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Ms. Kate Frame
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Re: Sheku Ahmed Tejan Bayoh

Dear Ms. Frame,

In your letter of August 13 of this year you posed four questions. Specifically, you wished to know (a) "the physiologic effect of the drugs detected in the toxicology sample, individually or in combination on the deceased in the circumstances of his arrest", (b) "the physiological effect of the CSS/PAVA spray individually or in combination on the deceased in the circumstances of his arrest"; (c) "the physiological effect of restraint of the deceased in the circumstances of his arrest", (d) "the physiological effect of (a), (b) and (c) on the deceased in combination in the circumstances of his arrest."

The answers to all four questions are interrelated. To answer them it was first necessary to perform my own histological examination of the heart, which I did on August 25, 2015, at Guy's Hospital in London, England. PIRC Investigator William Little was also present.

My review disclosed histological abnormalities that were apparently overlooked at the original autopsy. Because of their presence I conclude that the decedent suffered from pre-existing heart disease that could have been fatal in its own right. In addition, the three drugs found in Mr. Bayoh's body were, at a minimum, contributory causes of death and quite possibly the actual cause of death. Very little data about the effects of alpha-PVP exists, but the little that has been reported suggests it may well have been the sole cause of death. Because of its molecular interactions, alpha-PVP is a particularly dangerous drug, far more dangerous than MDA or MDMA, although all three operate by somewhat the same mechanism – disruption of the dopamine component of the neurotransmitter system.. Finally, while the microscopic alterations I observed in cardiac structure were mostly of a chronic nature, known consequences of both long-term

stimulant and steroid abuse, they could have caused sudden death at any time, even in the absence of all drugs. At the same time, acute microscopic alterations, also potentially fatal and a result of alpha-PCP usage were also observed [1].

Answers to your specific questions follow. All of the assertions below are supported by multiple studies in the peer-reviewed literature and a list of these references is appended. to these studies are appended. The histological changes discussed are not illustrated, but can be if it is so desired (the changes were particularly obvious in slides designated AG, AH, AA and Z in the original autopsy report).

Question #1: What was "the physiologic effect of the drugs detected in the toxicology sample, individually or in combination on the deceased in the circumstances of his arrest?"

Answer: All of the drugs detected (alpha=PVP, MDA and MDMA) cause acute and chronic cardiotoxicity. Any, or all of them, might have been the cause of death, but it is impossible to determine which drug actually did.

Explanation

1. Alpha-PVP (*a*-pyrrolidinovalerophenone)

a. Alpha-PVP belongs to the class of drugs known as synthetic cathinone derivatives, modified versions of the primary stimulant molecule (cathinone) found in the khat plant. Laboratory evidence suggests this molecule acts more or less like other members of the cathinone group and exerts amphetamine-like effects. There are no controlled autopsy studies of this drug, nor has its metabolism been characterized in the living. A number of case reports [2] and two collections of human case reports have been published [3] [4], but none of these cases, save for two, contain any detailed descriptions of the changes in the heart. The changes that are described exactly mirror those observed in Mr. Bayoh (uneven staining pattern of the myocardium, fragmentation and waviness of fibers, perivascular connective tissue growth, intramuscular fibrosis and scarring, disintegration of cardiomyocytes, nuclear disintegration, loss of cross-striations and thickening of blood vessel wall) [5]. The single case report by Nagi et al., showed extensive contraction band necrosis, a morphologic alteration that is non-specific, but which is often encountered in cases of sudden death [3][6] [7] These case reports are, of interest because they demonstrate there is no relationship between measured postmortem blood concentrations and apparent toxicity. MDMA and MDA which were also found at autopsy share some of the same cardiotoxic actions as synthetic cathinones, but the results of vitro studies suggest that alpha-PVP is many times more powerful and more dangerous than either MDMA or MDA [1].

b. MDA, MDMA, and alpha-PVP are each classified as Monamine Oxide Inhibitors (MAOI); they were the first group of drugs designed to treat depression. They do so by disrupting the mechanism of drugs that transmit messages from nerve cell to nerve cell. These transmitters are called monoamines (dopamine, norepinephrine and serotonin). MAOIs are antidepressant by virtue of their ability to increase brain dopamine concentrations resulting in improved mood or even euphoria. Their dangerous side effects have rendered them a second line drug [8]. However, if the increase in brain dopamine is too great, disruption of normal brain function may occur with lethal consequences, sometimes in the form of a disease known as excited delirium syndrome (ExDS) [9, 10]. Mr. Bayoh, the decedent, exhibited many of the features of excited delirium.

In clinical practice 10-13 symptoms are generally recognized as components of the Excited (or Agitated) delirium, depending upon who is drafting the list [11]. The list includes

a. extremely aggressive or violent behavior
b. constant or near constant physical activity
c. does not respond to police presence
d. attracted to/destructive of glass or other reflective surfaces
e. naked or inadequately clothed
f. attempts at "self-cooling, or skin hot to the touch
g. rapid breathing
h. profuse sweating Keening (makes unintelligible animal-like noises
i. insensitive to/extremely tolerant of pain
j. excessive strength (out of proportion)
k. does not tire despite heavy exertion

The results of thorough in vitro studies of human brains harvested from those who succumb suggest that most, probably all, of the symptoms listed are a consequence of dopamine excess [9]. As is apparent from a review of the list, dopamine excess could account for most of the behavior observed in Mr. Bayoh. What clouds the situation is that the decedent would have been suffering from three different syndromes at the same time: excited delirium, serotonin syndrome, and hyperadrenergic syndrome (due to an excess of norepinephrine causes by the drugs)..

