or private) should be allowed to practice in a forensic science discipline or testify as a forensic science professional without relevant certification"
- *Goal of the National Commission on Forensic Science to have all MDI's registry certified by 2020



Project ECHO®

SCHOOL OF MEDICINE

Extension for Community Healthcare Outcomes

*Launched in 2003 as a way to meet local healthcare needs
*Makes specialized medical knowledge accessible wherever it is needed
*Created so that primary care physicians could treat hepatitis C in their communities
*Puts local clinicians together with specialist teams in weekly virtual clinics
*Currently operates 39 HUBS for nearly 30 diseases/conditions in 22 states and five countries including sites within the Department of Defense

SCHOOL OF MEDICINE

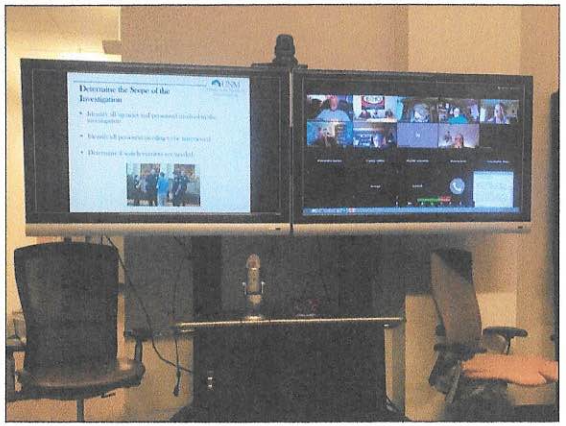
- Project ECHO exemplifies learning as described in the levels of continuing professional development by Moore
- To achieve desired results in continuing medical education the learning activity should produce the following:
  - Participation
  - Satisfaction
  - Learning
  - Performance
  - Patient health
  - Community health

- Donald Moore et al "Achieving Desired Results and Improved Outcomes: Integrating Planning and Assessment Throughout JOURNAL OF CONTINUING EDUCATION IN THE HEALTH PROFESSIONS, 29(1): 1–10, 2009

Project ECHO®

OMI Medicolegal Death Investigation

- ECHO: Medicolegal Death Investigation
  - Launched at the Office of the Medical Investigator in 2015
  - More than 100 unique participants including investigators in Oklahoma and Shasta County California
  - Created more than 140 hours of unique educational content
  - Model works exceptionally well in a widely distributed medical examiner/coroner system



Project ECHO®

OMI Medicolegal Death Investigation

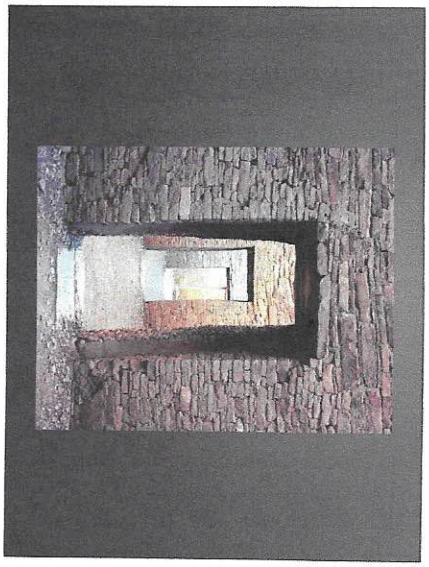
- ECHO: MDI Curriculum is based on the scope of knowledge required for the ABMDI registry certification exam as outlined in the ABMDI Performance Training Guidebook Checklist
  - Interacting with Federal, State and Local Agencies
  - Communicating
  - Interacting with families
  - Investigating deaths
  - Identifying and preserving evidence
  - Maintaining ethical and legal responsibilities
  - Demonstrating scientific knowledge
  - Coping with job-related stress

SCHOOL OF MEDICINE

- Accomplishments
  - In the past year:
    - 19 investigators signed up for our 18-month ABMDI registry certification curriculum
    - 3 investigators signed up for the ABMDI registry certification examination
- Future plans
  - Grant funding to cover an additional 25 field investigators to prepare for the ABMDI registry certification examination

