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Severe Isopropanolemia Without Acetonemia: Contamination of Specimens During Venipuncture?

To the Editor:

The recent report by Chan et al. (1) concerning a Japanese patient with a serum isopropanol concentration of 72 mmol/L, an increased serum osmolal gap of 81 mosmol/kg, lack of an increase in serum acetone, and no clinical manifestations of isopropanol intoxication must be considered a biological impossibility. The authors offer various explanations for their unusual findings except the most obvious one, namely, contamination of the se-

rum specimens with isopropanol derived from the swabs used to disinfect the skin during the blood sampling procedures.

The authors gave a detailed description of the analytical methods used to identify and quantitate the concentration of isopropanol in serum, and the analytical toxicology was sophisticated and difficult to fault. Moreover, the presence of isopropanol was confirmed by a control analysis made at an independent laboratory. However, nothing was mentioned about the procedures used to obtain the blood samples, such as the sampling site chosen, the use of any skin disinfection, whether evacuated tubes or syringe and needle were used, the volume of specimen, the mode of separating the serum, and the storage conditions prior to analysis. Apparently, only two specimens of serum were obtained, the first on admission and the second 15.5 h later. Swabbing the skin before sampling blood, although nowadays not usually necessary, is still a common practice at many hospitals, and isopropanol swabs are widely used for this purpose. The use of a sloppy sampling technique is known to cause contamination of the resulting blood specimen with alcohol (2-4). Moreover, just by chance the carryover of isopropanol to the second specimen tube might have been somewhat less than carryover to the first tube, thus giving the impression of a decreasing concentration of isopropanol during the time between taking the samples. Indeed, if this occurred, neither of the serum specimens would be expected to contain any acetone derived from isopropanol in vitro. The two serum samples were the only body fluids mentioned that were analyzed to confirm the presence of isopropanol; a sample of urine had been available from the patient but apparently was discarded. Even a simple breath-alcohol test for volatiles with the kind of hand-held instruments widely available in emergency medical departments would have helped to solve the mystery (5).

Chan et al. (1) speculate on various biochemical and (or) genetic factors that might account for their unusual findings, but the explanation proposed here, namely, contamination of specimens with isopropanol during phlebotomy, seems much more plausible. However, for this explanation to be valid, one must accept that both of the two specimens of serum were contaminated with isopropanol and that this occurred to a different extent. If the contamination theory is accepted, all the biochemical and clinical observations in this case can easily be ac-

counted for, including the abnormally high concentration of isopropanol in serum (72 mmol/L, 432 mg/dL) without the presence of its well-known metabolite (acetone) and the lack of any signs and symptoms of intoxication or the smell of alcohol on the patient's breath. The confirmation of isopropanol by two different laboratories and the good agreement of results with measurement of serum osmometry also fit with the notion of contamination. This simple and obvious explanation for such an unusual clinical report deserves careful consideration before embarking on fruitless attempts to discover novel biochemical mechanisms.

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The authors of the article referred to reply:

To the Editor:

We welcome Jones' raising the possibility of isopropanol contamination from the isopropanol swab used to prepare the venipuncture site as the cause of severe isopropanolemia in the Japanese patient we reported (1). Possible isopropanol contamination was one of our initial considerations. However, a measurement of the urine isopropanol concentration was not obtained because the specimen was not available for analysis before the patient was discharged. Given the lack of a urine specimen, we could not absolutely rule out swab contamination; however, we considered such a possi-

bility unlikely for the following reasons:

1) Isopropanol was detected in the patient's blood on more than one occasion during hospitalization. Specimens were drawn by different staff each time. Our current phlebotomy protocol specifically addresses the need to avoid isopropanol swab contamination. Considering the number of phlebotomists involved with the patient, it is difficult to support the contamination hypothesis.

2) Three Vacutainer Tubes received for the toxicological analyses on the patient were reasonably full. To have a blood isopropanol concentration of ~400 mg/dL due to contamination, the Vacutainer Tubes would have to be contaminated with ~60 μ L of 70% isopropanol. It is difficult to conceive how this much isopropanol could have been introduced into the specimen by contamination.

