Date: Wednesday, February 12, 2014, 7:00 pm – 8:30 pm

Topic: LABORATORY MEDICINE

Speaker:

Alan Wu, Ph.D., D.A.B.C.C., Professor, Laboratory Medicine

Biography

Alan H.B. Wu, Ph.D., is Chief of Clinical Chemistry and Toxicology at San Francisco General Hospital and Professor of Laboratory Medicine, University of California, San Francisco. He received B.S. degrees in chemistry and biology at Purdue University, West Lafayette, Indiana, and a Ph.D. degree in analytical chemistry at the University of Illinois, Champaign-Urbana, Illinois. He completed a postdoctoral fellowship in clinical chemistry at Hartford Hospital. He is certified by the American Board of Clinical Chemistry in Clinical Chemistry and Toxicological Chemistry.

Dr. Wu’s research interest has been in three areas within the field of clinical chemistry laboratory. He has been involved at the national and international levels with development and use of biochemical markers for cardiovascular disease including CK-MB, myoglobin, troponin, B-type natriuretic peptide, soluble ST2, and galectin-3 and markers of myocardial ischemia, and stroke. As also has a long history of analytical, clinical, and forensic toxicology. In both of these areas, Dr. Wu has co-authored the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines. More recently, Dr. Wu has developed research and clinical programs in pharmacogenomics in support of the UCSF clinical pharmacogenomics laboratory. Among the areas of interest include pharmacogenomics for anticoagulants, especially warfarin, chemotherapeutics (tamoxefin, irinotecan), and drugs that can induce hypersensitivity reactions (abacavir, anticonvulsants).
Toxicology! Because what you don’t know can kill you.

UCSF Osher Mini Medical School for the Public
Medical Detectives: Inside the Mind of Great Physicians

February 12, 2014
Alan Wu, Ph.D., UCSF
Dept. of Lab Medicine

What do you do for a living?

He: "I do drug testing in a lab."
She: "Are you some kind of narc?"
He: "No! I help patients who have been poisoned or overdosed."
She: "I have to powder my nose. Will you excuse me?"

Clinical laboratory and toxicology: promotion to the public

TOXICOLOGY! BECAUSE WHAT YOU DON’T KNOW CAN KILL YOU

Available through: www.alanhwu.com/

Tax testing that solved forensic cases

Available today!
Kindle: $6.99
Paperback: $14.99

THE HIDDEN ASSASSIN

Clin lab tests that solved cases or caused harm

Coming soon!
March 2014
“Slide Toxin”: what’s wrong with this picture?

FAA: Evacuation of all in 90 seconds?

Two evacuation chutes deployed inside trapping individuals to the floor. Bags were sliced open. Several passengers admitted to SFGH-ICU with significant delayed acidosis.

How do airplane chutes deploy?

Detection of azide in serum from 1-1000 nmol/mL


2 NaN₃ → 2 Na + 3 N₂
130 grams sodium azide ignited within msec producing 67 l of N₂
50 kg in airplane chute.
**Sample Azide Concentration**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Azide Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 Serum</td>
<td>None Detected</td>
</tr>
<tr>
<td>Patient 2 Serum</td>
<td>None Detected</td>
</tr>
<tr>
<td>Patient 2 Urine</td>
<td>None Detected</td>
</tr>
<tr>
<td>Patient 3 Serum</td>
<td>None Detected</td>
</tr>
<tr>
<td>Patient 3 Urine</td>
<td>None Detected</td>
</tr>
</tbody>
</table>

Method developed and samples analyzed in <3 days

**“Duffer dysfunction”**

JH was a marginally successful pro golfer. He joins the senior PGA tour in hopes of reviving his career and the accolades of being a pro golfer.

After a round, a woman finds him attractive and gives him keys to her hotel room. In preparation, JH takes “herbal-x” for erectile dysfunction. He doubles his dose....

