Dimethylsulphidemia: the significance of dimethyl sulphide in extra-oral, blood borne halitosis

C. N. Harvey-Woodworth¹

IN BRIEF

- Outlines the prevalence of halitosis in the general population, its classification and psychosocial implications.
- Reports that about 10% of genuine halitosis cases are caused by extra-oral phenomena, giving extra-oral halitosis an estimated prevalence of about 0.5–3% in the general population.
- Reviews the causes of extra-oral halitosis and how to differentiate these from intra-oral halitosis.

Halitosis is a symptom and not a diagnosis. Rather, the topic represents a spectrum of disorders, including intra-oral, otorhinolaryngological, metabolic, systemic, pulmonary, psychological and neurological conditions. Halitosis may be the third most common trigger for patients to seek dental care and can cause significant impact on patient quality of life. About 10% of all genuine halitosis cases are attributed to extra-oral processes. Some authorities have reported that the nasal cavity and the oropharynx are the most common sites of origin of extra-oral halitosis. However, recent evidence appears to suggest that blood borne halitosis may be the most common subtype of extra-oral halitosis. Tangerman and Winkel report that dimethyl sulphide was the main volatile implicated in extra-oral blood borne halitosis. They proposed a hitherto unknown metabolic condition by way of explanation for this finding, resulting in systemic presence of dimethyl sulphide in blood and alveolar breath. This paper reviews the knowledge base regarding the behaviour of dimethyl sulphide in physiological systems and those disorders in which blood borne halitosis secondary to dimethylsulphidemia is thought to have an aetiopathological role.

BACKGROUND

Several definitions of the term halitosis have been offered. It is generally accepted that odours on the nose breath, as well as the mouth breath, are included within this topic. Similarly included are those conditions that present with more pleasant breath odours eg, the 'fruity' breath of diabetic ketoacidosis and also those cases where there is no genuine odour in a patient complaining of halitosis, a scenario which has a myriad of causes.

Some have called for standardisation of protocols in halitosis research.¹ Perhaps due to a lack of consensus regarding diagnostic criteria and assessment methods, the reported prevalence varies, but this value is probably about 20%.^{2–5}

As such, it is rightly described as a common symptom⁶ and may even be the third most common trigger to seek dental care,

(after dental caries and periodontal diseases),^{7,8} showing that patients place great importance on it.

Halitosis is subject to great societal taboo and stigma.^{6,9} The evolutionary function of olfaction in humans serves to detect spoiled food sources and potentially infectious or harmful stimuli.^{10,11} It also has a role in mate selection.^{12–16} Unpleasant personal odour triggers repulsion in others. This is thought to be an evolutionary response to avoid mating with sick individuals.^{17,18} The need to belong has been identified as a fundamental human need.¹⁹ Social rejection and ostracism has been shown to have profound physical and psychological effects.^{20,21} This symptom can therefore have significant psychosocial implications, including social anxiety and avoidance behaviours, problems with integration, relationships and productivity, depression and reduced quality of life.^{6,22–25}

It has been suggested that clinicians are poorly informed about the causes and treatments for halitosis, and may even mismanage cases, promoting adverse psychological sequelae.^{8,26} It is also suggested that clinicians may need to be updated regarding the current evidence base.²⁷

Non-genuine halitosis

A proportion of patients who present complaining of halitosis will not have any detectable breath malodour. Various terms have been used to describe this, including delusional halitosis, psychogenic halitosis, pseudohalitosis and halitophobia. Estimates of non-genuine halitosis among those complaining of halitosis range from 5–72%.^{6,28–34} There are several possible reasons why a finding of non-genuine halitosis could be made.

Assessment errors and symptom transience

Malodour may have been present at the time of consultation and was not detected. Those involved in the management of patients complaining of halitosis ideally would be familiar with the principles of organoleptic assessment^{35,36} or even have access to breath analysis apparatus (for example, the 'OralChromaTM').³⁷ It is also possible that malodour was not present at the time of the assessment but may be present at other times. Clinicians frequently fail to recognise the variability of the presence and strength of the symptom.³⁸ Factors such as hydration, timing

¹Scientific Adviser to MEBO Research Inc, and Regional Centre for Oral and Maxillofacial Surgery, University Hospitals, Aintree, Liverpool
Correspondence to: Dr Colin Harvey-Woodworth
Email: harvey.mmx@gmail.com

and nature of last food consumption, time of day, menstrual status, nature of clinical environment and fluctuations in clinical olfactory acuity possibly affecting the detection threshold on any single occasion.

