

## TRIMETHYLAMINURIA: THE FISH MALODOR SYNDROME

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### ABSTRACT:

The fish malodor syndrome (also known as the fish odor syndrome and trimethylaminuria) is a metabolic disorder characterized by the presence of abnormal amounts of the dietary-derived tertiary amine, trimethylamine, in the urine, sweat, expired air, and other bodily secretions. Trimethylamine itself has the powerful aroma of rotting fish, and this confers upon the sufferer a highly objectionable body odor, which can be destructive to the personal, social,

and work life of the affected individual. In recent years, much progress has been made at all levels—clinical, epidemiological, biochemical, and genetic—in our understanding of this unfortunate condition. The present article summarizes this progress, draws attention to the different types of fish malodor syndrome, and highlights the current needs in the treatment of such patients.

Trimethylaminuria, also known colloquially as the fish malodor syndrome, provides an excellent example of how genetically determined variability in the metabolism of a dietary derived chemical, namely trimethylamine, can result in a distressing clinical condition. At a more general level it reflects just how genetic constitution can adversely influence interactions with one's diet. In the past 15 years much has been learned about this particular metabolic disorder, at one time considered to be extremely rare in its occurrence, but in the light of new information, opinions about this are now having to be revised.

Biochemically, the disorder is characterized by the excretion of excessive amounts of a simple tertiary aliphatic amine, trimethylamine, in the urine, sweat, and breath as well as other bodily secretions, and this confers upon an individual a very unpleasant body odor resembling that of rotting fish. These "greater-than-normal" amounts of trimethylamine are present due to a failure in removing it via the usual oxidation route to the non-odorous metabolite, trimethylamine *N*-oxide, owing to a mismatch in the enzymes capacity to undertake this reaction and the substrate load it has to process. At the clinical level, the condition can be extremely distressing for the affected individual and can be responsible for a general destructive effect on the schooling, personal and social lives, as well as having an impact in adult life upon careers. At its extreme, it can be accompanied by severe mental depression occasionally leading to suicidal tendencies. What follows now is not a full review of the disorder (Mitchell, 1996) but rather an attempt to summarize our current state of knowledge of this condition.

### Milestones in the History of the Disorder

Table 1 shows some of the key milestone events in relation to our knowledge and understanding of this particular disorder. Historically, it is a fascinating fact that anecdotal descriptions of individuals with the fish malodor syndrome, or at least something very like it, have

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TABLE 1

*Some milestone events in the history of the fish malodor syndrome*

Period	Anecdotal Observations
1000 BC	Mahabharata (Indian Epic)
1250 AD	Thai folklore
1600	Shakespeare, <i>The Tempest</i>
1735	Arbuthnot, <i>Nature of Aliments</i>
1948	Eisenschiml, autobiography
Period	Clinical Observations
1970	First clinical description; coining of the term "fish odor syndrome", associated with excessive trimethylamine excretion and Turner's syndrome.
1970–1985	Description of isolated and sporadic cases
1980	Recognition of the "tainted egg" syndrome. Breed of chicken with dysfunctional <i>N</i> -oxidation.
1980–1990	Clinical and biochemical case studies from several countries. Characterization of a human genetic polymorphism of trimethylamine <i>N</i> -oxidation.
1990s	Molecular genetics of the flavin monooxygenase enzyme and recognition of candidate mutations for the fish malodor syndrome

been recorded across various millennia and cultures. Thus, in the Mahabharata, the great Indian epic of the Bharata Dynasty, there is a description of a young woman, Satyavata, condemned to a solitary life as a ferry-woman and cast from society because she stank like "rotting fish". Fortunately, she received a miracle cure from a demi-god. The story was compiled about 400 AD but is considered to relate to events occurring about 1400 to 1000 BC. In Thai folklore, there is a narrative that the fish malodor syndrome, or something closely resembling it, was rumored to be the major cause of suicide among concubines in the Sukhothai period of Thai history, more than 750 years ago (Thithapandha, 1997).

That acute observer of the human situation, William Shakespeare (1564–1616), provides a description of a fish odor sufferer in the *Tempest* when the jester, Trinculo, speaks of Caliban, a savage and deformed slave: "What have we here? a man or a fish? Dead or alive? A fish: he smells like a fish; a very ancient and fish-like smell; a kind of not of the newest Poor John" (*The Tempest* II. ii. 26–29). A "Poor

John" in Elizabethan society was a salted and dried hake. Incidentally, Shakespeare also describes Caliban as of a melancholic disposition; a feature not unusual in some patients with the fish malodor syndrome.

