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Guillain Barré, or Something Worse?

By Olivia Iverson, BA, BM, and Theresa Kinard, MD

A middle-aged female presented to a local emergency department complaining of new-onset tingling and numbness in her hands and feet that started 2 days ago. The patient had no significant past medical or surgical history; family history was significant for a sister with systemic lupus erythematosus. The patient frequently enjoys camping throughout the northeast United States (US) but denied recent international travel. The patient reports a mild upper respiratory infection that was managed with over-the-counter medications after her last trip up to 1 week prior. She also reports that she received a coronavirus disease booster 4 weeks ago.

After thorough, standard-of-care evaluations, including insect-borne and travel-related infectious diseases, the preliminary primary diagnosis was Acute Inflammatory Demyelinating Peripheral Neuropathy, a clinical form of Guillain-Barré syndrome (GBS). Steroids and human immunoglobulin therapy were initiated but the neuropathy progressed. With rehabilitation, the patient began to show evidence of improvement with chronic immunoglobulin therapy over several weeks. In addition, mildly elevated fasting glucose prompted a 2-hour oral glucose tolerance test, which was abnormal. A trial of pregabalin 300 mg/day was initiated for concerns of diabetic neuropathy as a confounding factor.

Symptoms never resolved to baseline but the patient could resume normal activities. After a weekend outdoor barbecue, the patient developed nausea and vomiting that lasted 3 days. On day 4, she developed ascending pain in her bilateral lower extremities and called an ambulance for transportation to the emergency department. While in observation, her symptoms progressed to altered mental status and cardiovascular instability. Because the patient was previously diagnosed with GBS, admitting physicians were concerned about relapse. Aggressive empiric therapies were initiated for GBS and a lumbar puncture was performed to investigate possible etiologies of encephalitis. The patient had received immunoglobulin therapy within the week with no response, so therapeutic plasma exchange was initiated.

The nursing staff noted the presence of white bands across the patient's fingernails (Mees' lines), prompting a request to test for arsenic concentrations with reflex to speciation if elevated. While awaiting the results of heavy metal testing, the patient continued to deteriorate despite aggressive therapy and plasma exchange, suggesting past and current treatments were not effective. The patient was sedated and intubated for respiratory support. After transfer to the intensive care unit, the medical staff team observed that she began shedding hair and developed new cutaneous pustules on her arms. The onset of alopecia led to expanded toxicology testing.

Blood arsenic, mercury, and lead levels were all normal, but blood thallium concentrations were extremely elevated. After confirming that 24-hour urine thallium levels were also elevated, the patient was started on Prussian blue (ferric ferrocyanide) at 3 g, 3 times daily. After initiation of Prussian blue, blood thallium levels were observed to decrease throughout admission (Fig. 1). Unfortunately, the patient did not demonstrate significant neurologic improvement and remained ventilator-dependent at discharge to a skilled nursing facility.

Thallium Toxicity

Thallium is a rare heavy metal element in group III A of the periodic table. It is a soft, bluish-white metal that is odorless and tasteless in its pure form (1). Thallium exists naturally at low levels in the environment and is found naturally in several ores, including pyrites. However, thallium is more commonly released into the environment by human activity as a byproduct of iron, cadmium, copper,

Inside...

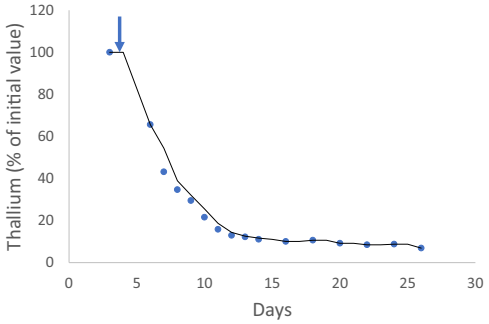

Fig. 1. Characteristic response of thallium to Prussian blue initiation (arrow).

zinc, and lead refining (1) as well as from the combustion of coal. It can be found concentrated in byproducts of industrial activity such as slag and fly ash. Historically, thallium compounds were used as potent rodenticides and insecticides in the US, but consumer use of thallium was banned in 1975 and these products were removed from the market. In several countries (notably China and Russia), thallium rodenticide is still available commercially. Thallium also has a variety of industrial uses such as in optical lens and semiconductor production.

