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*Editorial*

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# Forensic Toxicology: The Dangers of Chasing the Single Molecule

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On depictions dating from the Middle Ages, physicians are often shown holding a glass with a yellowish liquid: urine, the most accessible biological sample. Dipping their finger into the fluid and then licking it allowed them to taste sugar (if it was present) and therefore to diagnose diabetes. Mothers of babies with cystic fibrosis tasted the saltiness of their offspring on kissing them and knew that something was terribly wrong. The sweet smell of ketones would announce the imminent demise of patients in diabetic coma.

From the early primitive use of our senses to identify sweet, salty, or aromatic substances (and diagnose conditions), we have come quite a long way. Today, forensic toxicology – the analysis of biological samples for the presence of toxins, including drugs – is a recognized and respected discipline.

The progress made by technology in the area of forensic toxicology is truly amazing: the limits of detection are continuously being pushed lower and lower. Indeed, we are not far away from being able to identify the presence of single molecules in a sample. While such analytical miracles based on solid technology have robust and reproducible results (may be not if one indeed has single molecules in a sample), the interpretation of results is far from simple. At one period in my life, I had the opportunity to travel to exotic, faraway kingdoms; before entering the foreign places I had to fill out immigration forms where the warning "Death penalty for drug possession" was indeed printed in bold red letters. Not that I ever used opiates, but I was well aware that some of our potential intestinal parasites were able to produce traces of morphine in order to reduce our ability to get rid of them through defecation (i.e., to induce constipation).[1,2] Now imagine the following scenario: for whatever reason, a biological sample from your body is analyzed and found positive for traces of morphine. You are brought in front of a judge, and your defense line sounds like this: "*I didn't do it, your honor; it was my intestinal parasites*." To make things worse, the most efficient morphine producer is apparently the nematode Ascaris suum, the large roundworm of pigs (and people).

Not likely to elicit sympathy in the aforementioned judge. Start composing your obituary. Of course, such a thing could never happen to me, since I decided to use mebendazole prophylactically. But there are plenty of other options to get in trouble…..

While I am not a vegetarian, I could in theory consume large amounts of healthful foods not realizing the associated risks. Many vegetables and grains produce and therefore contain benzodiazepine sedative-hypnotics.[3,4] Now imagine the following scenario: after a car accident in which you are involved, a biological sample is analyzed and found positive for diazepam. The line "*I ate too many potatoes*" will not help you keep your driving license or your fortune (if you live in a society enamored of litigation and run by lawyers).

But that was only a benign scenario; let's figure out a way to get on the coveted "*No fly list*" that is regularly updated by Homeland Security. What about traces of organophosphates (cholinesterase inhibitors; ChE-I) in your luggage?

While non-organophosphate inhibitors of cholinesterase are very common in nature,

their numbers running in the hundreds,[5] it has only recently been recognized that potent pesticide and nerve gas – like organophosphate inhibitors of cholinesterase also occur in nature, produced by bacteria, algae, and marine sponges, and possibly by many other creatures. Rainer Neumann and Heinrich H Peter, working in Switzerland for Ciba-Geigy, were the first to point out that "Nature made them first": they isolated two related furo-dioxa-phosphepin cholinesterase inhibitors from cultures of the soil microorganism Streptomyces antibioticus.[6] The identification of a closely related compound named cyclophostin, from Streptomyces lavendulae, was reported a few years later by a Japanese group.[7] A structurally different imidazole phosphor ester named anatoxin-A(s), produced by green-blue algae, was also reported.[8] Finally another imidazole phosphor ester, ulosantoin, was isolated and identified from a marine sponge named Ulosa ruetzleri (Orange Lumpy Encrusting Sponge); the compound has an ChE inhibitory potency comparable to that of paraoxon, in the low nanomolar range.[9]

In conclusion, while our ability to identify substances at lower and lower concentrations, virtually chasing the single molecule, is impressive to say the least, results need to be interpreted with caution and in context. Possible explanations for the presence of restricted substances in biological samples, although sometimes really weird and unlikely, nevertheless need to be explored. One must never forget that truth is, in the words of Lord Byron, "*stranger than fiction*".[10]

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