**Analysis of herbal supplements**

**Herbal X**

- Claims to increase libido
- Most ingredients have been studies for their role in supporting healthy sexual performance and increased libido
- Listed ingredients: Acorus rhizome, Cornus, Alpinia, Lycium, Cherokee Rose fruits, Black walnut seed, Cimicifuga rhizome, Cordyceps mycelium, Poria sclerotium, and Glycyrrhiza, Panax Ginseng, and Rehmania roots

**MS-TOF Qualitative Analysis**

- Methanol extract of Herbal X contains very high formula matches for:
  - acetildenafil (structural analogue of Viagra)
  - hydroxyhomosildenafil (derivative of Cialis)
- Both have been reported as dopants in traditional Chinese medicine

<table>
<thead>
<tr>
<th>Name</th>
<th>Score (MFG)</th>
<th>RT</th>
<th>Mass</th>
<th>Ions</th>
<th>Height</th>
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<tbody>
<tr>
<td>Acetildenafil</td>
<td>84.05</td>
<td>4.147</td>
<td>466.2700</td>
<td>4</td>
<td>1548390</td>
</tr>
<tr>
<td>Hydroxyhomosildenafil</td>
<td>91.08</td>
<td>4.602</td>
<td>488.2208</td>
<td>7</td>
<td>1118324</td>
</tr>
</tbody>
</table>

He dies of a heart attack during intercourse.
“Tree Trunks Trudy”

- An overweight hypothyroid woman who has deep vein thrombosis undergoes an MRI angiography.
- She is teased in school as having “tree trunk thighs.” Creatinine testing is performed (renal function test).
- An error is made by a resident resulting in a falsely low result.

Renal function testing for radiology

- Iodinated contrast media is used for MRI and interventional radiology but suffers from acute renal failure.
- Gadolinium-based media is thought to be safer?

Ga-induced nephrogenic systemic fibrosis

- Fibrosis of the skin, eyes, joints and organs.
- NSF occurs in patients with eGFR <60 mL/min or creatinine >3 mg/dL.

“Missing Lights”

- A Hispanic maid is raped in a hotel by a white rock and roll musician and delivers a premature baby.
- Due to the dark skin of the child, a transcutaneous bilirubin test is canceled. The blood test doesn’t get ordered.
Neonatal jaundice

- Jaundice evident in about 60% of term and near term infants during the first week.
- Hyperbilirubinemia (total >12.9 mg/dL) occurs in 10% of infants
- Phototherapy used to treat hyperbilirubinemia.
- The child develops kernicterus lead to irreversible brain damage.

“Spice of Dyslife”

A 36-y old female actress is preparing for a part. Her agent tries to relax her by baking “cookies” containing synthetic cannabinoids. She eats the cookies and becomes hallucinogenic. Calls husband says, “I want to jump out of a window.” Husband rushes home, but while in bathroom, she jumps out the window. Dies of traumatic injuries.

Urine drug screen is negative for THC.

Spice... History

- 1990's Synthetic cannabinoids are synthesized in the lab of John W Huffman (JWH) at Clemson University
- 2002 Spice first appeared in Asia as herbal incense
- 2004 Spice became available in Europe
- 2008 Japan and Germany started analyzing herbal incense samples bought from headshops/ internet
- Feb, 2009 First published articles on SPICE being adulterated with synthetic cannabinoids
- Apr, 2009 German lab quantified adulterants in SPICE; more JWH compds found
- April, 2010 JWH-018 metabolites identified

Synthetic cannabinoids

Classical cannabinoids
- HU- 120

Cyclohexylphenols
- CP 47,497

Naphthoylindoles
- JWH- 018

Phenylacetylindoles
- JWH- 250

Naphthoylpyrroles
- JWH-030

THC
Case summary

JWH-072 identified present in blood of decedent.
Agent up for involuntary manslaughter

“Rave review”

• 11 Patients distributed in 4 hospitals
• 3 referred to SFGH
  • AM- 23yo male, critically ill; (admitted 5/30 0021H, died 5/30 2030H
  • JMT-19yo female condition progressively became worse
  • LS- 24yo female doing better
• Both critically ill patients presented with hyperthermia, seizure, acute onset of internal bleeding and kidney failure
Rave or adulterant?
Labs- Capsule analysis
Fifteen capsules/pills were submitted by the DCPD for analysis

CASE 34A- XZ- White Capsule (135mg)
• Compsd with RT, Formula matches
  • MDMA ~110 mg, MDEA~ 40ug
  • Ketamine
• Compsd with Formula matches
  • DMA, TMA

CASE 34B- VT- Light Yellow Capsule (275mg)
• Compsd with RT, Formula matches
  • MDMA ~270mg, MDEA~25ug
• Compsd with Formula matches
  • TMA, Methylenedioxy-2-methoxyamphetamine

Dosage of Regular Ecstasy in the Black Market: 80-120mg/ pill

“No Snack for Yew”

A 30-y-o moderately obese male with a history of infantile autism pica, mental retardation who was admitted to a group home 2 d prior to death. He was found unresponsive in the bath tub.

