International Dental Journal (2002) 52, 201-206

Halitosis in medicine: a review

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This review deals with the different forms of halitosis. Halitosis can be subdivided according to its original location. At present, halitosis of oral origin is quite well understood and some excellent reviews have already appeared in the literature. Special attention is given here to extra-oral halitosis. Extra-oral halitosis can be subdivided into: halitosis from the upper respiratory tract including the nose; halitosis from the lower respiratory tract; blood-borne halitosis. In blood-borne halitosis, malodourant compounds in the bloodstream are carried to the lungs where they volatilise and enter the breath. Potential sources of blood-borne halitosis are some systemic diseases, metabolic disorders, medication and certain foods. The methods of analysis of halitosis are critically reviewed. Attention is also given to odour characterisation of various odourants.

Key words: Halitosis, oral malodour, extra-oral halitosis, odour characterisation, analysis

Until recently, halitosis or bad breath received more attention in popular, humorous literature than in the scientific, as witnessed by phrases such as 'Please don't breathe until you have reached the desert'. However, halitosis is a concern to millions of people. Most adults suffer from bad breath occasionally, an estimated 10 to 30 per cent of the USA population on a regular basis[1]. This may lead to personal discomfort and social embarrassment. It is still one of the biggest taboos in our society. In the last decade, halitosis has received much more scientific attention, especially through the development of the Halimeter®, an apparatus that is designed to measure volatile odorous substances (sulphur gases) in a semi-quantitative manner[2].

Halitosis is the general term used to describe any disagreeable odour in expired air, regardless of whether the odorous substances originate from oral or non-oral sources. Other names used are *fetor ex ore*, *fetor oris*, bad or foul breath, breath malodour, and oral malodour. The latter term is reserved for halitosis from the mouth.

The general population and, unfortunately many physicians and dentists, are still poorly informed about the causes and treatments of halitosis. Many people still believe that bad breath originates in the stomach. However, this is seldom the case. Odours cannot escape from the stomach except during belching or vomiting, because the oesophagus, which connects the stomach with the mouth, is not an open tube and is normally

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0020-6539/02/03201-06

collapsed[3]. Halitosis is rarely a gastrointestinal condition. Regrettably, many patients have undergone a completely unnecessary gastroscopy before visiting a breath clinic. Research reports now agree that, in the vast majority of cases, halitosis (80 to 90 per cent) originates within the oral cavity, where anaerobic bacteria degrade sulphur-containing amino acids to the foul smelling volatile sulphur compounds, namely hydrogen sulphide and methylmercaptan[3–6]. An estimated 10 to 20 per cent of halitosis has non-oral causes. Oral malodour[4,6–9] can be treated effectively, in contrast to many cases of extra-oral halitosis[3,5,6,8–11], which might be a manifestation of a serious disease. It is therefore of utmost importance to differentiate between oral malodour and extra-oral halitosis. Differentiation can be easily done by comparing mouth breath with nose breath[5,6,8–10]. When extra-oral halitosis has been established, the patient should be referred to an appropriate clinic (otorhinolarygology clinic, metabolic ward, and internal medicine) where the cause of malodour can be further investigated. Among the host of extra-oral disorders, only a few have been investigated using analytical techniques to identify the volatile organic compounds associated with the odour. This is highly important, in order to diagnose the case and to set up a treatment plan.

Oral malodour

In order to distinguish extra-oral halitosis from other halitosis, oral malodour originating from the oral cavity must first be differentiated. Accordingly, practitioners are required to understand the features of oral malodour. Disorders of the oral cavity cause 80 per cent to 90 per cent of all cases of halitosis. Anaerobic bacteria within the oral cavity are responsible for bad breath. They degrade the sulphur-containing amino acids cystine, cysteine, and methionine to the foul-smelling volatile sulphur compounds (VSC) hydrogen sulphide (H_2S) and methylmercaptan (methanethiol, CH_3SH)[4,12]. Dimethyl sulphide (CH_3SCH_3) is a minor component of bad breath. Halitosis of oral origin is associated with poor oral hygiene, dental plaque, dental caries, gingivitis, stomatitis, periodontitis, tongue coating, and oral carcinoma[3]. Dry mouth (xerostomia) might also promote oral malodour[5,9,10], although a correlation is not always observed[6].