SCHOOL OF MEDICINE

- Acknowledgements
  - Amy Wyman
  - Yvonne Villalobos
  - Anthony Cervantes
  - Alex Garley
  - Ross Zumwalt
  - Nancy Mance
  - Lauren Decker
  - Lauren Edelman
  - Project ECHO®



2017 – 2018
API TECHNOLOGY PILOT

Automated Drug-Involved Death Data Collection Pilot
CDC Funded: 200-2017-96227

Steven Clark, PhD

1

DISCLAIMER

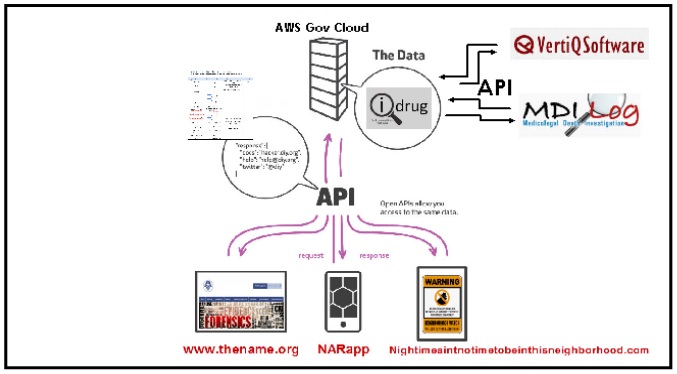
- The MDILog software service is owned Occupational Research and Assessment (Steve Clark)
- VertiQ Case Management software is owned by VertiQ Software LLC
- (Anthony Kessel)

2

PROJECT TASKS

- Receive endorsement from NAME and IAC&ME
- NAME Ad Hoc Committee
- Select two ME/C Case Management Software Programs
- Identify Accredited Pilot Sites using case management systems
- Develop Data Export Schema
- Modify Software Programming Code
- Develop Data Collection Site (iDrug)
- Activate Pilot Site (pending toxicology – complete – inactive)
- Develop Application Programming Interface (API) Document

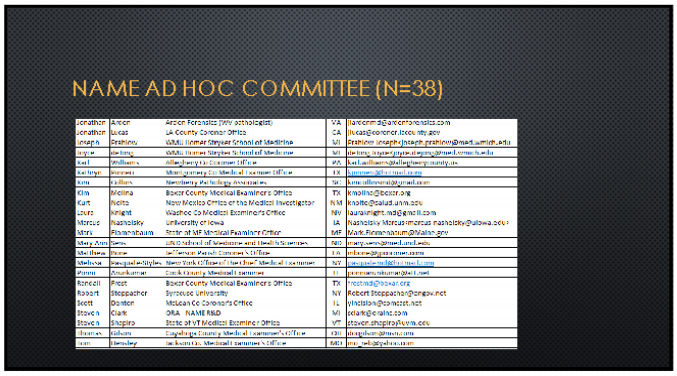
3


AWS Gov Cloud
The Data
VertiQSoftware
API
drug
MDILog
API
Open APIs allow you access to the same data.
request
response
FORENSICS
WARNING
www.thename.org
NARapp
Nightimeaintnotimetobeinthisneighborhood.com

4


Cleartrip integrates with Uber API to offer local activities
Online travel and activities platform Cleartrip today said it partnered with global ride sharing company Uber that will the latter's Application program interface (API) to make co local activity suggestions.
cleartrip
Flights
Hotels
Local
Flight + Hotel
Trains
Flight Deals
Search flig
Fly anywhere. Fly e
One way
From
Depart on
Pick a date
Zillow
Buy
Rent
Sell
Mortgages
Agent finder
More
Overview
Widgets
Data & API
Overview
Reviews
Neighborhood Boundaries
Branding
Terms Of Use
FAQ
Zillow Neighborhood Boundaries
The Zillow data team has created a database of over 17,300 neighborhood bound
the largest cities in the U.S. And we'd like to share them with you! We're sharing
neighborhoods under a Creative Commons license to allow people to use and co
to our growing database. What does this mean to users of the data?