Case Report (con’t)
He was semi-conscious, has v-tach. Unable to obtain BP. He was shocked at 360 v and remained in asystole. ECG: bradycardia of undetermined origin, rate 42, multiple atrial premature complexes, 1° AV LBBB block. He dies after 3 h.

On the day of his death, he had been let alone in an enclosed courtyard of the facility, where he was found eating a variety of plants.

Autopsy findings
R.I. ME.'s office

- Respiratory system: large fresh red thromboemboli occluding the proximal portions of both pulmonary arteries.
- GI: The esophagus is unremarkable. No ulcers in stomach or duodenum. Stomach has ~300 cc of greenish/tan fluid with fragments of string bean vegetable-like material and fine bits of dark green plants. The cecal region contains softer tan fecal material containing fine flat green flecks of vegetable-like material.
Autopsy findings

Botanical examinations: species identified
- Yew (Taxus species)
- Japanese holly (Ilex crenta)
- Caroline rhododendron (rhododendron carolinianum)
- Poinsettia (spurges)
- Crown-of-thorns euphorbia (Euphorbia milli)

Cause of death

- ME: “Although the plants can cause GI distress and may be toxic when ingested in large amounts, there is no clinical nor pathologic evidence that the decedent ingested toxic quantities.”
- Cause of death: pulmonary thromboembolus due to bilateral deep vein thrombosis due to hypertensive and atherosclerotic cardiovascular disease.

Conflicting view

(hired forensic pathologist expert)
- Uncommon cause of death in this age group without precipitating condition (e.g., lower leg injury or immobilization).
- ME’s description suggests more of a generalized state of hypercoagulability.
- Clots show only the earliest stages of organization, i.e., formation within hours before death, not well-organized DVT that traveled to lungs.

CA PCC Plant toxicity rating

- Yew 1
- Holly (berries) 2
- Rhododendron 1
- Poinsettia 2,4
- Crown-of-thorns 2,4

1=major, serious illness or death
2=minor, vomiting or diarrhea
4=dermatitis, skin rash or irritation
Yew toxicity

- Taxine produces respiratory and cardiac depression.
- Symptoms include bradycardia, nervousness, trembling, dyspnea, incoordination within a few hours after ingestion.
- All parts of the plant contain Taxine including seeds of berries, but not the fleshy part.
- Lethal dose: 0.1-0.5% of body weight.
- No specific antidote besides supportive care.

Taxus sp. biochemistry

- Extract is used to produce Taxol for ovarian cancer tx. (paclitaxel)
- Drug metabolizes to benzoic acid and 3,5-dimethoxyphenol and is cardiotoxic

Yew toxicity to other animals (LD$_{min}$)

<table>
<thead>
<tr>
<th>Animal</th>
<th>LD$_{min}$ (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.7</td>
</tr>
<tr>
<td>Pig</td>
<td>0.7</td>
</tr>
<tr>
<td>Human</td>
<td>0.5-1.0  g</td>
</tr>
<tr>
<td>Sheep</td>
<td>2.5</td>
</tr>
<tr>
<td>Cow</td>
<td>2.0</td>
</tr>
<tr>
<td>Dog</td>
<td>2.3</td>
</tr>
<tr>
<td>Chicken</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Legal case report

- Challenge to R.I. ME's findings.
- Family members sues mental retardation facility.
- Chief complaint: lack of supervision of decedent given history of pica.
Illinois Poison Center Report  
JAMA 2001;286:271

- August to September 2000, reported 4 unintentional plant poisoning, 1 death from developmentally disabled adults.
- Postmortem exam of the death revealed 300 ccs of mulch, grass, twigs, and pine needles resembling those of the yew plant (Taxus species).
- Conclusion: removal of all toxic plants from areas surrounding facilities for developmentally disabled.