In healthy subjects, tongue coating is by far the most important source of malodour, most of the odour coming from the dorsoposterior surface of the tongue where the crypts are the favoured sites for the growth of the anaerobic bacteria responsible for halitosis[6,8,10,13,18]. A reduced saliva flow during sleep favours anaerobic bacterial putrefaction, giving rise to so-called 'morning breath', a transient condition which disappears after a meal[4,10,14]. In an estimated 10 to 30 per cent of the population the problem remains more persistent[1] and halitosis persists during the whole day. The latter condition of chronic oral malodour can now be treated very effectively by removing the tongue coating by means of a tongue cleaner[6,15] and by appropriate mouthwashes. Chlorhexidine reduces the number of bacteria[9], zinc salts bind the VSC[7,16], and ClO_2 and H_2O_2 oxidise VSC to non-odoriferous salts[8,14]. The oxidation potential of the latter two mouthrinses is very promising and might also affect the sulphur-containing amino acids, thereby inhibiting formation of VSC[15]. However, these mouthwashes are generally not effective in improving extra-oral halitosis.

Some investigators believe that, besides VSC, other volatiles produced by oral putrefaction processes such as organic acids, ammonia, and amines may also cause oral malodour[15,17]. This has been contradicted by the excellent work of Tonzetich[4]. He showed that the VSC are the central elements of oral malodour. The odour of volatile NH_3 was considered sweet and pleasant. Incorporation of large concentrations of methylamine and cadaverine into saliva did not intensify the odour of saliva, because these are vapourised only at extremely high pH. To the contrary he found that the diamines putrescine and cadaverine inhibited odour formation. No correlation was obtained between the odour intensity and concentrations of either indole or skatole.

The best way to prove a causative relationship between oral malodour and any malodourous volatile is to simulate breath samples with concentrations similar to those found in the breath. Tonzetich[18] defined the objectionability threshold values of 0.5ng/10ml air (1nmol/l or 24ppb) for CH_3SH and of 1.5ng/10ml air (4.4nmol/l or 106ppb) for H_2S. This means that concentrations above these values can be deemed objectionable. The concentrations of the VSC in early morning mouth air of approximately 50 per cent of the population exceeded these threshold values, showing that CH_3SH and H_2S are present in sufficient concentrations to account alone for the oral malodour, although other volatile compounds might modify the quality or intensity of the odour. The supposition that volatiles other than VSC might contribute to oral malodour has never been substantiated by such simulation experiments and has been disputed by many authors[4,7,9,19].

CH_3SH and H_2S occur in approximately equivalent amounts in oral malodour[4,14]. In patients with periodontal disease, CH_3SH was found to be the most abundant species[5]. CH_3SH is much more unpleasant and possesses a threshold of objectionability at least four times lower than that of H_2S. Oral malodour has more similarity with the pungent smell of CH_3SH than with the 'rotten eggs' smell of H_2S.

Table 1 Breath volatile sulphur compounds and amines, together with some of their odour characteristics[25].

Formula	Name	Odour qualification	Odour index	100% Odour recogn. conc.
H_2S	hydrogen sulphide	rotten eggs	17,000,000	1000 ppb
CH_3SH	methyl mercaptan	pungent, rotten cabbage	53,300,000	35 ppb
CH_3SCH_3	dimethyl sulphide	unpleasantly sweet	2,750,000	100 ppb
CH_3SSCH_3	dimethyl disulphide	pungent		7 ppb
$CH_2{=}CHCH_2SH$	allyl mercaptan	garlic-like		0.05 ppb
$CH_2{=}CHCH_2SCH_3$	allyl methyl sulphide	garlic-like		
$CH_3CH_2CH_2SH$	propyl mercaptan	unpleasant, pungent	263,000,000	0.7 ppb
$CH_3CH_2CH_2SCH_3$	methyl propyl sulphide			
CS_2	carbon disulphide	slightly pungent	1,600,000	900 ppb
NH_3	ammonia	pleasantly sweet	167,300	55,000 ppb
$(CH_3)_2NH$	dimethylamine	fishy, ammoniacal	280,000	6,000 ppb
$(CH_3)_3N$	trimethylamine	fishy, ammoniacal	493,500	4,000 ppb