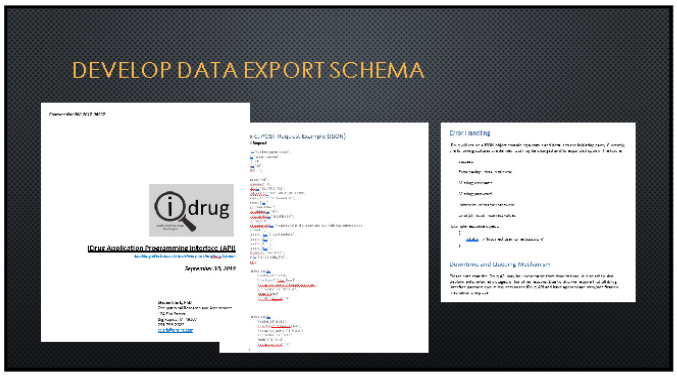
5


NAME AD HOC COMMITTEE (N=38)

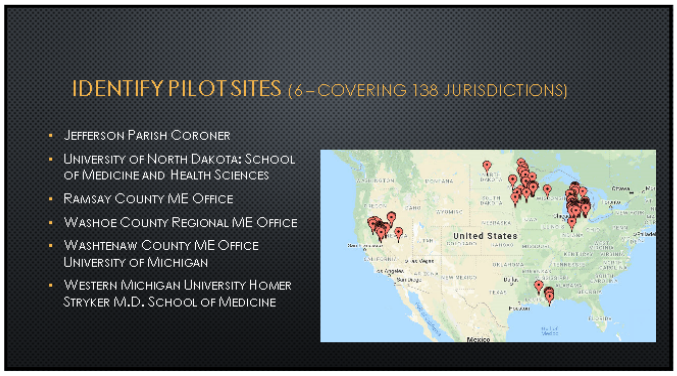
6


MDI Log
Medicolegal Death Investigation
VertiQ Software
Washtenaw UM Group
Kalamazoo WMed Group
North Dakota UND Group
Jefferson Parrish Group
Ramsey County Group
Washoe County Group
idrug

7


DEVELOP DATA EXPORT SCHEMA
idrug

8


IDENTIFY PILOT SITES (6 – COVERING 138 JURISDICTIONS)
Jefferson Parish Coroner
University of North Dakota: School of Medicine and Health Sciences
Ramsay County ME Office
Washoe County Regional ME Office
Washtenaw County ME Office University of Michigan
Western Michigan University Homer Stryker M.D. School of Medicine
United States