3) An experiment was conducted where blood samples from volunteers were drawn immediately after wiping their arms with isopropanol swab. When the 7- or 10-mL Vacutainer Tubes were filled with blood and the blood was analyzed for volatiles, isopropanol was not detected.

4) Of the ~30 blood specimens received daily for analysis of volatiles during the patient's hospitalization, none showed any pattern that suggested isopropanol contamination from a venipuncture site.

These observations and studies, in our opinion, make unlikely the possibility of isopropanol contamination during venipuncture of the patient.

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Was Paganini Born with Ehlers-Danlos Syndrome Phenotype 4 or 3?

To the Editor:

I read with interest the Special Report by Wolf (1) about diseases that

affected famous painters, composers, and political leaders. Papers on such paramedical subjects are very pleasant in the journal, I think, and I enjoyed this one very much. I have some criticism, however, relating to the discussion of famous composer and violinist Niccolò Paganini.

Wolf wrote: "Paganini was born with Ehlers-Danlos syndrome, a connective tissue disease causing a diffuse looseness of the connective tissue. The Ehlers-Danlos 4 phenotype, related to mutations in collagen type III on chromosome 2, results in a flexibility of all of one's joints." Indeed, Paganini is reported to have been able to bend his thumb back so far that the thumbnail touched the back of his hand. Owing to this remarkable flexibility in his wrist and finger joints, Paganini could span three octaves with little effort (2).

Ehlers-Danlos syndrome (EDS) refers to a group of connective tissue disorders, of which there are at least 10 known types. EDS 4 phenotype is the most severe form among the 10 types because of its grave consequences. In patients with EDS 4 phenotype the main symptoms are as following: thin, translucent skin with visible veins; marked bruising; and arterial, bowel, and uterine rupture. Skin and joints have normal extensibility in this form. Arterial fragility may manifest as sudden death, stroke, shock from retroperitoneal or intraabdominal bleeding, or compartmental syndromes, depending on the site of vessel rupture. Therefore, life expectancy is considerably shortened (3), whereas Paganini lived for 58 years (from 1782 to 1840). Moreover, Paganini also suffered from other severe diseases, including syphilis and pulmonary tuberculosis.

Among the EDS phenotypes, the EDS 3 phenotype is a more likely diagnosis for Paganini. In this form of EDS the major manifestation is joint hypermobility (the type name is familial hypermobility), and life expectancy is normal.

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The author of the report referred to comments:

To the Editor:

Yücel's suggestion that Paganini may have suffered from the Ehlers-Danlos phenotype 3 instead of phenotype 4, which I implied (1), has merit (2). However, because hypermobility of joints occurs in several types of Ehlers-Danlos syndrome, including types 1, 2, 3, 5, 6, 7, 8, and 10 (3), it seems more appropriate and prudent that a specific phenotype of Ehlers-Danlos syndrome not be assigned to Paganini. If Paganini was affected by Ehlers-Danlos syndrome, the contemporary clinical chemist may have been able to identify several of the phenotypes: e.g., type 4, abnormal collagen (type III) synthesis; type 6, lysyl hydroxylase deficiency; type 7, defective conversion of type 1 procollagen to collagen; type 9, abnormal copper utilization with defect in lysyl oxidase; type 10, defect in fibronectin (3). Thus, I would recommend a cautious approach since other speculations exist relevant to Paganini's demonic virtuosity.

Paganini's physician, Francesco Benati, believed that the violinist's flexibility of his left hand was inherited (4). Benati observed that there was increased elasticity of Paganini's shoulders, elbows, wrists, and upper joints of the fingers of his left hand. When Paganini played, he crossed his elbows practically one on the top of the other. Schoenfeld speculated that Paganini suffered from Marfan syndrome (5). However, he was not abnormally tall and his hands were of normal size without arachnodactyly; thus, this theory has been discounted. The distinguished writer Francois-Joseph Tetis believed that Paganini's unusual flexibility was acquired due to years of practice (6). Paganini's hyperextension of his left thumb was demonstrated in Fig. 4 of my report. Fig. 1 here demonstrates



Fig. 1. Individual with Ehlers-Danlos syndrome, demonstrating hypermobility of the thumb.

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