Methods of analysis in the medical field

CH_3SH seems to be the causative factor of oral malodour. In this respect, it is somewhat peculiar that the Halimeter®, using an electrochemical gas sensor cell, has become the primary tool in chronic halitosis research and diagnosis[2]. The Halimeter® is approximately twice as sensitive to H_2S as it is to CH_3SH[2,8]. It is therefore possible that patients with high CH_3SH relative to H_2S in their mouth air may produce normal Halimeter® measurements despite significant organoleptically detectable breath malodour[8]. Conversely, patients with low CH_3SH relative to H_2S may have elevated Halimeter® measurements and no organoleptically-discernable breath malodour. Moreover, Halimeter® readings are significantly influenced by other oral gases such as chewing gum, strong mouthrinse odours, alcohol, shampoo, body lotion, smoking, and even water vapours. Some researchers claim organoleptic assessments are the golden standard in breath malodour[19,20]. However, such organoleptic measurements have their own quantitative problems, such as inconsistent results among judges[14,15]. Organoleptic ratings may also be influenced by other factors, such as the degree of humidity.

Gas chromatography is by far the most appropriate method to detect halitosis of different origins and should be considered as the golden standard. It is an objective means to obtain exact values for the various odorous volatiles. Moreover, it is a very sensitive method, especially in combination with preconcentration of breath samples onto Tenax traps[11,21,22]. A flame photometer detector is usually employed for the detection of VSC[12,14,21,23]. Other non-sulphur-containing compounds in human breath have been measured using a flame ionization detector[22,24]. Gas chromatography may also be combined with mass spectrometry, enlarging the scope of the method[11,24].

When a simple determination of oral malodour is required, the spoon test is preferred. In the spoon test, the posterior area of the dorsal surface of the tongue is assessed by thorough scraping, using a disposable plastic spoon. Afterwards, the spoon can be smelled; it has a very repulsive odour in patients with severe oral malodour[6,15].

Odour compounds and odour thresholds

Table 1 shows the most common odorous volatile sulphur compounds and some amines found in the breath of patients with halitosis of different origins, together with some of their known odour characteristics[25]. In odour research, there are three different odour thresholds that have been determined to be important:

- The perception threshold
- The recognition threshold
- The objectionability threshold[25].

Sense-of-smell results must be a statistical average because of biological variability. The thresholds normally used are those for 50 per cent and for 100 per cent of an odour panel. The 100 per cent recognition threshold (*Table 1*) is the concentration at which 100 per cent of the odour panel defined the odour as being representative of the odorant being studied. At the perception threshold concentration one is barely certain that an odour is detected, and it is too faint to identify further. In general, the recognition threshold concentrations are somewhat higher than those of the objectionability threshold and considerably higher than the concentrations of the perception threshold concentrations. The objectionability threshold concentrations are the most important ones in halitosis research and should be determined experimentally. The odour index is the ratio between the vapor pressure of an odourant and the 100 per cent recognition threshold, in other words, the ratio of the driving force to introduce an odourant into the air versus the ability of an odourant to create a recognised response. Usually, volatiles with the highest odour index and the lowest recognition