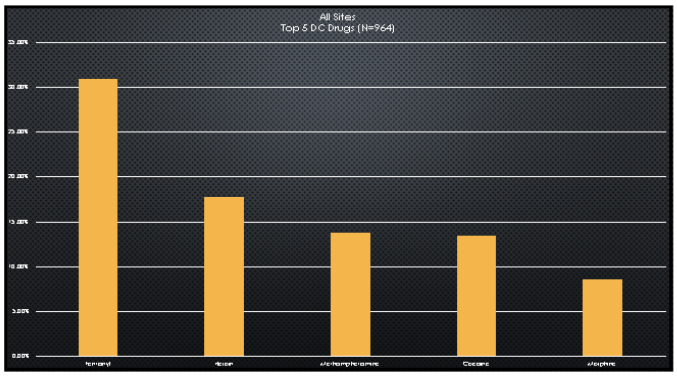
9

ALL SITES COVERED MULTIPLE COUNTIES/PARISHES

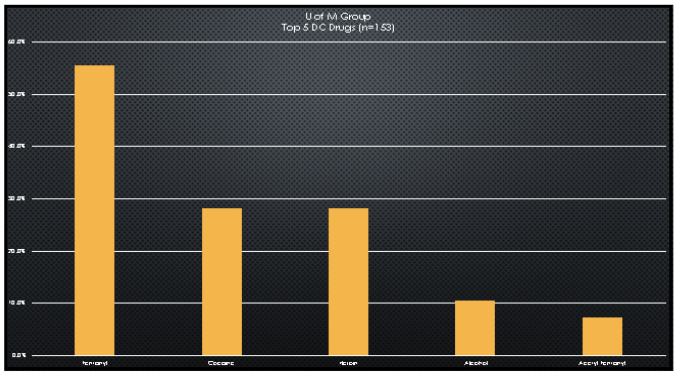
Washoe County is the primary jurisdiction of the Regional Medical Examiner's Office. It also services thirteen additional Nevada counties and five California counties through interlocal agreements.

Washoe	NV	446903
Carson City	NV	54521
Lyon	NV	52685
Elko	NV	51935
Douglas	NV	47710
Nye	NV	42477
Lassen	CA	31345
Churchill	NV	24200
Plumas	CA	18409
Humboldt	NV	17019
Pershing	NV	6834
Lander	NV	5903
		799841

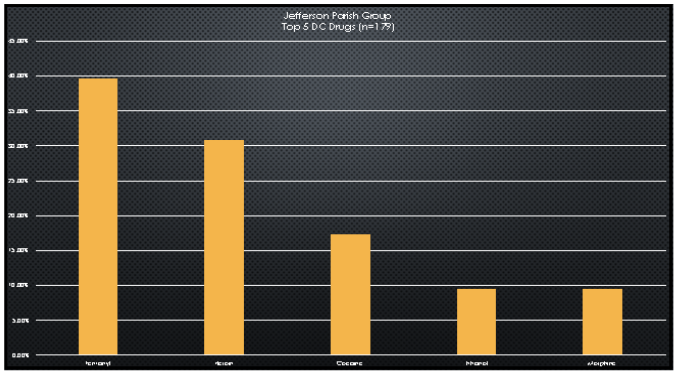
10



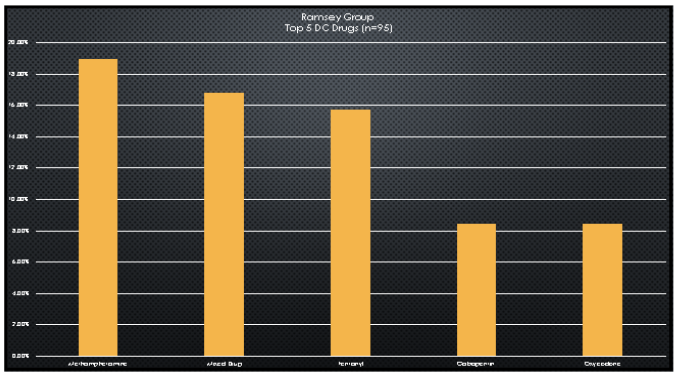
11



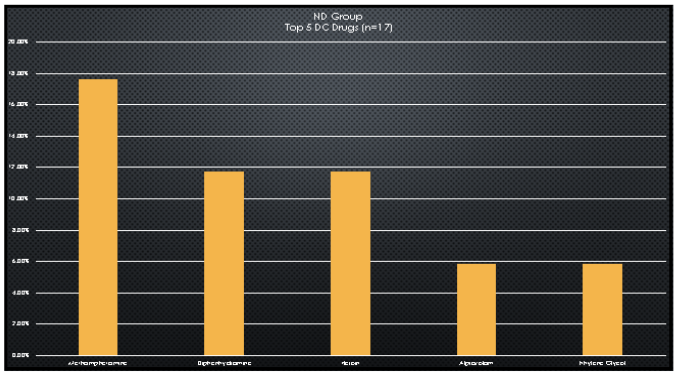
12


Jefferson Parish Group
Top 5 DC Drugs (n=179)