A century later, John Arbuthnot (1667–1735), a mathematician and physician, wrote in his treatise on nutrition and foods, "The oils with which fishes abound often turn rancid, and lie heavy on the stomach, and affect the very sweat with a rancid smell, which is found to be true in some places, where the inhabitants live entirely upon fish" (Arbuthnot, 1735). Were these cases of fish malodor syndrome?

Two suspicious reports made their way into the medical literature around the middle of the 19th century. One concerns a middle-aged man who was "attacked by a complicated disorder of the digestive system" and the "symptom which gave most annoyance was the exhalation of a fetid odour from all the surface of his body, which supervened an hour or two after each meal. The patient paid a scrupulous regard to cleanliness and had tried various remedies without success". (Anonymous, 1842). The other report concerned a patient with "foetid breath and its allied annoyance, foetid perspiration" to which the physician recommended the "avoidance of strong-smelling articles of the diet including, among many others, fried fish" (Pidduck, 1858). These appear to be descriptions of the fish malodor syndrome.

In the 20th century there is reference to a curious case, which in all likelihood was the fish malodor syndrome, in the autobiography, "Without Fame; The Romance of a Profession" by the chemist Otto Eisenschiml. During a period of his career he took up private cosmetic formulation work and in respect to this he writes, "My studies in human perspiration stood me in good stead later in my consulting work. Once a physician called on me to get my advice on a peculiar case he was treating. His patient was a woman of considerable means whose body odour was so strong that she had become morbid about it. She would not leave her apartment, shunned visitors, and was threatened with melancholy unless a remedy could be found for her affliction" (Eisenschiml, 1948). Once again such behavior is not uncommon in patients with the fish malodor syndrome.

### The First Clinical Reports

The first clinical description of a case of fish malodor syndrome is attributed Humbert and colleagues (1970). The patient was a 6-year-old girl with a history of multiple pulmonary infections since the neonatal period. The child had the clinical stigmata of Turner's syndrome, splenomegaly, mild anemia and neutropenia, abnormal platelet function, and decreased deformability of the red cells. Her mother related that the child intermittently had a peculiar "fishy odour". This triggered off a search for trimethylamine, which was known to smell of fish. Biochemical studies following an oral challenge dose of trimethylamine showed that there was a marked increase in the excretion of the free amine in her urine as well as a pronounced exacerbation of her odor problem. Three healthy controls did not show these increases (Humbert et al., 1970). A subsequent study on a biopsy liver sample taken from this patient revealed a defective trimethylamine *N*-oxidizing system; the defect manifested itself in a  $K_m$  value for trimethylamine that was five times higher than that typical of other normal "preparations" (Higgins et al., 1972). Over subsequent years, there appeared a number of sporadic reports of the fish malodor syndrome in both adults (Spellacy et al., 1979) and young children (Lee et al., 1976). These early studies showed that the condition could affect infants, children, and adults, and it was confirmed to be associated with the excretion of excessive amounts of trimethylamine, sometimes on a sporadic basis. Earlier thinking had associated fish malodor syndrome with Turner's and Noonan's syndromes but subsequent experience showed that this was incorrect.

### Recognition of the "Tainted Egg Syndrome" in Chickens

A further significant milestone in the evolution of our understanding of the fish malodor syndrome were the studies that showed that a certain breed of chicken carried an inherited defect in the *N*-oxidation of trimethylamine. These studies triggered an inquiry into the possible polymorphism of *N*-oxidation of trimethylamine in humans on the simplistic assumption that if it is found in an animal species, it may well be found in humans. Experience had shown that a certain breed of Rhode Island Red chicken produced eggs that were "tainted" due to the presence of trimethylamine, and customers were reluctant to purchase these for obvious reasons. These studies showed that the fishy contamination associated with "tainters" was due to an inherited impairment of the hens' ability to *N*-oxidize trimethylamine to its *N*-oxide, coupled with the consumption of a diet (rape seed meal) rich in precursors of trimethylamine (Pearson et al., 1979). Furthermore, it was demonstrated that the capacity of the fowl for trimethylamine *N*-oxidation was an inherited trait and was consistent with the involvement of a single, autosomal, semidominant gene (Pearson and Butler, 1983).