Genuine bad tastes and dysgeusia

Although gustation and olfaction are closely related senses, a bad taste often does not necessarily translate to detectable malodour by others. Disorders of taste can present as a complaint related to smell and *vice versa*. Genuine bad tastes can be caused by any number of factors, including poor oral hygiene, dental caries, periodontal diseases (for example, acute necrotising ulcerative gingivitis), oral cancer, diabetes and uraemia.³⁹

Patients may also experience dysgeusia (taste disturbance), which has many causes, commonly smoking, xerostomia, ageing, infection, trauma involving the mouth, nose or head, or nerve damage involving the chorda tympani, lingual or facial nerves, gastro-oesophageal reflux disease (GORD) and deficiency states (B12 or zinc). For a more extensive list of the rarer causes of dysgeusia, readers are directed to dedicated reviews of the topic.^{40–43} Iatrogenic effect of various medications may cause both genuine bad tastes and dysgeusia.

Dysosmia (olfactory disturbance)

Parosmia is the misinterpretation or distortion of odour stimuli and may occur with upper respiratory tract infections, head trauma or accompany ageing.⁴⁴

Phantosmia is perception of a smell in the absence of any odour stimuli. Phantosmia can occur with conditions such as alcoholic psychosis, pregnancy, chemo- or radiotherapy, Parkinson's disease, Alzheimer's disease, schizophrenia, temporal lobe epilepsy or lesions impinging upon the olfactory bulb or tract (for example, a meningioma or neuroblastoma).^{45–48}

Patients with genuine halitosis develop olfactory fatigue when their symptom is present, making them poor judges of their own odour.⁴⁹ This is the physiological phenomena where a temporary reduced awareness of an olfactory stimulus follows continuous exposure. Often, the only trigger for patients to medical or dental advice is the behaviour of those they come into contact with. Conversely, patients with

phantosmia may report self detection of an odour which others do not seem to comment on.

Psychological condition

Halitophobia can be defined as follows, 'when there is no physical or social confirmation to suggest that halitosis is present, which can persist after therapy for either genuine halitosis or pseudohalitosis'.³⁵ Some consider halitophobia to be a type of olfactory reference syndrome (ORS), where there is preoccupation with the belief that one emits a foul or offensive odour, although this odour is not perceived by others.⁵⁰ These patients are said to misinterpret the behaviour of others, reinforcing this preoccupation and engage in obsessive activities such as excessive bathing or oral hygiene. ORS is not, however, included as a diagnosis in DSM-IV, and will only be included under 'conditions that require further research' in DSM-5. The persistence of adverse psychosocial sequelae after treatment for genuine halitosis is perhaps testament to the distress it can cause in some patients. Distressed patients may display behaviours that inappropriately prompt clinicians to assume a tendency towards delusional symptoms.

Recently, Falcão *et al.* challenged the current concepts of pseudohalitosis and halitophobia, drawing attention to altered chemo-sensory function states, but also proposed that retronasal olfaction may offer explanation for halitosis complaints that cannot be detected by others.⁵¹

The author therefore advises that a finding of non-genuine halitosis not be made without a full and competent halitological consultation, or be based upon the findings of a single occasion. Furthermore, this finding should not serve as a diagnosis, as it is a symptom in its own right with many possible causes that may warrant further investigation and management.

Genuine halitosis

Where the malodour is real and detectable, this is known as genuine halitosis. Estimations of the proportion of genuine halitosis cases among those complaining of halitosis range from 28–95%.^{6,28–34,52} Genuine halitosis is then sub-classified according to the location of the origin of the malodour, namely, intra- or extra-oral halitosis.