If too much serotonin accumulates, a different, but related disorder called "serotonin syndrome" occurs. Serotonin syndrome has been observed in other users of alpha-PVP related cathinones. When too much norepinephrine accumulates, "hyperadrenergic syndromes" result. Excess adrenergic activity compromises circulatory status, damages the heart, and sometimes leads to the occurrence of lethal cardiac arrhythmias. Both the clinical history and the

observed cardiac lesions, suggest a scenario where all three drugs detected combined to cause death in this case.

2. Methylenedioxyphene (MDA)

a. This drug belongs to the amphetamine family of drugs, but seems to be taken more for the psychogenic effects than for the stimulant actions normally associated with amphetamines. MDA and MDMA ("ecstasy") have slightly different structures than drugs like alpha-PVP, but nonetheless exert many of the same effects [12] [13]. Pharmacologically, MDA acts as a serotonin-norepinephrine-dopamine releasing agent and reuptake inhibitor, essentially the same effects produced by the cathinones. Its effects, when taken with alpha-PVP can be presumed to be additive, which means that the same type of toxicity and the same syndromes can be produced as those caused by the cathinone alpha-PVP.

3. Nandrolone

a. High doses of nandrolone elicit cardiotoxic effects including cardiac remodeling and injury. There is also laboratory evidence that they my provoke arrhythmias. As myocardial remodeling of both ventricles was apparent on my examination of the heart, it seems only reasonable to conclude that nandrolone contributed to the process, as did all of the other stimulant drugs. There is also evidence that, by methods yet to be determined, nandrolone facilitates the occurrence of myocardial arrhythmias, the apparent cause of Mr. Bayoh's demise [14] [15].

4. Myocardial Disease

a. Myocardial remodeling and necrosis: Myocardial remodeling is the term general used to describe changes in the size, shape, and structure of the heart after it has been injured [16]. It was first introduced to describe the increased muscle mass that can be found surrounding areas of healing myocardial infarction. The increase occurs to compensate for the muscle lost in a heart attack, and to that extent is beneficial. However, remodeling is not always beneficial or always the result of infarction [17]. It is commonly caused by chronic high blood pressure, heart valve disease, and often by stimulant drug abuse. In all of these later situations remodeling is detrimental. In fact, the presence of remodeling is an established independent risk factor for the occurrence of sudden cardiac death (SCD). My microscopic examination disclosed remodeling changes throughout the heart. These changes included the presence of enlarged heart cells with abnormal cell nuclei and abnormal fibrous tissue located between the heart cells and around blood vessels [17]. The blood vessels themselves were

abnormally narrowed and many of the vessels were surrounded by abnormal fibrous tissue that would act to diminish blood flow to the rest of the heart, favoring arrhythmia and sudden death.

b. In addition to changes characteristic of remodeling, other areas of cellular destruction were apparent throughout the heart and some of these areas were surrounded by the type of cells normally seen in cases of "heart attack"; the term "micro-infarction" seems most descriptive [18] [19]. This sort of destruction is seen whenever concentrations of norepinephrine, or norepinephrine-like drugs, are present in excess, especially in methamphetamine and cocaine abusers. Since alpha-PVP elevates norepinephrine blood concentrations (as do MDA and MDMA), one would presume the drugs detected at autopsy caused these acute changes. Cellular damage of this type facilitates the occurrence of myocardial arrhythmias as well.

Question #2 was about "the physiological effects of the CS/PAVA spray individually, or in combination, on the deceased in the circumstances of his arrest."

Answer: These agents are toxic to the extent that they cause damage to the respiratory tract. Respiratory tract damage was not found at autopsy, only pulmonary edema, which can occur as complication of either spray component, but only if the spray directly enters the lungs. The exact same type of fluid accumulation occurs as a consequence of heart failure, as well as stimulant and narcotic abuse. In other words, it is a non-specific finding. It is reasonable to conclude that neither of these agents found in the spray contributed to the cause of death, because autopsy disclosed no evidence that either of the agents had entered the throat (there would have been visible damage to the respiratory tract).

Explanation: According to a recent paper in the *Journal of the Royal Army Medical Corps*, CN, CS and OC are effective riot control agents. In the majority of exposures, significant clinical effects are not anticipated [20]. Other controlled experiments with human volunteers have shown no significant effect of these agents when applied as directed [21] There is no evidence that CS/PAVA was applied incorrectly. The irritant effects can be minimized both by rapid evacuation from sites of exposure, decontamination and appropriate supportive care. When toxicity has been reported it is almost always after exposure to very high concentrations in confined spaces. If there is underlying disease, the outcome is likely to be even worse [22].

