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Trimethylaminuria (fish-odour syndrome) and oral malodour

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A small but important percentage of oral malodour cases have an extra-oral aetiology and certain of these fall into the category of 'blood-borne halitosis'. Odoriferous substances generated within the body and transported to the lungs via the circulatory system may, if sufficiently volatile, leave with the exhaled air and impart a foetid odour to the breath. The aliphatic tertiary amine, trimethylamine, is such a volatile compound that is generated to excess in patients with a metabolic disorder known as trimethylaminuria (fish-odour syndrome). This article highlights this condition and draws attention to its potential role in the causation of recalcitrant oral malodour.
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Introduction

Oral malodour (halitosis, bad breath) is a relatively common complaint that may lead to serious consequences throughout an individual's private and professional life. Determining the incidence of this condition is difficult but it has been suggested that up to half of the general population may, at sometime, exhale 'socially unacceptable breath' (Messadi, 1997; Meningaud *et al*, 1999; Sanz *et al*, 2001; Tomas *et al*, 2001). The oral cavity is the major source of this malodour, particularly the posterior dorsum of the tongue, although other associated factors such as food impaction, gingivitis, periodontal disease and oral carcinoma may play a part. However, about 10–15% of halitosis cases have an extra-oral aetiology and may be indicative of other disorders. Such causes may include problems with the respiratory tract (chronic tonsillitis and sinusitis, infection, bronchiectasis, pulmonary abscess), the gastrointestinal system (obstructions or inflammatory gastrointestinal processes) or at anatomically distant sites linked via the circulatory system (hepatic insufficiency, liver cirrhosis, renal failure, diabetes mellitus and diabetic acidosis) (Preti *et al*, 1992; Durham *et al*, 1993; Touyz, 1993; Spielman *et al*, 1996). These latter systemic diseases and metabolic disorders, together with the effects of certain medications and foods, may be grouped into the category of 'blood-borne halitosis' in which malodorous compounds in the bloodstream are transported to the lungs where they volatize and are exhaled in the breath (Tangerman, 2002).

The intensity of breath odour has shown a correlation with the presence of volatile sulphur-containing compounds, such as hydrogen sulphide, methanethiol and dimethyl sulphide, that may be produced by microbial metabolism. However, in certain cases the odour itself, or contributions to the odour, may arise from other volatile compounds that have been detected in the air expelled from the oral cavity. These candidates include short chain fatty acids (acetic, propionic, butyric), aromatics (indoles, skatole), methanol, ethanol, acetone, acetaldehyde and pentane, with the amine, cadaverine, being detected in saliva (Solis-Gaffar *et al*, 1975; Tonzetich, 1977; Tonzetich *et al*, 1991; Goldberg *et al*, 1994; Meningaud *et al*, 1999; Sanz *et al*, 2001; Volozhin *et al*, 2001). In cases of 'blood-borne halitosis' it is quite possible that virtually any odourous compound that satisfies the criteria of volatility, if generated within the body and having access to the bloodstream, could give rise to an oral malodour. Trimethylamine is such a compound. It is a simple tertiary aliphatic amine with a pungent ammoniacal odour approaching that of rotten fish at low concentrations and the human nose is extremely sensitive to this molecule, with some individuals being able to detect less than one part in 10^9 (Willey, 1985). It is produced in excess in a metabolic disorder known as trimethylaminuria or the 'fish-odour syndrome' (Table 1; Mitchell, 1996; Mitchell and Smith, 2001).

Trimethylaminuria

Biochemically, the disorder is characterized by the presence of 'greater than normal' amounts of trimethylamine within the body. These high levels are present owing to a failure in removing the amine via the usual oxidation route to the non-odourous metabolite, trimethylamine N-oxide. This situation arises from a

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Table 1 Key events in the clinical history of the trimethylaminuria (fish-odour syndrome)