Intra-oral halitosis (oral malodour)

About 90% of genuine halitosis cases have a cause within the oral cavity, that is, intra-oral halitosis (oral malodour).^{6,28–34} The leading cause of intra-oral halitosis is release of volatile sulphur compounds (VSC) from halitogenic biofilm on the posterior dorsal tongue, and/or within gingival crevices/periodontal pockets. The causative organisms are usually gram-negative, anaerobic spp. VSC are generated by bacterial degradation of sulphur containing amino acid substrates, for example, methionine, cystine and cysteine.³⁵ The main odourants implicated in intra-oral halitosis are methyl mercaptan (MM, CH₃SH) and hydrogen sulphide (H₂S).⁵³ Intra-oral halitosis has been the subject of increasingly detailed study in recent times and the symptom could be considered clinically manageable in the vast majority of cases, provided a well informed clinician and motivated patient. Readers are directed to the many comprehensive reviews available on the subject.^{6,35,36,54–65}

Extra-oral halitosis

Some 10% of genuine halitosis cases are not caused by intra-oral phenomena, giving extra-oral halitosis an estimated prevalence of 0.5–3% in the general population.^{28,30,32} Extra-oral halitosis is by contrast less well researched and understood and represents a greater diagnostic and therapeutic challenge. It has been classified according to location and aetiology (Table 1).^{27,35–37,66}

Traditionally, it was thought that the stomach was responsible for many cases of halitosis, however, it has now been shown that only very rarely is this the case. The oesophagus is a collapsed tube (except during deglutition, eructation, or emesis), denying the transit of odourant volatiles through to the aerodigestive tract.^{66,67} Gastrointestinal conditions, for example, *Helicobacter pylori* infection and GORD, have been investigated with regards a potential relationship with halitosis.^{68–82} Currently, the overall picture appears to be a lack of positive correlation or unconvincing evidence.

Otorhinolaryngological pathoses are thought by many researchers to account for the majority of extra-oral causes of halitosis, especially tonsillar²⁹ and sino-nasal conditions.⁸³ Others suggest that

Table 1 Classification of extra-oral halitosis with example diagnoses^{27,35–37,66}**Upper respiratory tract (sinonasal, pharyngeal, laryngeal), eg**

Pharyngitis
 Purulent sinusitis
 'Post nasal drip'
 Ozena (a subtype of chronic atrophic rhinitis)
 Tonsillitis, tonsillolithiasis, tonsillar actinomycosis
 Foreign body in nasal cavity
 Nasopharyngeal abscess
 Laryngeal carcinoma

Lower respiratory tract (trachea, bronchi, alveoli), eg

Chronic bronchitis
 Bronchiectasis
 Pulmonary abscess
 Bronchial carcinoma

Blood borne halitosis (causative odourant volatile(s) in parenthesis)*Temporary effects of certain foodstuffs:*

- Garlic (mainly allyl methyl sulphide)
- Onion (methyl propyl sulphide)

Side effects of certain medications:

- Disulphiram (carbon disulphide)
- Cysteamine (dimethyl sulphide)
- Dimethyl sulfoxide (dimethyl sulphide)
- Suplatast tosilate (dimethyl sulphide)

Metabolic states/systemic disease:

- Uraemia (ammonia, dimethyl amine, trimethylamine)
- Ketoacidosis (acetone)
- Dimethylsulphidemia (dimethyl sulphide)
- Hypermethioninaemia (dimethyl sulphide)
- Trimethylaminuria (trimethylamine)

Table 2 Theoretical criteria for any particular chemical to cause symptoms of blood borne halitosis*Must be able to enter the systemic circulation*

- Absorption of volatiles (or precursors) via gastrointestinal lining
- Endogenously produced volatiles eg, secondary to organ system insufficiency, as in uraemic fetor
- Parenteral administration of volatiles (or precursors) that enter the circulation

*Must be stable in blood (usually requires the chemical to be neutral)**Must survive or bypass hepatic metabolism*

- Compromise of hepatic metabolism
- Substrate overload of the relevant enzymatic pathway
- Portal shunting of blood (congenital or acquired) bypasses liver and alters the journey of volatiles which would normally immediately be subject to first pass metabolism

*Must be able to be transferred to the exhaled breath during alveolar gas exchange**Must be an odourant*

- Must be volatile (to be carried in the air to the olfactory chemoreceptor cells of other individuals)
- Must be lipid or water soluble
- Present at high enough concentration to trigger the olfactory cells to signal

obstructive nasal pathology can secondarily cause mouth breathing, with resultant xerostomia and halitosis.⁸⁴ It is known that mouth-breathing is associated with halitosis.⁸⁵ With regards the proportion of genuine halitosis cases that secondary to ear nose and throat (ENT) conditions, reported estimates range from between 2.9–10%,^{6,30,34,86,87}

However, recent evidence suggests that a mechanism known as blood borne halitosis may account for the majority of extra-oral halitosis.³²