In the most recently published study, 10 lethal cases of death from riot control agents (RCA) were analyzed [23]. In three cases, RCAs (riot control agents) were found to be the sole cause of death; in three cases, RCAs were ruled a secondary cause of death due asphyxia or asthma subsequent to exposure to RCAs; and in four cases, RCAs were contributory factors to death. In three cases the responsible agents were identified as

Chloroacetophenone (CN), Chlorobenzylidene malononitrile (CS) and Oleoresin capsicum (OC) and in the remaining seven cases, the agent was OC alone. **As there are no specific findings in suspected cases of death associated with RCA use, establishing cause of death and whether RCAs are the sole cause or only a contributory factor will be based on the elimination of other possible causes of death**. I have highlighted the fact that the authors say the diagnosis of death by OC is a diagnosis of exclusion. Given all the operative factors in this case, exclusion of other, much more compelling causes is impossible.

PAVA spray is a synthetic form of pepper spray, i.e., a synthetic capsaicinoid (the abbreviation stands for pelargonic acid vanillylamine) found in chili peppers, and sometimes used as a food ingredient. The only significant difference is, to the best of my knowledge, no deaths have ever been attributed to PAVA.

Finally, another experiment testing the effects of capiscum spray on humans should be noted. A randomized, cross-over controlled trial was performed. Thirty-five subjects were exposed to OC or placebo spray, followed by 10 minutes of sitting or prone maximal restraint position (PMRP). Spirometry, oximetry, and end-tidal CO2 levels were collected at baseline and throughout the 10 minutes. Data were compared between groups (ANOVA) and with predefined normal values. In the sitting position, OC did not result in any significant changes in mean percent predicted forced vital capacity (%predFVC), percent predicted forced expiratory volume in 1 s (%predFEV1), oxygen, or CO2 levels. When the subjects were fully hogtied there was no evidence of hypoxemia or hypercapnia in either group. OC exposure did not result in abnormal spirometry, hypoxemia, or hypoventilation when compared to placebo in either sitting or "hogtying" positions [21].

Question 3: "What is the physiological effect of restraint of the deceased in the circumstances of his arrest?"

Answer: *Given the details of this situation the effect of physical restraint would have been di minimus.*

Explanation

a. Mechanical Asphyxia

It has been postulated by some that the mechanical obstruction of chest movement, called asphyxia, because air exchange within the lungs is diminished, could be caused by multiple officers overlying the body, thereby leading to asphyxial death [24] [25]. There is no evidence that sufficient pressure was applied to the decedent's lungs. Petechiae, subconjunctival hemorrhage, and pulmonary edema were present but both of these abnormalities are utterly non-specific findings [26]. Even if weight was placed on the decedent's back,

experiments with human volunteers, published in peer-reviewed journals, have shown that when increasing amounts of weight were placed on the backs of maximally restrained volunteers (up to 250 pounds - 100 kg) no clinically significant effects were observed [27]. Indeed, the whole "concept" of restraint asphyxia, as applied in this case, has been refuted many times in the peer-reviewed literature [28] [29].

b. Primary Effects of Prone Positioning

Theories involving the "hogtie," properly known as MPRP or "Maximal Prone Restraint Positioning" or "hobble restraint," as a cause of death, also called "positional asphyxia," were first proposed late in 1992. However, the results of the initial research were ultimately withdrawn (in open court) by the very author who first suggested the idea. A large body of literature suggests MPRP has very little clinical effect. It is surprising, given the lack of evidence, that anyone would suggest that it can. It is equally surprising that this outmoded idea remains in the vocabulary of of modern forensic pathologists, given the complete lack of supporting evidence.

c. Epidemiologic and Laboratory Studies

Measurable circulatory effects can be produced by placing large amounts of weight on volunteers backs, but the effect produced is not clinical significant (baring the presence of serious underlying disease). Hall studied 4828 consecutive use-of-force events (August 2006-March 2013) in seven Canadian police agencies. It was observed that 81.5% (an almost universal finding when "positional asphyxia" is invoked as a cause of death) of the subjects were alcohol-drug intoxicated, and/or emotionally distressed at the scene. Significantly more subjects remained in a non-prone vs. prone position; but over 2000 subjects remained prone. One individual died during the course of the study. Death was sudden and unexpectedly occurred in the non-prone position. The individual who died exhibited all 10 features of excited delirium syndrome. No subject died in the prone position. In a second study the same researcher found that out of 1269 physical encounters, the majority (57.2%) of subjects were also left in a non-prone position; the remainders were left in the prone position [30] [31].

Question 4: What was "the physiological effect of (a), (b) and (c) on the deceased in combination in the circumstances of his arrest?"

Answer: I concluded Factor (c) is irrelevant as there is no proof that such a disease entity even exists. Factor (b) is similarly irrelevant as there is no evidence of toxicity present, and as there are many more convincing elements, in particular, all of the drugs as enumerated in Question (a). The inherent cardiotoxicity of these drugs, together with

obvious pre-existing heart disease, just makes the probability of cardiac arrests even greater. [redacted]

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