Table 2 Odourous volatiles in the breath of patients with blood-borne halitosis

Causes of blood-borne halitosis	Odourant	References
Systemic diseases		
Hepatic failure/liver cirrhosis	Dimethyl sulphide	26, 27, 28
Uraemia/kidney failure	Dimethylamine, trimethylamine	29
Diabetic ketoacidosis, diabetes mellitus	Acetone	30
Metabolic disorders		
Isolated persistent hypermethioninemia	Dimethyl sulphide	31
Fish odour syndrome, trimethylaminuria	Trimethylamine	32
Medication		
Disulfiram	Carbon disulphide	33
Dimethyl sulphoxide	Dimethyl sulphide	3, 10
Cysteamine	Dimethyl sulphide	34
Food		
Garlic	Allyl methyl sulphide	35
Onion	Methyl propyl sulphide	

threshold are the most odorous ones. Of all chemical classes, the unsaturated mercaptans (allyl mercaptan in garlic) and the unsaturated sulphides (allyl methyl sulphide in garlic) are the most odorous ones, followed by the saturated mercaptans (Propyl mercaptan in onion, methyl mercaptan, and hydrogen sulphide), disulphides (dimethyl disulphide), and sulphides (methyl propyl sulphide in onion and dimethyl sulphide).

Extra-oral halitosis

Halitosis of the upper and lower respiratory tract

Examples of halitosis of the upper respiratory tract are chronic sinusitis, nasal obstruction, nasopharyngeal abscess, and carcinoma of the larynx. Examples of halitosis of the lower respiratory tract are bronchitis, bronchiectasis, pneumonia, pulmonary abscess, and carcinoma of the lung[3,5,9,10]. All these anaerobic infections, ulcerations and/or cancer are reported to produce halitosis. These reports have largely been case reports based upon organoleptic evaluations. The breath and sputum of patients with anaerobic pulmonary infections have been described as having a putrid or feculent odour, similar to the odour of VSC[5,10]. However, the odourants have not been identified[11] in any of the above cases.

Blood-borne halitosis

Malodourous volatile substances can be absorbed from anywhere in the body (for example, mouth, stomach, intestines, and liver) into the bloodstream and later transferred to the pulmonary alveoli. Pulmonary excretion of these volatiles into the alveolar air then causes halitosis, if the malodourous volatiles are present in objectionable concentrations in the breath. Blood-borne halitosis has been reported to arise from some systemic diseases, metabolic disorders, medications, and from the consumption of certain foods (*Table 2*)[8]. Most of the reported cases of blood-borne halitosis are also caused by odorous volatile sulphur compounds. However, the nature of the compounds differs from that of the volatiles found in halitosis of oral origin. While oral malodour is largely caused by CH_3SH and to a lesser extent by H_2S, these compounds cannot be found in blood-borne halitosis. *In-vitro* experiments have shown[36] that the thiol CH_3SH, containing a free –SH group, immediately reacts with blood within seconds, resulting in irreversible binding and oxidation, thereby preventing transportation of CH_3SH from the blood into alveolar air and thus into the breath. The same holds for H_2S. This is not true for dimethyl sulphide (CH_3SCH_3), a neutral molecule which is stable in blood and can be transported from blood into alveolar air and breath. Other volatiles found in blood-borne halitosis are also stable in blood. The neutral nature of most volatiles found in blood-borne halitosis is one of the reasons why these compounds are difficult to remove from the breath, in contrast with the very reactive thiols CH_3SH and H_2S found in oral malodour. As mentioned above, in oral malodour conditions, the latter thiols can be effectively removed from the breath, for example by binding with zinc salts or by oxidation.

Systemic diseases

The *fetor hepaticus* in patients with liver cirrhosis is caused by dimethyl sulphide[26]. This was proven by simulating breath samples with the same concentrations of dimethyl sulphide as found in cirrhotic patients. The smell of these simulated samples was similar to that of *fetor hepaticus*. The dimethyl sulphide originates from the gut. Extensive shunting of portal blood around the liver in cirrhotics results in elevated dimethyl sulphide concentrations in systemic blood and thus in the breath. Others have claimed that methyl mercaptan is also a component of *fetor hepaticus*[27,28]. However, as explained above, this supposition must be false. The aliphatic acids C_2-C_3, also claimed as components of *fetor hapaticus*[17], are also highly unlikely to cause the condition. The odour indices of these aliphatic acids are quite low. Moreover, these acids are present in blood in their non-volatile salt form and cannot be present in threshold concentrations in alveolar air. Neither is *Fetor hepaticus* caused by amines, as reported by some researchers[3,10]. In patients with end-stage renal disease, an accumulation of dimethylamine and trimethylamine in their blood and breath correlated with the classic fishy odour. There are also doubts that the acetone found in diabetic ketoacidosis may play a role in causing halitosis. The odour of acetone has been described as a sweet fruity odour[3].