Blood borne halitosis

It has long been known that volatile chemicals present in the blood can be transferred to the exhaled breath. Breath analysis for trace chemicals offers a non invasive investigation that can be applied in a huge range of conditions. For example, hydrogen and/or methane breath analysis can be carried out following oral administration of poorly absorbable carbohydrate (for example, lactulose).⁸⁸ Hydrogen and methane are products of gut microbiota fermentation, hence this breath test is thought to be a measure of gut microbiological activity. This testing is carried out by some in conditions like small intestinal bacterial overgrowth (SIBO),⁸⁹ although somewhat controversial due to imperfect sensitivity. These odourless gases have been absorbed from the gut and transferred to the alveolar breath.⁹⁰ The same VSC that are reported to be the most important volatiles in halitosis (H₂S, MM and DMS) are implicated as being the greatest contributors to the malodorous character of flatus and faeces.^{91–93} Of this trio, only DMS is stable in blood and capable of creating blood borne halitosis.

The general mechanism involved in blood borne halitosis is as follows. Volatiles enter the systemic circulation (several routes possible but most usually via the portal system following absorption from the gut), and are then circulated to the lungs, where there is intimate associated between the pulmonary alveoli and capillary networks. During gas exchange of waste carbon dioxide and inhaled oxygen, chemicals present in the blood, may also be exchanged, and may be perceptible on the exhaled breath if they fulfil certain criteria (Table 2). The detection of a volatile on the breath by objective

measurement does not imply its contribution to perceptible malodour. Although all odourants are volatile, not all volatiles are odourants. An odourant must also be present in high enough concentrations to stimulate olfactory detection. For this to happen, great enough quantities of the volatile must be liberated from solution (that is, respiratory tract secretions, saliva). Whether the chemical is liberated into the gas phase, and in what quantities, is dependent upon such factors as pH and temperature of the solution and the concentration of the volatile in the solution.

However, since the blood goes almost everywhere, blood borne volatiles may also be expressed via other routes of excretion, for example, sweat, saliva and urine. An example of a blood borne volatile being expressed via multiple routes, and not just the breath, is trimethylamine (TMA),⁹⁴ which has a fish-like odour *in vitro*, becoming ammoniacal at higher concentrations. Indeed when TMA is present in the urine, the rare disorder trimethylaminuria (TMAU) should be considered, although there are other causes of elevated urine TMA.⁹⁵ Dimethylglycinuria is another rare cause of fish odour.⁹⁶

Tangerman and Winkel³² reported that dimethyl sulphide (DMS, CH₃SC₂H₅) was the most common volatile in extra-oral halitosis, which could not be attributed to recent ingestion of volatile foodstuffs. They estimated this DMS-related blood borne halitosis may affect some 0.25–1.5% of the general population. These estimates were based upon a cohort of 58 patients complaining of halitosis, and the findings extrapolated assuming 10–30% prevalence of halitosis in the general population and 5–10% of genuine halitosis being extra-oral in aetiology.³²

Multidisciplinary management

The classification into intra- and extra-oral, and the sub-classification of extra-oral halitosis is useful as it guides clinical practice according to which disciplines may need to be involved,⁹⁷ eg, ENT for upper respiratory tract and respiratory medicine for lower respiratory tract. The referral in blood borne halitosis is cause-related, for example, endocrinology.

There are in existence a handful of joint halitosis clinics, sometimes consisting of specialists in ENT, periodontology and psychiatry. Some suggest that this problem

is best managed at such multidisciplinary centres. Practically, however, general dentistry is the primary setting involved, given that most patients will first present to the dentist and that the majority of causes of halitosis are intra-oral.

The role of the dentist in management of halitosis is to take a history and carry out a meticulous intra-oral and oropharyngeal examination for halitogenic factors. This is followed by an organoleptic assessment, to ascertain the presence or absence of malodour. Absence of any detectable malodour at repeated consultations likely represents non-genuine halitosis. It is inappropriate for these patients to receive treatments aimed at odour reduction. Simple reassurance may be carried out in general practice, however, as discussed above, non-genuine halitosis complaints may represent psychiatric or neurological conditions and referral may be indicated. Malodour that is more detectable on the mouth breath compared to the nose breath may indicate intra-oral halitosis, whereas the reverse (ie nasal foetor) may indicate sino-nasal pathology. Malodour that is equally objectionable on both the nose and the mouth breath usually indicates extra-oral halitosis.