Verdict of civil case: facility found not guilty.

“Hospital Daycare”

Munchausen Syndrome
Historical Aspects

- Named after Baron Karl Fredrick von Munchausen (1720-1979), known for his imaginative tales.
- Condition whereby an individual presenting with an "apparent acute illness" that is fabricated with a dramatic untruthful medical history.

Munchausen Syndrome by Proxy

- Parents who by falsification, caused their children harmful hospital procedures
- In 9% of cases, a sibling also died, almost all due to unusual circumstances
- All cases were mothers (98% biological, 2% adopted).
- Mothers found themselves with a sense of purpose and safety in midst of disasters that they themselves created
A 3-mo boy brought to the ED with a 10 d history of feeding intolerance, lethargy & tachypnea. pH 7.02, AG=26, bicarb=3, +ve ketones, glucose=52, acetone=215 mg/L, ethylene glycol=180 mg/L. The MO Div. of Family Services took custody of the child. During a supervised visit, mother fed baby a bottle. Child became lethargic, had muscle spasms, and hyperventilation. Foster parents took child to ED, EtG=911 mg/L. The child dies after 3 d. The mother was tried and convicted of 1st degree murder and incarcerated. Two weeks later, the sibling became acidotic. Urine from the child was tested for EtG. Samples were retested and propionic acid, a metabolite of methymalonic acidemia was found. The mother was exonerated and released from prison.

A 5-wk old male presents to with lethargy, weakness, and respiratory distress. The child had a mild metabolic acidosis with a very high serum osmolality. He was poisoned with methanol. He was treated with folate and ethanol, and survived without complications. Mother recently attended class at UCSF on poisonings. No accidental source of methanol exposure could be found at home. Baby bottle contained trace methanol. The child was removed from the mother and placed into a foster home.

Was this a true positive or another false positive?
“Fatal Dedication”

A woman joins a cult religion. She becomes ill and is sent to the emergency room.

Autopsy Findings

- **Initial findings-external**
- Head & neck: abrasions on tip of nose
- Extremities: dark brown lesions consistent with insect bites
- Sclera: clear
- Chest, abdomen, back, teeth: unremarkable
- Deceased is incontinent of feces
- Left thigh: confluent old hematoma, 2-1/2 ".

**Final Anatomic Diagnoses**

- Thromboembolus left main pulmonary artery
Putative site of injury leading to emboli.

### Original Laboratory Results

(serum and vitreous humor)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Serum</th>
<th>Vitr.*</th>
<th>Normal (serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>180</td>
<td>180</td>
<td>135-145</td>
</tr>
<tr>
<td>Potassium</td>
<td>13.9</td>
<td>14.2</td>
<td>3.4-5.2</td>
</tr>
<tr>
<td>Chloride</td>
<td>163</td>
<td>161</td>
<td>93-109</td>
</tr>
<tr>
<td>BUN</td>
<td>NA</td>
<td>300</td>
<td>10-20</td>
</tr>
<tr>
<td>Creatinine</td>
<td>NA</td>
<td>2.6</td>
<td>0.5-1.4</td>
</tr>
<tr>
<td>Glucose</td>
<td>NA</td>
<td>15</td>
<td>70-105</td>
</tr>
</tbody>
</table>

*Vitreous humor analysis conducted 2 months after autopsy.

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### Dehydration and Pulmonary Emboli

- No published connection between dehydration and risk factor for pulmonary emboli.
- Ketones present in patients with dehydration.
- Vitreous urea can increase post mortem with prolonged time between death and fluid removal.

### Postmortem Changes in Canine VH

Expert Opinions

- Forensic photo-anthropometric image comparison: “results of linear-grid comparison for anthropometric measurements of forensic [pre- and postmortem] images, showed the decedent had not sustained an appreciable alteration of tissue mass.
- M. Baden review: “The manner of death is accidental. I find no evidence that malnutrition or dehydration contributed.” This conclusion based on photos of her 2 mo. prior to death.

Explanation for Increased BUN

- Sample dehydration during storage?
- Analytical assay artifact/interferent?
- Orbital proteins breakdown?
- Urea-producing microbiological contamination?
- Inadvertent contamination of sample?
- Purposeful adulteration?