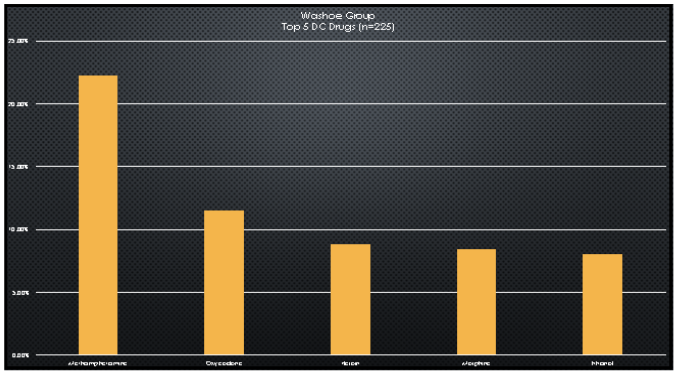
13


Ramsey Group
Top 5 DC Drugs (n=95)

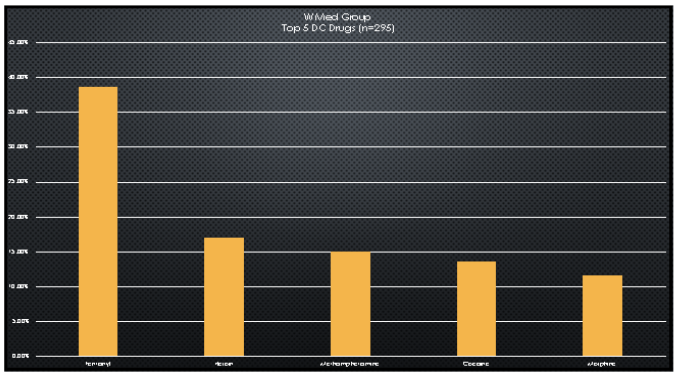
14


ND Group
Top 5 DC Drugs (n=17)

15



16



17

PILOT DATA OVERVIEW (10/07/18)

JURISDICTIONS: 138 STATES: 8
DRUG DEATHS: 966 NO TOXICOLOGY >90 DAYS: 48 (~5%)
TOP FIVE DRUG(S) CATEGORIES: 1. AMPHETAMINE (54%)
2. OPIATES (52.4%)
3. BENZODIAZEPINES (34.3%)
4. COCAINE (21.7%)
5. ALCOHOL (19.7%)
SEX: MALE: 64.2%) FEMALE: 35.3%
AGE RANGE: 26-44 (43%) 45-64 (40.1%) AVERAGE AGE:
RACE: WHITE (81.2%)
MOD: ACCIDENT (79.5%) SUICIDE (7.5% UNDETERMINED (5%)

18

SPECIAL THANKS!

NAME
IAC&ME
Gerry Cvitanovich, MD
Joyce deJong, DO
Jeffrey Jentzen, MD, PhD
Laura Knight, MD
Michael McGee, MD
Mary Ann Sens, MD, PhD
Anthony Kessel
ORA Team

CDC

19

PREVENTING CONSUMER PRODUCT-RELATED INJURIES AND DEATHS

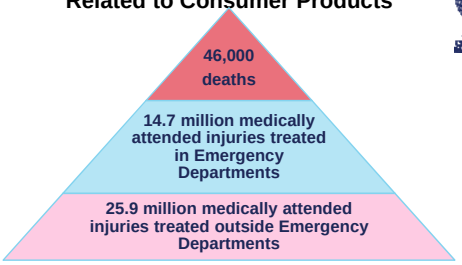
THE VITAL ROLE OF MEDICAL EXAMINERS

MEDICAL EXAMINERS AND CORONERS ALERT PROJECT

Yolanda Nash, Program Analyst
CPSC's Division of Epidemiology
October 22, 2019

This presentation has not been reviewed or approved by the Commission and may not reflect its views.

Annual Burden of Injuries and Deaths Related to Consumer Products



Based on 2017 NEISS data and 2016 CDC/NCHS mortality data

What Is the Medical Examiners and Coroners Alert Project (MECAP)?