The dentist may then treat any clinical intra-oral halitosis, or to refer if extra-oral halitosis is suspected. Further investigation of extra-oral halitosis it is perhaps more appropriately carried out by relevant specialities.⁹⁸ Equally, dentists may need to be aware of patients who are referred from general medical practitioners and who are found to have signs of extra-oral halitosis.

DIMETHYL SULPHIDE, *IN VIVO* BEHAVIOUR: SYNTHESIS, METABOLISM AND EXCRETION

DMS is a volatile organosulphur compound, constituting a sulphur atom covalently bonded to two methyl groups. The *in vitro* odour character has been variably described as wild radish or cabbage-like,⁹⁹ or unpleasantly sweet,³² but invariably the terms used have unpleasant connotations. DMS was shown to reduce mood compared to more pleasant scents.¹⁰⁰ DMS has an exceptionally low odour detection threshold, meaning that it is detectably malodorous even at very low concentrations (24–100 ppb).⁵³ The gas can be fatally

noxious¹⁰¹ and it is also a mild skin and eye irritant,¹⁰² although even at the pathological concentrations reported in disease this is probably not a feature.

In mammals, free DMS is the only form known to be present.⁹¹ DMS can be catabolised from dietary precursors in plants (*S*-methylmethionine/vitamin U, and dimethylsufoniopropionate).^{91,103,104} DMS can be synthesised from transamination of methionine,¹⁰⁵ or methylation of methyl mercaptan (which itself can be methylated from H₂S).^{106,107} Methylation of H₂S and MM is thought to be a detoxification pathway.⁹¹ Dimethylsulphoxide (DMSO) can be reduced to DMS.^{102,108} Bacterial spp. known to synthesise DMS have been demonstrated in the human GI tract.^{109–111} DMS is a component of flatus and faeces^{91,112} and it is assumed that this is the result of intestinal bacterial activity. There is evidence that suggests of all the VSC produced in the colon >90% are absorbed by the lining rather than being emitted as flatus, and H₂S and MM are thought to be metabolised by caecal lining tissue (to thiosulphate). DMS, however, is not broken down here, instead passing straight to blood.^{113–115} Free DMS is neutral molecule, it does not contain a reactive thiol group (unlike MM and H₂S), hence it is stable in blood as it is unreactive with proteins. MM and H₂S both react rapidly in blood and are therefore not implicated in blood borne halitosis.³² DMS that is absorbed into the bloodstream appears to be a substrate of both CYP450 and flavin containing monooxygenases (FMO).^{116,117}

DMS is known to be subject to renal and pulmonary excretion.^{102,118,119} Dietary loading with either methionine or DMS also produced DMS in the milk of cows.¹²⁰ After the work of Tangerman's group, where Tenax trapping and gas chromatography was used to objectively measure free DMS concentrations, the normal range can be taken as <7 nM in peripheral venous blood.¹²¹ Breath DMS is also very low in health. Normal subjects in one study were reported to have a breath DMS range of 0.13–0.65 nM.¹²² Urine DMS is reported as being generally below the 3 nM detection minimum for gas chromatography.⁹¹

CONDITIONS WHERE ELEVATED BLOOD DMS IS A FEATURE

The author suggests the term

Table 3 Dimethylsulphidemia: differential diagnosis

Metabolic
Hypermethioninemia
Condition under study ³²
Systemic
Fetor hepaticus
Medications
Dimethylsulphoxide
Cysteamine
Suplatast tosilate

dimethylsulphidemia (DMSE, or hyperdimethylsulphidemia) to describe abnormal elevations of DMS in the blood. DMSE could be defined as >7 nM (normal range <7 nM). The threshold above which blood DMS begins to cause blood borne halitosis is undefined, although there was close correlation between blood and breath DMS reported.^{91,121} DMSE, (with corresponding elevated breath DMS and 'dimethylsulphiduria'), is a feature of several different conditions (Table 3), and it therefore should be considered a sign rather than a diagnosis.