Period	*Clinical observation*
1840–1860	Two isolated reports in the medical literature, suggestive of the condition
1970	First clinical description linking condition with Turner's Syndrome
	First use of the term, 'fish odour syndrome'
1970–1985	Single cases reported sporadically and concealed within world literature
1980	Recognition of a breed of domestic fowl deficient in trimethylamine N-oxidation and its relationship to the 'tainted egg syndrome'
1980–1990	Characterization of the human genetic polymorphism of trimethylamine N-oxidation.
	Recognition of the condition as a separate phenomenon
1990s	Molecular genetic basis of condition established
	Flavin monooxygenase enzyme (FMO3) mutations identified as causation
2000	Realisation of sub-types of the syndrome leading to a new classification
	Multiple factors involved in the overall causation of the condition

For more details on historical aspects see references (Mitchell, 1996; Mitchell and Smith, 2001).

mismatch in the enzyme's capacity to undertake this metabolic reaction and the substrate load it has to process (Mitchell, 1996; Mitchell and Smith, 2001). Consequently, in principle, it appears that there are two major sub-types of the condition. Firstly, there are those forms that are related to a dysfunction of the normal enzyme activity owing to genetic, hormonal or inhibitory-chemical influences. Secondly, are those forms arising from substrate overload of the enzyme activity (normal or depressed) such as an excess of dietary precursors of trimethylamine or variations in gut microorganisms resulting in enhanced liberation of trimethylamine substrate. Clearly, these are two intimately related aspects. A substrate burden that is easily handled by one individual may become a substrate overload in another that has a decreased enzyme function for whatever reasons (Mitchell, 1999). The following system of classification has been adopted in an attempt to allay this confusion (Mitchell and Smith, 2001).

Primary genetic form

This is probably the best understood of the various forms of the disorder and accounts for the majority of reported cases. It results from the failure of an isoform of the hepatic flavin monooxygenase enzyme (FMO3) to oxidize trimethylamine, provided via enterobacterial action on dietary precursors, into the non-odourous trimethylamine N-oxide. Recent work has shown that human FMO3 is highly polymorphic and some of the mutations, either alone or in combination, are associated with dysfunctional enzyme activity and the metabolic disorder, whereas other mutations appear to be benign (Dolphin *et al*, 1997; Treacy *et al*, 1998; Ackerman *et al*, 1999). In the near future it should be possible to employ gene array technologies to identify carriers (heterozygotes) for this condition.

Acquired form

There are at least three cases known of individuals with clinical and biochemical symptoms of fish odour where this condition appeared to emerge in adult life. In all instances, there was no previous history in childhood and there was no familial background to the disorder. What appeared common to the three subjects was evidence of hepatitis, possibly viral, in adult life and this may have been responsible for precipitation of the condition. However, once acquired, the condition did not appear to abate when the liver problems had resolved, suggesting some permanent damage perhaps at the genetic level (Ruocco *et al*, 1989; Mitchell and Smith, 2001).

Transient childhood forms

A report in the literature describes a premature infant (29-weeks old) developing a fish-like odour whilst being fed with a choline-containing food supplement. However, when the supplement was withdrawn the odour disappeared, and it failed to reappear at 8 months of age when the food supplement was reinstated. Similarly, when the supplements were given to three other preterm infants of similar age and weights, one of these developed a fish-like odour. The authors attributed the fish-like odour associated with choline-containing supplements to the immaturity of the N-oxidase enzyme (Blumenthal *et al*, 1980). Since then other cases of paediatric fish malodour syndrome have been described (Mayatepek and Kohlmuller, 1998; Zschocke *et al*, 1999).

Transient form associated with menstruation

Several female patients have reported anecdotally that their fish-like odour seemed to intensify with the onset of menstruation (Ayesh *et al*, 1993). A subsequent study of a single female fish malodour patient showed that her trimethylaminuric condition deepened just before the onset of menstruation and that this biochemical feature related closely to her own subjective descriptions (Zhang *et al*, 1996a). A systematic study has confirmed that in normal healthy women of menstruating age there occurs a short episode of trimethylaminuria just at the onset of and during menstruation that then disappears. By contrast, in male subjects there was no evidence of this cyclical variation (Mitchell and Smith, 2001).