### The Search for a Human Genetic Polymorphism of Trimethylamine *N*-Oxidation

A population and pedigree study confirmed that the *N*-oxidation of trimethylamine in a White Caucasian population was under genetic control and displayed polymorphism (Al-Waiz et al., 1987). This study of a random British white population group ( $n = 169$ ) showed that the ability to *N*-oxidize trimethylamine derived from the diet was skewed in terms of the population distribution. Based upon a metabolic ratio of urinary trimethylamine/trimethylamine *N*-oxide, metabolic "outliers" could be discerned. Patients diagnosed with fish malodor syndrome occupied one extreme of the distribution, and pedigree studies involving the use of an oral trimethylamine challenge test (Al-Waiz et al., 1989) revealed that the parents could be identified as carriers or heterozygotes for dysfunctional *N*-oxidation. Heterozygotes show clear evidence of limited *N*-oxidation capacity when challenged with oral doses (600 mg) of trimethylamine but not with lower doses. Although the test is somewhat unpleasant for the subject, the procedure has been found invaluable for the characterization of heterozygotes. This study suggested an incidence of about 1% of heterozygotes in the British Caucasian population with a degree of uncertainty. A subsequent larger investigation of British subjects ( $n = 421$ ) confirmed these conclusions and verified that the *N*-oxidation of dietary-derived trimethylamine showed a discontinuous distribution and that about 1% of the population was of possible carrier status. Interestingly this study showed an over-representation of women in the affected group and this will be remarked upon later (Zhang et al., 1996a).

### Biochemical Features of Fish Malodor Syndrome

The outstanding biochemical feature in the fish malodor syndrome is the excessive excretion in the urine of un-oxidized trimethylamine. British individuals on the average Western diet excrete in the urine daily about 50 mg of trimethylamine *N*-oxide and about 1 to 2 mg of free trimethylamine; that is, the *N*-oxide accounts for greater than 90% of the total daily excretion of trimethylamine-related material. The total amounts vary, however, according to the composition of the diet and particularly if marine fish are eaten because they contain high levels of trimethylamine *N*-oxide.

Table 2 shows a summary of the pattern of urinary excretion of trimethylamine and its *N*-oxide for a group of unaffected controls, known heterozygotes (parents of children with fish malodor syn-

TABLE 2

*N*-Oxidation of trimethylamine in fish malodor patients, heterozygotes (carriers), and unaffected individuals following a normal diet and a 600-mg trimethylamine oral challenge dose

Results are expressed as the mean  $\pm$  S.D. Ranges are given in parentheses.

Group	Following a Normal Diet	
	Free Trimethylamine as a Percentage of Total Excretion	Trimethylamine/ <i>N</i> -Oxide Ratio
Fish malodor		
Males = 4	78.5 $\pm$ 13.3 (59–89)	3.65
Females = 9	71.8 $\pm$ 15.7 (46–90)	2.55
Heterozygotes ( <i>n</i> = 13)	4.5 $\pm$ 1.8 (2–8)	0.047
Unaffected controls ( <i>n</i> = 75)	4.3 $\pm$ 2.5 (2–9)	0.045
Group	Following a 600-mg Challenge Dose	
	Free Trimethylamine as a Percentage of Total Excretion	Trimethylamine/ <i>N</i> -Oxide Ratio
Fish malodor		
Males = 4	91.5 $\pm$ 5.1 (84–95)	10.76
Females = 6	85.8 $\pm$ 7.1 (77–93)	6.04
Heterozygotes ( <i>n</i> = 13)	24.5 $\pm$ 2.7 (21–29)	0.32
Unaffected controls ( <i>n</i> = 75)	6.6 $\pm$ 3.0 (1–13)	0.071

drome), and some patients with the fish malodor syndrome. The results are expressed as a percentage of the total trimethylamine-related material excreted in the urine as the free amine on a normal diet as well as after an oral challenge “load” test (600 mg of trimethylamine). The finding for the two groups are also expressed in terms of the ratio: percentage trimethylamine/percentage trimethylamine *N*-oxide, which is diagnostic for a deficiency of *N*-oxidation. It can be seen that both the male and female patients excrete most (circa 70–80%) of the total trimethylamine derived from the diet as the free amine compared with only 4% found for healthy controls. The dysfunctional *N*-oxidation is clearly reflected in the high values seen for the ratio. After the challenge test, the fish malodor patients excreted even more free amine (circa 90%) whereas this remained unaffected for the control subjects. The heterozygotes, who coped with the normal dietary input and were indistinguishable from the unaffected controls, were shown to falter when challenged with the 600-mg oral load, and their *N*-oxidation capacities decreased; this is the basis of the challenge test for heterozygotes or carriers mentioned previously.