Apart from the conditions listed in Table 3, several curious correlations of breath DMS have been reported. Old age, female gender, HDL cholesterol, history of colon polyps and asthma were all shown to correlate with breath DMS above the organoleptic threshold.¹²³ Elevated MM on the mouth air also correlated with DMS, possibly since MM is methylated to DMS. When investigating breath DMS attributed to DMSE, some researchers work around this artefact by measuring DMS on both mouth breath and nose breath (the small amount of DMS that could be attributed to methylation of MM intra-orally would not be detectable on the nose breath). Male pattern baldness was also correlated to elevated breath DMS in elderly men and this relationship was stronger in the presence of GI tract and metabolic disorders.¹²⁴ Interestingly, cystic fibrosis patients demonstrated a lower breath DMS than a healthy control arm.¹²⁵ Perhaps this could be attributed to altered gas exchange efficiency and pathological changes in pulmonary and gastrointestinal secretions. Occupational exposure in certain industries can lead to elevated exposure to DMS, which is demonstrable on the breath.^{126,127}

The hypermethioninemias

Methionine is an essential sulphur containing amino acid. It is normally metabolised in a pathway resulting in cysteine. As discussed previously, DMS can be synthesised from transamination reactions of methionine. Thus hypermethioninaemia (HME) will accompany DMSE. HME is a sign, rather than a diagnosis, and represents several distinct clinical entities, both genetic and non-genetic.¹²⁸ Many of the hypermethioninemias are syndromes presenting at birth and compromise more medically serious symptoms rather than malodour alone, such as brain demyelination.¹²⁹ Methionine adenosyltransferase (MAT) I and III are the two isoenzymes that catalyse a vital stage in the methionine cycle, viz. the synthesis of S-adenosylmethionine from methionine. MAT I/III deficiency, secondary to mutations in the coding gene, MAT A1, have been described.^{130–133} MAT I/III deficiency may be implicated in isolated persistent hypermethioninaemia, an idiopathic cause of elevated methionine, in which hepatic MAT activity is normal and yet there are few serious clinical manifestations.¹³⁴ Blood borne halitosis may still be a feature. Since DMSE accompanies HME, breath DMS can be used to screen for HME.^{135–137} A breath DMS level of 96 nM was reported in a patient with isolated persistent hypermethioninaemia secondary to MAT deficiency.¹²² Since DMSE can be caused by other conditions, elevated breath DMS is not specific for HME.

Foetor hepaticus

Portal hypertension and resultant portosystemic shunting can be caused by conditions like liver cirrhosis. Blood bypasses the portal circulation and hence volatiles that are absorbed from the GI tract are not immediately exposed to first pass metabolism. Traditionally, this foetor has been attributed to ketones and ammonia, however, more recent evidence suggests that DMS is the main odourant volatile, although ketones contribute to a lesser extent.^{138–141} *In vitro* experimentation with DMS solutions was reported to produce an odour very similar to that produced in fetor hepaticus.¹⁴² Mercaptans do not seem to directly cause hepatic encephalopathy, rather they just accumulate systemically.^{143–144} Awano *et al.* demonstrated elevated breath DMS in patients with various liver diseases.¹⁴⁵ Interestingly, the

same study showed correlation of elevated breath DMS with cerebrovascular disease. A secondary form of TMAU is also associated with liver disease, and blood borne TMA may even be contributory to the odour of foetor hepaticus.^{146,147} The character of foetor hepaticus has been varyingly described as musty, 'mousy' or sweetly faecal. There are also descriptions likening it to 'the smell of dead mice' or 'the breath of the dead'. Since DMS is the greatest contributor to the odour of foetor hepaticus, perhaps we can surmise that the *in vivo* expression and odour character of DMS is similar to that described for this condition. It is unlikely that DMSE and a related halitosis would be monosymptomatic for portal shunting, since this is frequently a late feature of decompensated liver cirrhosis, which comes with many other serious signs and symptoms. DMSE levels of 7–50 nM and breath DMS of 0.5–14.1 nM were demonstrated in patients with liver cirrhosis.¹⁴²

Volatile foodstuffs

DMS, along with other VSC, contribute to the flavour of some foodstuffs and beverages.^{104,148–151} The metabolism of methionine was previously discussed, as were other DMS dietary precursors in plants. DMS in cabbage, among other VSC derivatives, have been investigated for their antimicrobial activity.¹⁵² Urinary DMS has been shown to be elevated after asparagus consumption,¹⁵³ although DMS was not the major volatile produced.