“A Fib about A-fib”

- A real estate agent develops atrial fibrillation and is put on a standard dose of warfarin.
- When she questions him about the appropriateness of this dose, the doctor says to trust her.
Limited efficacy/response to drugs already on the market

- ACE inhibitors: 10-30%
- Beta Blockers: 15-35%
- Statins: 10-60%
- Alzheimer’s: 30%
- Analgesics: 80%
- Asthma: 60%
- Cardiac Arrythmias: 60%
- Depression (SSRI): 62%
- Diabetes: 57%

- Hepatitis C: 47%
- Incontinence: 40%
- Migraine (acute): 52%
- Migraine (prophylaxis): 50%
- Oncology: 25%
- Rheumatoid arthritis: 50%
- Schizophrenia: 60%

No PGx useful

Warfarin has a complex dose-response relationship making safe and effective use a challenge.
- More than 7% of outpatients suffer a major hemorrhage*
- 1/3 of INR values > target therapeutic range in first month*

Challenges in warfarin treatment

Warfarin dosing difficulties
Figure 1: INR values and warfarin doses of a patient with CYP2C9*3 allele variant requiring over 1 year to maintain a therapeutic INR.
“A Fib about A-fib”

- The agent has a VKORC1 variant and a 5 mg warfarin dose leads to a hemorrhagic stroke.
- In the end, the MD had “A fib about A-fib.”

“The Vacationing Rapist”

Darien, CT

Chronology of Kelly Case

- 2/10/86: Kelly offers ride to 16 y girl and is has sex in back of a Jeep.

Kelly: confident high school wrestler
Chronology of Kelly Case

- Kelly has fled to Europe for 8 years.
- Family meets Kelly in Switzerland, goes skiing.
- 7/18/94: Search warrant of Kelly’s parents home reveals Kelly’s residence.
- 1/19/95: Kelly surrenders to Swiss police.
- 5/4/95: Extradicted to U.S.
- 95,96: Two trials heard in Stamford CT.

Forensic Evidence

Trial #1, Carpet from Jeep contained 10-year old dried blood spots from victim. Spots extracted and tested by enzyme immunoassay. No confirmation testing (QNS).

- Trial #2: 10-year old dried blood spots from underwear from victim is analyzed by negative chemical ionization mass spectrometry (single ion monitoring) for THC-COOH. (where do the keep finding these samples?)
- Work was performed in a garage in Houston TX toxicologist.

Chromatogram of Dried Blood Standard
Chromatogram of Dried Blood
Dried Blood Spot Extract

Signal Created from Noise

Signal Created from Noise
Alex Kelly found guilty of rape

Given a 16-year sentence

Kelly's response: "Are you serious? I am not guilty. I am not guilty. I didn't do this. Why are you doing this to me?"

Paroled in 2007

Adrienne Bak & Hillary Buchanan asked that the parole board deny parole. (AP) Mar. 3, 2005. Two years later he is paroled with an ankle tracking bracelet.

Epilog:

“The Return of Alex Kelly”
105 min, USA, 1999

Directed by Ted Kotchoff, Starring Margot Kidder, Cassidy Rae, and Matthew Settle

Robert Ito “Sam” of “Quincy” plays the part of Alan Wu

The world changed due to the existence of a lab test.
"Bladder Control"

- Hubert Humphrey had undiagnosed bladder cancer when he ran for president in 1968.
- With permission from Muriel, his bladder biopsy was re-examined 25 years later revealing a p53 mutation.
- In history, Humphrey supported Johnson's war policy that cost him the election.
- **What if:** knowing his own mortality, he went against Johnson's administration earlier?
- A change of 153,000 votes out of 73 million in 4 states (IL, MO, OH, NJ) was needed to win or Nixon.
- How would the US be different had he been president?

"Purple Reign"

- King George III of England ruled during the US Revolutionary War.
- Centuries later, medical historians suggested he had porphyria, causing angry neurological fits and hallucinations.
- He went against advisors when the “colonists” wanted representation in the Parliament.
- **What if:** lab tests for porphyria were known in the 1700s and he was treated for porphyria (fluids, avoidance of sunlight) and altered his personality?
- How would the US be different today if there were no Revolutionary War?

What do you do for a living?

She: “I have to powder my nose. Will you excuse me?”

She leaves and doesn’t come back.