Thallium and its compounds are more water-soluble than other heavy metal compounds and are easily spread through aqueous routes into soil and food crops. Acute toxicity of thallium to humans and animals is on par with or greater than many other metals such as cadmium and lead. The lethal dose of acute thallium ingestion is estimated to be approximately 10 to 15 mg/kg, although death has been reported at lower doses (2).

As a result of its high water solubility and significant toxicity, thallium contamination of soil and groundwater is a potential mechanism of exposure to dangerous amounts. Widespread chronic poisoning has been documented in areas with high soil thallium concentrations, most notably in Guizhou Province, China in the 1960s through 1970s as a result of waste slag pollution of cropland. There have also been cases of poisoning from occupational industrial exposure, mainly attributed to skin contact and inhalation in handling flue and pyrite dust (1). Additionally, due to its colorless, tasteless, odorless nature and extreme toxicity, thallium has been intentionally used as a poison since the discovery of the element in the 1860s.

Thallium is absorbed through the gastrointestinal tract and skin and undergoes enterohepatic recirculation. The mechanism of thallium toxicity is thought to be related to its similarity in charge and ion radius to potassium. Thallium can displace potassium in various enzymes and ion channels, broadly inhibiting cellular energy production. It also disrupts cysteine disulfide bonds, which is the mechanism behind the classic presentation of alopecia. Due to its similarity in charge and ion radius, thallium deposits in tissues with high potassium concentrations such as neurons, myocardium, and renal tissue, with the highest concentrations found in the kidney after ingestion (3). The half-life of thallium in human tissue ranges from 1 to 30 days depending on the initial dose. It is primarily renally excreted in the first 24 hours after ingestion, after which point fecal excretion becomes significant (3, 4).

The 2021 Annual Report of the National Poison Data System reported 66 single exposures to thallium in the US (5). Of these, 24 exposures were reported as unintentional, whereas 25 were categorized as "other" and 3 as adverse reactions (defined as an allergic, hypersensitivity, or idiosyncratic response to a substance). Of the individuals exposed, 44 were greater than 20 years old and 12 were 19 years old or younger. No deaths due to thallium exposure were reported, but 3 major outcomes, 4 moderate outcomes, and 3 minor outcomes were recorded. A major outcome is defined by the report as involving life-threatening signs or symptoms or resulting in significant residual disability or disfigurement. Moderate outcomes are defined as requiring treatment but not life-threatening and not resulting in disability or disfigurement. A minor outcome is one that is minimally bothersome and generally resolved rapidly.

Clinical Presentation

The clinical presentation of acute thallium ingestion (a single, large exposure) typically

Table 1. Acute thallium poisoning: symptoms timeline.

Stage 1 24 to 96 hours	Gastrointestinal	Nausea, vomiting, abdominal pain, cramping, diarrhea, or constipation
Stage 2 1 to 5 days	Neurologic	Pain (ascending peripheral neuropathies) sometimes accompanied by motor neuropathy, weakness, ataxia, tremor, cranial nerve palsies, headache, seizures, coma, death, ophthalmologic disturbances (diplopia, optic neuropathy), or respiratory disturbances (pneumonitis, ARDS, and pulmonary edema)
Stage 3 2 to 3 weeks	Dermatologic	Alopecia, skin scaling, acneiform, or pustular eruptions, Mees lines

involves gastroenteritis, neuropathy, and alopecia (Table 1). Symptoms of thallium toxicity are dose-dependent. Exposure to small doses of thallium can present with delayed symptoms, while large doses may produce symptoms within minutes.

Within the first 48 hours after exposure, gastrointestinal symptoms are predominant, including abdominal pain, vomiting, constipation, diarrhea, and gastrointestinal hemorrhage (3). Neurological symptoms typically appear 2 to 14 days after exposure. The classic neurologic symptom of thallium poisoning is painful sensory neuropathy affecting the distal limbs (often termed a "stocking-and-glove" distribution), but motor neuropathy may also occur (3, 4). Central nervous system toxicity manifests as delirium, hallucinations, cranial nerve dysfunction (most commonly of cranial nerves II, III, IV, and VI), nystagmus, ataxia, seizures, and coma (3, 4, 6). Neurologic effects may last for weeks to months and may be permanent.