Precursor overload

Trimethylamine is mostly derived from dietary presursors such as choline, carnitine and trimethylamine N-oxide through enterobacterial metabolism. Exposure to unusually high levels of such precursors may hasten a fish malodour syndrome especially if the individual is a haplotype for certain mutations. Large oral therapeutic doses of choline (8–20 g day^{-1}) have been used to treat Huntington's chorea, with patients complaining of a striking fish-like odour that was attributed to the generation of excessive amounts of trimethylamine

overloading their N-oxidation capacity (Growdan *et al*, 1977). Similar problems have also been reported following choline therapy for Alzheimer's disease (Etienne *et al*, 1978). It is noteworthy that precursors of trimethylamine, choline and lecithin (phosphatidylcholine), are sometimes recommended in quite high doses in health foods, food supplements and alternative diets.

Disease states

Impaired hepatocellular function or the existence of portosystemic shunts in patients with liver cirrhosis may interfere considerably with the first-pass metabolism and extraction of trimethylamine absorbed from the gut. The consequent increased blood levels of this amine observed in such patients may play a role in the development of hepatic encephalopathy and coma and associated *foetor hepaticus* (Wranne, 1956; Marks *et al*, 1978; Mitchell *et al*, 1999). In uraemic patients the abnormal overgrowth of bacteria in the small intestine greatly increases the liberation of trimethylamine from precursors within the diet. Compounded by reduced kidney function and subsequent decreased renal clearance, the amine levels in the blood increase, perhaps playing a role in nephritic neurological conditions as well as escaping via the breath (Simenhoff *et al*, 1977; Wills and Savory, 1981).

Concluding remarks

Since the presence of excess trimethylamine depends upon interplay of numerous events, the odour problems associated with this condition usually vary in intensity and may be transient in nature. When levels of trimethylamine are high, the volatile compound will leave the body via many routes (e.g. urine, sweat, breath, bodily secretions) bestowing upon the patient an odourous aura resembling that of rotten or decaying fish. However, when the levels of trimethylamine are lower, then the odour may only be noticeable arising from freshly voided tepid urine or exhaled on the warm breath. This may be particularly true for individuals who are heterozygous for the condition, in whom free trimethylamine only approaches threshold levels when several factors unfortunately occur in concert (Mitchell, 1999).

New cases of the 'fish odour syndrome' are being recognized constantly as an increased awareness of this metabolic problem permeates the medical and scientific communities. In terms of frequency of occurrence, it appears that the condition should no longer be regarded as 'rare' but more appropriately as 'uncommon' (Mitchell and Smith, 2001). The compromised ability to produce trimethylamine N-oxide has been detected in several ethnic groups and is not restricted to one area of the world's population (Table 2). A limited study in a British population has intimated that about one in 10 000 individuals may suffer from decreased N-oxidation capacity sufficiently severe to precipitate the clinical symptoms of the 'fish odour syndrome'. Although this particular study was small, applying simple Mendelian genetics and the Hardy–Weinberg quadratic suggests that up to 1% of the population may be heterozygous for this condition (Zhang *et al*, 1995). This is in broad agreement with indications from the population data (Table 2).

Table 2 Comparative incidence of dysfunctional N-oxidation of trimethylamine in various populations

		Subjects excreting less than 80% total material as N-oxide[a]			
Population	*Size*	*n*	*%*	*95% CI*[b]	*Reference*
British	421	6	1.4	0.3–2.6	Zhang *et al* (1996b)
Chinese	159	2	1.3	0.8–1.7	Lee *et al* (2000)
Ecuadorian	80	3	3.8	1.6–5.9	Mitchell *et al* (1997)
Jordanian	116	2	1.7	0.5–2.9	Mitchell *et al* (1997)
Jordanian	82	8	9.8	6.5–13.0	Hadidi *et al* (1995)
New Guinean	100	11	11.0	7.9–14.1	Mitchell *et al* (1997)
Thai	103	5	4.9	1.9–7.8	Thithapandha (1997)

[a]The amount of trimethylamine N-oxide is expressed as a percentage of the total 0–24 h urinary excretion of both trimethylamine and trimethylamine N-oxide. This is used as a measure of an individual's trimethylamine N-oxidation capacity.
[b]95% Confidence interval.

In instances where oral malodour, that may be transient in nature, cannot be assigned to problems within the oral cavity, where the levels of sulphur-containing volatiles in the exhaled breath are not diagnostically high and where no obvious extra-oral causation is present, mild cases of trimethylaminuria (fish odour syndrome), perhaps in the heterozygous state, should be considered as a possible causative factor.

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