Medications

Dimethylsulphoxide (DMSO) is used as vehicle for several drugs,¹⁵⁴ as it is able to penetrate skin and other membranes without damage,¹⁵⁵ but it can also be used as a therapeutic agent in its own right.^{156–159} It has uses as a topical agent, where interestingly its cutaneous administration can lead to a side effect of a garlic taste in the mouth.¹⁶⁰ Whether this is due to blood borne presence of the DMS is unclear. A similar phenomenon is observed with disulphiram, where this is attributed to metabolism of the drug to carbon disulphide (CS₂).¹⁶¹ CS₂, a neurotoxin not thought to be endogenously produced, was also reported to be raised on the breath of patients with schizophrenia.¹⁶² DMSO is metabolised to dimethyl sulphone (DMSO₂)

and DMS, which is then subject to renal and pulmonary excretion.^{102,163–167}

Nephropathic cystinosis, a rare autosomal recessive lysosomal storage condition, was previously a death sentence, however, cysteamine therapy now slows the progression of the disease and can prevent or delay the life threatening complications.¹⁶⁸ Cysteamine removes the accumulated cystine from lysosome, however, an unfortunate side effect of this therapy is halitosis,¹⁶⁹ which has been shown to be mostly due to presence of DMS in the blood. Hence, cystinotic patients on this therapy were shown to have elevated DMS in urine and breath.¹⁷⁰

A case report documented elevated breath DMS in an asthmatic patient being treated with the anti-allergenic drug, suplatast tosilate,¹⁷¹ which appears to be metabolised to DMS.

Condition under study

The new metabolic condition that has potentially been identified by Tangerman and Winkle, awaits further investigation to identify the exact pathogenesis. Whether the dimethylsulphidemia is related to defects in the methionine cycle, or indeed another cause remains to be elucidated. The prevalence of the potential new condition has been estimated at 0.25–1.25% of the general population,³² which would make it more prevalent than other 'blood borne malodour' conditions previously identified. The extra-oral nature of the halitosis in these patients was deduced by demonstrating equal levels of DMS on the nose and mouth breath. Furthermore, blood DMS was shown to correlate perfectly with breath DMS. Experimentation with solutions of DMS was found to have an odour comparable to the character of halitosis in this group. Patients with this proposed metabolic condition are reported to have breath DMS levels of 0.5–2.5 nM⁹¹ and blood DMS levels of 10–80 n mol/l.³²

Interestingly, a patient in this group showed significantly raised breath DMS 12 hours after consuming 12 glasses of beer. After this experiment, the patient in question was said to switch to drinking wine, and reported fewer complaints of bad breath.⁶⁶

These findings could be interpreted with caution as they are based on a small sample, and are as yet uncorroborated by other researchers.

DISCUSSION

'Systemic candidiasis syndrome'

There is a general belief among some sections of the public that *Candida* overgrowth is a leading cause of halitosis, or even body malodour. It is interesting to note the evolution of a commercial industry revolving around the theory that a so called 'systemic candidiasis syndrome' (also termed 'candida hypersensitivity syndrome') is widely prevalent. This is a medically unrecognised condition and falls within the realms of pseudoscience and alternative medicine. To the author's knowledge, there is no published scientific paper that has proven *Candida albicans* or other yeasts as a cause of oral malodour or extra-oral halitosis. Indeed, one paper reported low *Candida albicans* carriage rates in halitosis patients.³³ *Candida* is a normal oral commensal organism in a high percentage of the general population. Yeasts ferment carbohydrates to produce ethanol, which has an odour character described as 'strong alcoholic, ethereal or medical'.¹⁷² Whether high carriage rates of *Candida* spp. or even clinical evidence of oral candidiasis would produce a great enough concentration of ethanol or other metabolic by-products to create a malodour detectable by others is unknown. There is a feasible indirect, but not causative link between candidiasis and halitosis. Oral candidiasis frequently develops where there is xerostomia. Decreased salivary flow rates will reduce both the antimicrobial and mechanical cleansing action of saliva, resulting in increased growth of bacterial spp. in addition to *Candida* spp. The increased bacterial load could then lead to increased VSC levels and hence halitosis. In practice however, there does not seem to be any link between *Candida* and halitosis.

The so called 'systemic candidiasis syndrome', among its vast range of claimed symptoms, is described as giving a halitosis and/or body odour that is musty, 'mousy' or 'yeasty'. These particular odour descriptions are reminiscent of the odour character of DMS.