Acute cardiovascular effects of thallium ingestion involve hypotension and bradycardia, followed by hypertension and tachycardia as vagal nerve degeneration occurs (3). Respiratory sequelae may also be seen, including pneumonitis, pulmonary edema, or acute respiratory distress syndrome. Alopecia is perhaps the most well-known effect of thallium poisoning. It classically involves the scalp and lateral eyebrows but can involve body hair. Classically, the hair root also develops black pigmentation. Alopecia begins typically 7 to 12 days after ingestion and is complete by approximately 1 month. Hair loss is typically not permanent and re-grows over days to weeks (6).

Chronic thallium poisoning may only present with alopecia and neuropathy, with gastrointestinal symptoms often mild or nonexistent (6). Other major symptoms of chronic poisoning include headache, anorexia, and abnormal pain (3, 4).

Differential Diagnosis

The symptoms of thallium poisoning are often missed given the rare use of thallium as a rodenticide in the US today. The differential diagnosis for thallium poisoning includes arsenic poisoning, which can cause abdominal pain, diarrhea, and paresthesias (6). Colchicine toxicity also presents with gastroenteritis acutely and peripheral neuropathy chronically (7).

The differential diagnosis for thallium poisoning also includes botulism and GBS. Similar to thallium toxicity, GBS can present with paresthesias, limb weakness, and cranial nerve dysfunction. In fact, a 2021 case report describes a 43-year-old man with thallium poisoning who was mistakenly diagnosed with GBS, gastroenteritis, and diabetic peripheral neuropathy (8). Despite the normalization of blood thallium levels in this patient after 2 months of Prussian blue treatment, at a 6-year follow-up, he continued to suffer weakness and lower extremity numbness. A literature review associated with this case report found polyneuropathy to be the most common presenting symptom of thallium toxicity, followed by alopecia.

Chronic selenium toxicity is also on the differential as it can cause hair and fingernail loss, numbness, and paralysis (3, 4). Exposure to other heavy metals, most notably arsenic and mercury, can result in alopecia. Additionally, patients with alopecia due to chronic thallium poisoning may be mistakenly diagnosed with other causes of hair loss such as alopecia areata or telogen effluvium. In general, when peripheral neuropathy is accompanied by alopecia, thallium poisoning should be suspected.

Laboratory Testing

Thallium toxicity can be confirmed by finding elevated thallium levels in body fluids such as blood, urine, saliva, and feces as well as in the hair and nails. Thallium is cleared quickly from the blood, so in the absence of ongoing exposure blood levels may no longer be elevated by the time the classic symptom of hair loss manifests (6). A 24-hour urine thallium concentration is often the most accurate way to confirm toxicity.

Blood and urine thallium testing in the US is frequently performed by inductively coupled plasma mass spectrometry (9). Inductively coupled plasma mass spectrometry uses high-temperature plasma (typically ionized argon gas) to atomize and ionize samples, and determines component elements according to mass-to-charge ratio (m/z). Reference values for blood thallium are generally in the range of <2 ng/mL. Urine reference values vary depending on whether specimens are random or 24-hour collections, and whether results are normalized to creatinine.

Other methodologies to measure thallium include flameless or flame atomic absorption spectroscopy, often with sample extraction and/or chelation preceding analysis. Spectroscopic methods tend to be slightly less sensitive than inductively coupled plasma mass spectrometry, with correspondingly higher reference values, often around <5 to 10 ng/mL.

Thallium blood concentrations in survivors of accidental or intentional thallium poisoning averaged 290 ng/mL (range 70-740 ng/mL); fatal cases reported mean blood concentration of 4200 ng/mL (range 500-11000 ng/mL) (9).

Treatment and Outcomes

Whole-bowel irrigation with polyethylene glycol is recommended in the setting of recent ingestion (5). Thallium binds well to activated charcoal, unlike other heavy metals, and multiple-dose activated charcoal can be administered with a cathartic agent. Multiple-dose activated charcoal reduces

enterohepatic circulation of thallium and enhances excretion (10).

Prussian blue is a chelating agent that binds thallium better than activated charcoal and is the preferred mechanism for enhancing the elimination of thallium (10). However, Prussian blue may be difficult for healthcare facilities to acquire in amounts necessary for the treatment of thallium poisoning (dosing is 250 mg/kg/day (6)). Prussian blue sequesters thallium and disrupts enterohepatic circulation, creating a gradient that draws more thallium into the lumen of the gut and allows for increased excretion (6). Chelation decreases the biological half-life of thallium to as low as 2 to 3 days in blood.