MECAP is a system of collecting fatality reports from medical examiners and coroner's offices by the Consumer Product Safety Commission (CPSC)

CPSC collects timely data about unintentional injury fatalities that involve a consumer product

4

Reports Collected

Over 3,000 MECAP reports are collected by CPSC annually

What Data Is Collected?

WHO?
- Age/gender/race
- Who was involved?

WHAT?
- What was the product?

WHERE?
- Locale of the incident
- Home? Work? Store?

WHEN?
- When did the fatality occur?

WHY?and HOW?
- How did the fatality occur?

Example of a Bucket Drowning

A 16-month-old-male infant was at home with his mother. His mother stepped outside for a few minutes. When she returned, the decedent was slumped over a 5-gallon bucket filled with water and a cleaning agent. The infant's head and face were submerged in the liquid. The decedent was taken to a hospital and pronounced dead.

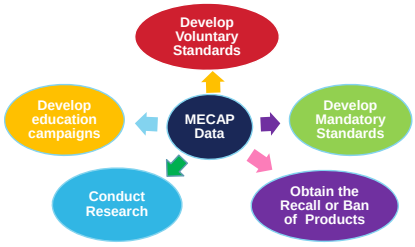
Example of a Furniture and Television Tip-Over Investigated by CPSC

A 4-year-old female decedent died from a furniture tip-over where a television was involved. The decedent was in her room watching television when the mother heard a crash in the decedent's bedroom. The mother ran into the room and found the decedent on the floor with a large, old, heavy-tube television and dresser on her head and chest. The decedent was transported by ambulance to a local hospital where she was met by air ambulance and transferred to another hospital. The decedent was pronounced dead as a result of her injuries. The cause of death was blunt force trauma to the head.

Example of an Above-Ground Pool Drowning

A 2-year-old male was found unresponsive and submerged in an above-ground pool at his home. The decedent was last seen at bedtime and was discovered the following morning. He had wandered outside unnoticed to where an above-ground pool was located. He was discovered in the pool by his mother. First responders administered CPR at the scene and transported the decedent to a hospital. Despite resuscitative efforts, the child was pronounced dead in the ER. The pool had a 3-step ladder attached, but no covering or safety features. The cause of death was drowning.

How are MECAP reports used?



10

How are MECAP reports used?

Develop Voluntary Standards

CPSC was first alerted to the problem of infants drowning in 5-gallon buckets by a MECAP report. Manufacturers have voluntarily placed warning labels on buckets in English and Spanish to inform and educate the public of the hazard.

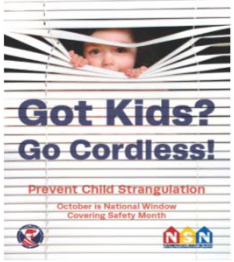
CPSC's Major Safety Campaigns

- *Pool Safely*
- Anchor It!

- Fireworks Safety
- Safe Sleep for Babies

Other CPSC Safety Campaigns

- Window Covering Safety
- Halloween Safety
- Holiday Toy Safety
- Holiday Decorating Safety
- Smoke/CO alarms
- Portable gas generators
- ATVs/ROVs
- Poison Prevention



Agency Websites

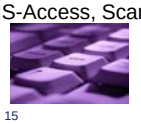
- **CPSC.gov**
- **SaferProducts.gov**
- **PoolSafely.gov**
- **AnchorIt.gov**

SaferProducts.gov

Anchor It!

Filing a Report

- Internet at **http://www.saferproducts.gov**
- Phone to 1-800-638-8095
- Fax to (301) 504-0038
- E-mail epdsfax@cpsc.gov (*e.g.,* Excel, MS-Access, Scanned Reports)



15

CPSC Stands for Safety

THANK YOU!

QUESTIONS? COMMENTS?

Contact Information

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MECAP Reporting: www.saferproducts.gov
(Click on Report an Unsafe Product)

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