Blood borne halitosis may also cause other malodour complaints

Blood borne halitosis is caused by odourant volatiles present in the systemic circulation that are then transferred to the exhaled breath during pulmonary gas

exchange. However, the blood goes just about everywhere. It is known that in other conditions, blood borne volatiles can be expressed via several routes of excretion, leading to the presence of volatiles in sweat, saliva and urine etc. This may cause multiple symptoms of malodour in these patients, for example, body odour, malodorous urine, etc. Thus, the concept of blood borne volatiles causing blood borne halitosis monosymptomatically may be an oversimplification. It is likely with many of these volatiles that pulmonary excretion is the main form of elimination, since this is a highly efficient system. The term blood borne body odour has been offered, but this again may be too constrictive and misleading. The author suggests the term 'blood borne malodour condition' to describe these conditions and to reflect the multiple malodour complaints that they may be capable of triggering.

There are logistical problems involved in breath analysis,¹⁷³ and its availability may be limited in some areas. The relevance of breath analysis in the management of halitosis is undisputed, but it may be useful to perform urinalysis or blood biochemistry in selected cases, eg, where blood borne halitosis is suspected and there is a failure of standard therapy for intra-oral halitosis to control the symptom which cannot be better explained. These alternative routes may be more available and familiar to clinicians. Further research would be needed to validate these methods as being predictive for malodour symptoms and if so at what threshold concentration in the blood is required to create symptoms.

Trimethylaminuria

Trimethylaminuria (TMAU) has dominated researchers' interest into blood borne malodour conditions. The implicated enzyme pathway is the xenobiotic metabolising enzyme (XME) group, flavin containing mono-oxygenases (FMO), particularly FMO3. FMO has been implicated as being of perhaps equal importance to CYP450.¹⁷⁴ Evidence suggests that FMO is also involved in the metabolism of certain drugs.^{175–178} The main role of the FMO pathway appears to be as a scavenger system with a low specificity, carrying out oxidation of thousands of substrates, most notably nucleophilic amines and sulphides.¹⁷⁴

One of these substrates is trimethylamine (TMA), which has a fish like odour, becoming ammoniacal at higher concentrations. Genetic mutations of FMO3 that result in reduced efficiency when acting on the volatile TMA, (normally N-oxidised to trimethylamine N-oxide), leading to presence of TMA in the systemic circulation. This is said to create a fish-like blood borne body odour and halitosis.¹⁷⁹ Secondary forms of TMAU, where FMO efficiency may be at normal levels and an increase in the production of volatiles may overload the pathway, creating a mismatch between the substrate work load and the enzymes' ability to act on them.¹⁸⁰ There also appears to be a lack of consensus regarding the ideal diagnostic threshold.

Reported incidence of heterozygous (carrier) TMAU incidence has been estimated at 0.5–1% in the white British population.^{95,181} Patients with the heterozygote phenotype are thought by some to be 'at risk' of having their already compromised enzyme pathway overloaded easily,¹⁸⁰ possibly producing a transient presence of blood borne volatiles and an intermittent malodour symptom. Evidently, the number of patients with symptomatic TMAU is likely lower than these figures. This notion is supported when one looks at reported data from a major TMAU testing centre for over a decade. The number of patients receiving a positive diagnosis is low, around 30%. If we assume that a high percentage of these patients have genuine malodour symptoms (since they have been referred by a clinician for the test), then it appears that TMAU does not explain the majority of patients with suspected blood borne malodour conditions.

Anecdotally, only a minority of TMAU positive patients and patients who test negatively for TMAU, display the classically described fish odour, instead a range of odours are reported, such as faeculant body odour and halitosis. It is currently unknown whether other odourant volatiles normally dealt with by FMO3 could become elevated systemically as a result of dysfunction or overload of this enzyme pathway. It is interesting to note that FMO may be at least partly responsible for metabolism of DMS,^{117,182,183} and also reports of the potential contribution of TMA along with DMS in the odour of foetor hepaticus.

CONCLUSION

Frequently extra-oral halitosis, particularly blood borne halitosis, represents a far greater diagnostic and therapeutic challenge than 'straightforward' intra-oral halitosis. It has been suggested that a general lack of practitioner awareness is leading to ineffective management, and long delays in diagnosis of potentially treatable cases, possibly increasing detrimental psychosocial implications. This is a rapidly developing area in halitology and it is anticipated that diagnosis and management of blood borne malodour conditions will soon be better understood, allowing more effective management to address unmet patient needs.

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