Metabolic disorders

Patients with isolated persistent hypermethioninemia have elevated methionine levels in their blood. The severe form results in a highly elevated methionine transamination, resulting in elevated dimethyl sulphide levels in blood, urine, and breath[31].

In the fish odour syndrome, oxidation of trimethylamine to the odourless trimethylamine N-oxide is impaired, leading to elevated trimethylamine levels in blood, urine, sweat, and breath[32].

Medication

Some medications might give rise to blood-borne halitosis. Disulfiram, a drug used in treating alcoholics, is metabolised to carbon disulphide. Dimethyl sulphoxide is prescribed for some patients suffering from muscle pain or from interstitial cystitis[10]. It is metabolised and reduced to dimethyl sulphide, giving off the 'garlic-like' odour of dimethyl sulphide. Cysteamine is used in patients with nephropathic cystinosis and can be metabolised to dimethyl sulphide. Certain drugs can also alter the sense of taste and smell, causing subjective halitosis[3], or may diminish saliva production thereby stimulating oral putrefaction and thus oral malodour[10].

Food

Certain foods including garlic, onions, and some spices are absorbed from the intestine, possibly metabolised in the liver, released into the bloodstream and excreted via the lungs and other routes. For garlic it was found[35] that halitosis may be of oral and/or gut origin. The oral component consisted of the thiols allyl mercaptan and methyl mercaptan and was present in the breath immediately after garlic ingestion. This component had almost disappeared after one hour. The gut component (blood-borne halitosis) consisted of allyl methyl sulphide and was the predominant one after three hours. No thiols were present in the gut component. This was explained by assuming a rapid metabolisation of these thiols by gut mucosa and liver tissue. Metabolism of these thiols by blood, as cited above, might be even more important[36]. Onions do contain large concentrations of propyl mercaptan[38]. The gut component of 'onion halitosis' consisted of methyl propyl mercaptan (personal observation).

Other conditions

There is controversy as to whether conditions below the gastroesophageal junction can cause halitosis. The current view is that halitosis, if present in conjunction with gastrointestinal disorders, is actually caused by disorders of the oral cavity[3]. Some authors have claimed a possible relationship between *Helicobacter pylori* and halitosis[39], while others have contradicted this relationship[40].

Many people try to overcome their halitosis by smoking. This may result in a strong smoker's breath. A history of smoking has been implicated in a deterioration in olfactory sensitivity. Halitosis patients are advised to stop smoking[6,9,10].

An increased oral malodour in some women during menstruation or certain menstrual cycles has been reported. Elevated VSC were found in mouth air during mid-cycle and around menstruation (menstrual breath)[41].

Some patients for whom no objective evidence of halitosis can be identified complain of chronic halitosis. This condition is known as halitophobia, pseudo-halitosis, imaginary halitosis, delusional halitosis, psychogenic halitosis, or olfactory reference syndrome. Halitophobia is a recognised psychiatric condition. It may drive people to complete social isolation and should be approached carefully[3,6,8,42].

This review has focused on malodourous volatiles in the breath. However, breath contains many more non-odourous volatiles which might give clues to many diseases. Breath tests might become a valuable tool as an alternative to invasive diagnostic procedures[24,33].

Conclusions

Halitosis is usually due to benign oral disorders, which can be treated quite effectively. Extra-oral halitosis might be a manifestation of a serious disease. This halitosis is more persistent unless the systemic disease is treated. It is therefore of utmost importance to differentiate between oral- and extra-oral halitosis. To detect halitosis of different origins, gas chromatography is by far the most appropriate method and should be considered to become the gold standard in halitosis research.

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