Hemodialysis, hemoperfusion, and continuous renal replacement therapy can also be used to enhance clearance of thallium and should be used as soon as possible if available (11). Although a 2019 case report implies that plasma exchange in conjunction with Prussian blue was successful in treating thallium poisoning (12), in our experience plasma exchange is not effective at reducing blood thallium levels.

Patient outcomes vary widely, depending somewhat on whether exposure is acute or chronic, and how rapidly a diagnosis is made. The wide range of alternative diagnoses for initial neurological and gastrointestinal symptoms, combined with delayed onset of more definitive indicators such as alopecia, can result in delayed recognition of thallium exposure, particularly in regions where thallium-containing compounds are banned. Some case reports describe prolonged symptoms for years after exposure, even in patients whose blood thallium was successfully lowered with therapy.

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The authors have nothing to disclose.

Bupropion Intoxication

By Sarah Riley, PhD

Case Presentation

A 52-year-old female with a history of suicide attempts presented to the Emergency Department with her son, who said that his mother had called him after she intentionally ingested 70, 325 mg of bupropion tablets (approximately 22 g). In the Emergency Department, she appeared somewhat agitated, but properly oriented, and her vital signs were normal. However, given this history of ingestion, she was admitted for observation. About 2 h after admission, she became increasingly agitated and showed signs of delirium. She developed tachycardia (93 bpm) and hypertension (125/90). Within an hour of developing these symptoms, she began to have tonic-clonic seizures that persisted over 5 min. Shortly after the onset of seizure activity, she developed severe hypotension. An electrocardiogram (EKG) showed QRS widening and QT/QTc interval prolongation. Despite attempts to rectify the cardiac symptoms, she progressed to cardiovascular shock. She was pronounced dead 7 h after her admission. Bupropion was measured in postmortem blood and determined at 982 ng/mL.

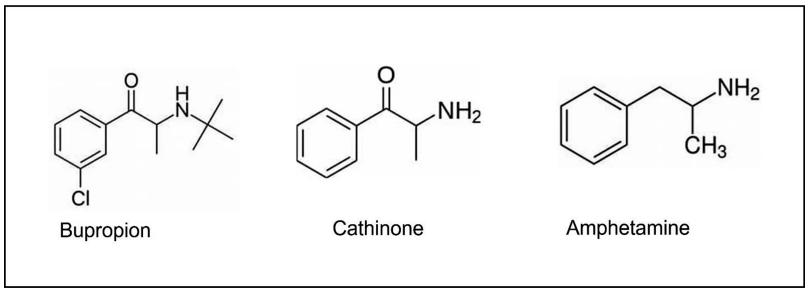

Fig. 1. Chemical structures of bupropion, cathinone, and amphetamine.

What Is Bupropion?

Bupropion (Wellbutrin) is an antidepressant drug and an N-tert-butyl analog of cathinone. Structurally and pharmacodynamically, bupropion works similarly to amphetamines (Fig. 1). Bupropion exerts its antidepressant effects by inhibition of dopamine and norepinephrine reuptake activity. It is also a nicotinic acetylcholine receptor antagonist. Unlike many other antidepressants, it has minimal effect on serotonin activity (1). Peak serum concentrations are achieved ~1.5 h after dosing with immediate-release formations, and 5 h after dosing with extended-release formulations. Bupropion undergoes hepatic metabolism via microsomal CYP2B6 to the major metabolite hydroxybupropion, which has about 50% activity of the parent drug. Metabolism is a slow first-order process, with a half-life of nearly 21 h. The half-life can extend even longer in individuals with impaired hepatic function (2).

Bupropion has a wider therapeutic index than tricyclic antidepressants and has been increasingly replacing these drugs for the treatment of depression. It is also prescribed for tobacco use cessation, obesity, and ADHD. Its use for ADHD is primarily in the pediatric population. Typical therapeutic doses range from 150–300 mg per day, and the drug is available in both standard and extended-release formulations. Bupropion is typically well tolerated at therapeutic doses, with the main side effects being dry mouth, facial flushing, and insomnia. These effects are likely due to antagonism of the nicotinic acetylcholine receptor. Bupropion does lower the seizure threshold, and seizures can occur at therapeutic doses. While this can happen with bupropion as the sole therapeutic, the risk is greater in individuals with a history of seizures or taking other therapeutics that also lower the threshold (2).

Toxicity of Bupropion

Higher doses associated with bupropion misuse can be toxic (1-3). Unique from other antidepressants, bupropion can cause cardiogenic shock (3). Bupropion toxicity can present in 4 phases (4, 5):

1. Latent phase; characterized by absent or minimal symptoms. An EKG and vital signs may be normal. While seemingly benign, the latent phase is dangerous because it may result in the early discharge of a seemingly normal patient. Ingestions of delayed-release formulations are especially at risk for early discharge (6).
2. Neurotoxic with mild symptoms; characterized by delirium and sympathetic activation. The patient may have tachycardia and hypertension. Delirium may present as the prodrome to seizures (phase 3) (7).
3. Neurotoxic with seizures; characterized by seizures that are often repeated. This may progress to status epilepticus and the patient may need to be intubated. While doses as low as 575 mg have been associated with seizures, the risk becomes increasingly likely with doses greater than 3 grams (7).
4. Cardiotoxic phase; is characterized by prolonged QTc and QRS intervals, hypotension, bradycardia, and systolic heart failure with reduced ejection fraction. This may progress to coma and death. The risk of cardiac toxicity becomes increasingly likely with doses greater than 10 g (8).

Bupropion overdose can mimic brain death. The patient can have a complete lack of brainstem reflexes, with fixed and dilated pupils, and burst suppression on EEG. These patients can have

Table 1. Bupropion and hydroxybupropion reference intervals are offered by 3 major reference labs in the United States. Lab 2 reports the reference interval as the average of steady-state concentrations in a number of patients taking specific doses of bupropion. Neither Lab 2 nor Lab 3 report "toxic" intervals.

	BUP Therap. (ng/mL)	HB Therap. (ng/mL)	BUP Toxic (ng/mL)	HB Toxic (ng/mL)
Lab 1	10–100	850–1500	≥ 400	≥ 2000
Lab 2	120–270	1000	not given	not given
Lab 3	50–100	600–2000	not given	not given

BUP: Bupropion; HB: Hydroxybupropion; Therap: Therapeutic Interval; Toxic: Toxic Interval.

excellent neurologic outcomes. Referred to in the literature as the "Lazarus effect," a full neurologic recovery can be achieved 3–5 days after the presentation of "brain death" (9).

The diagnosis of bupropion intoxication is primarily based on exposure history. The most common overdoses of bupropion are associated with either intentional self-harm or recreational use. Because it inhibits dopamine reuptake, it seems reasonable that there would be some addictive potential, like amphetamines or cocaine. Reports of recreational use first appeared in 2002, mainly among teenagers experimenting with drug misuse. Since then, there have been numerous published cases of bupropion misuse, especially in the incarcerated population. Street names for bupropion include "jail house coke," "wellies," "dubs," and "Barnies" (referring to the purple color of some formulations). In misuse situations, bupropion may be ingested, insufflated, or injected (1).

Bupropion and hydroxybupropion can be detected and quantified in serum and urine by HPLC with ultraviolet detector, GC/MS, and LC/MS techniques. Not surprisingly due to the structural similarities, bupropion can cause false positive amphetamine screens by immunoassays (11,12).

There are no defined therapeutic serum concentrations for bupropion for therapeutic drug monitoring. Three different major reference labs in the United States offer the reference intervals detailed in Table 1. Complicating any effort to monitor serum concentrations is the inherent instability of the drug. Postmortem concentrations should be interpreted with these facts in mind, and the clinical presentation and use history should be considered when evaluating a postmortem case of potential bupropion overdose (10). Hydroxybupropion is more stable than the parent drug, and it has been suggested that the parent and metabolite both be measured when considering serum concentrations (13).

CYP2B6 phenotyping may be used for assessing those at risk for abnormal metabolism of bupropion and potentially at risk for either toxicity or failure to respond.

The patient described in the introductory case is a classic example of bupropion toxicity. She presented in the latent phase of toxicity, progressing rapidly through the neurotoxic and cardiotoxic phases of toxicity. This was consistent with her reported overdose of 22 g of bupropion. Despite all efforts, she was unable to be revived after progressing to cardiogenic shock. Clinical and forensic toxicologists and other laboratory scientists should be aware of bupropion toxicity to be ready to assist the bedside provider in medical management.

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2023 Society of Forensic Toxicologists (SOFT) Annual Meeting Recap

By Sarah Riley, PhD

Society of Forensic Toxicologists (SOFT) 2023 convened at the Gaylord of the Rockies in Denver, Colorado, from October 29 to November 3, 2023. The local hosts, Dan Anderson, Vanessa Beal, and their planning committee, orchestrated a

remarkable meeting filled with opportunities for learning, networking, celebration, and enjoyment.

The event commenced with 2 days of workshops, a notable change being that all were half-day sessions, allowing attendees to tailor their experience. Covering a spectrum from beginner to advanced levels, the workshops spanned various subjects such as pharmacology, forensic interpretation, pediatric toxicology, cannabis testimony, measurement uncertainty, Lean Six Sigma principles, and career development in forensic toxicology.

Scientific platform sessions unfolded from November 1 to November 3. The first day's sessions, expertly moderated by Marilyn Huestis and Cristina Sempio, explored dose effects of oral and vaporized Delta-8-THC, comparisons with Delta-9-THC, and trends in meconium marijuana prevalence. Subsequent sessions, hosted by Karen Scott and Curt Harper, investigated alternative matrices for analysis, including oral fluid THC results in a "green lab" setting and the evaluation of novel psychoactive substance drug loss during storage. The "Postmortem" session, moderated by Samantha Tolliver and Marissa J. Finkelstein, covered intriguing topics like foam cones in postmortem cases and their correlation with opioid-related deaths, the emergence of fentanyl-related deaths in specific areas, and investigations into caffeine-induced fatalities. The day concluded with a clinical aspects session overseen by moderators Frank Peters and Marta Concheiro-Guisan, presenting findings on adverse events and plasma pharmacokinetics after controlled oral kratom leaf administration, the impact of anabolic-androgenic steroids on drug-drug interactions, the prevalence of high body mass index in people with opioid use disorder, and challenges associated with fentanyl use interpretation.

Simon Elliott and Sara Walton moderated the "Novel Psychoactive Substances" session, covering surveys of forensic laboratories testing for NPS, their prevalence in routine prescription drug monitoring, and in-depth explorations of fentanyl analogues, synthetic opioids, and emerging compounds in the recreational drug supply. The "Analytical Methods" session, moderated by Jochen Beyer and Sara Dempsey, featured discussions on identifying major hydroxylated metabolites of cannabidiol (CBD), developing a standard test method for ethanol in the blood, quantifying cannabinoids in human plasma and umbilical cord as a matrix, untargeted LC-HRMS screening methods, and automated sample preparation methods.

Friday's focus was on "Drugs and Driving," moderated by Rebecca L. Hartman and Nathalie Desrosiers. Topics included combining toxicology testing with field sobriety test results for improved cannabis impairment classification, evaluating the efficacy of field sobriety tests in identifying drivers under the influence of cannabis, cross-reactivity of cannabinoid analogs, application of LC-QTOF-MS for data analysis in blood specimens, and acute and chronic oral dosing of cannabidiol (CBD). The day concluded with insights into underreported methamphetamine positives, interference of novel designer benzodiazepines with alprazolam analysis, and toxicological results from drug-facilitated sexual assault cases. The scientific session wrapped up with "Best Practices," moderated by Sumandeep Rana and Sue Pearring, discussing a trial program for a reduced workweek in forensic toxicology laboratories, updates on standards development activities, implementation of consensus-based standards, and the potential for Chat GPT to produce court-ready interpretations of toxicology reports.

In addition to the sessions, 125 posters were presented on Wednesday and Thursday, covering diverse topics such as the analysis of cannabinoids and opioids, new and designer drugs, toxicity studies and poisoning cases, method development and validation, impaired driving investigations, pediatric and demographic studies, and best practices, standardization, and certification. The poster sessions were bustling and well-attended, reflecting the richness of the content presented.

SOFT 2023 was given a special touch by moving tributes to Liz Kiely, a very beloved member of the forensic toxicology community. The vendor hall was named the Liz Kiely exhibit hall, and her mother and brother were present at the Annual Business Meeting to receive the Distinguished Service Award on her behalf. These were poignant reminders of the closeness of our professional society.

SOFT 2024 will take place from October 27 through November 2 in St. Louis, MO. Mark your calendars now!

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The author has nothing to disclose.

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