In our experience there appears to be a threshold for the appearance of fish malodor symptoms. The loss of “larger-than-normal” amounts of trimethylamine via the sweat and breath appears to occur in concordance with a urinary level of free trimethylamine of 10  $\mu$ g/ml (18–20  $\mu$ mol/mmol creatinine) or above. Depending upon urinary volumes, this correlates with a urinary trimethylamine output of about 15 to 20 mg/day.

The intriguing question remains as to whether or not there are other endogenous or dietary substrates whose metabolism is also affected in the fish malodor syndrome. Bearing in mind that many sulfur and basic nitrogenous compounds are substrates for the enzyme system involved, this appears to be highly likely but the question remains unanswered as yet.

### Incidence of Fish Malodor Syndrome

A question that is frequently asked is what is the incidence of the fish malodor syndrome? This cannot be answered with any certainty as new cases are continually being recognized because of a greater awareness of this metabolic problem. In terms of frequency of occurrence, it appears that it should no longer be regarded as a “rare” disorder but more appropriately as an “uncommon” one. As of the present, it would seem that well over 200 cases of the condition have

TABLE 3

Data available on the occurrence of the fish malodor syndrome

Country	Number of Patients	Male	Female
United States	102	33	69
United Kingdom	50	22	38
Canada	20		
Australia	20		
Thailand	5	1	4
Israel	2	0	2
Italy	1	1	0

been described on a world-wide basis, and this figure is almost certainly underestimated (Table 3).

The information available to date shows that the metabolic syndrome has been found in several countries, and the bias at the moment seems to be in favor of those areas that have populations derived from British/Scottish/Irish descent, but this leaning is probably more apparent than real. The condition has been observed in both males and females, although overall there appears to have been a preponderance of females reported with this condition.

### Types of Fish Malodor Syndrome

With the uncovering of many more cases of the fish malodor syndrome, it has become apparent that there are several different types of this disorder and that there is a need to develop a more adequate system of classification. One is proposed below based on presently available data. In principle, it appears that there are two major subtypes of fish malodor syndrome: first, those forms that are related to a dysfunction of the normal enzyme activity due to genetic, hormonal, or inhibitory-chemical influences; second, 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 the gut microflora resulting in enhanced liberation of trimethylamine. Clearly, these are two intimately interrelated 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). A classification of the various forms of fish malodor syndrome is given in Table 4.

**1. Primary Genetic Form.** The primary genetic form of the fish malodor syndrome is probably the best understood of the various forms of the disorder and accounts for a large proportion of the known cases. In recent years, there has been rapid progress in the elucidation of the enzymology of trimethylamine *N*-oxidation, and the realization that the flavin monooxygenase (FMO<sup>1</sup>) family of enzymes is responsible for this reaction. The unraveling of the isoenzymic nature of the human flavin monooxygenase system has been achieved over the past decade as well as details of their individual molecular characterization (Phillips et al., 1995). Briefly, this has shown that there are five distinct members of the human flavin monooxygenase family [FMO1, FMO2, FMO3, FMO4, FMO5 (also FMO6)], which can vary in terms of their functional activities and tissue expression. The form that is most abundant in human liver and appears to be most closely involved in the *N*-oxidation of trimethylamine is flavin monooxygenase 3 (FMO3), and for this reason the molecular identification of candidate mutant forms has centered on this isozyme and with considerable success.

Recent students have shown the human FMO3 to be highly polymorphic and some of the mutations, either alone, or in combination are associated with dysfunctional enzyme activity and the metabolic disorder whereas some mutations appear to be benign (Dolphin et al., 1997; Treacy et al., 1998; Akerman et al., 1999b).

<sup>1</sup> Abbreviation used is: FMO, flavin monooxygenase.

TABLE 4

*Proposed classification of various types of fish malodor syndrome*

1. Primary genetic
2. Acquired/viral infection
3. Transient childhood
4. Transient menstruation
5. Precursor overload

Two apparently relative common polymorphisms, P153L and E305X, appear to account for the majority of severe cases of fish malodor seen in patients to date (Dolphin et al., 1997; Treacy et al., 1998). One of these, P153L, has been found to cosegregate within a family pedigree with expression of the disorder. Besides these, other mutations of FMO3 (see Table 5) have been described, some associated with the inactivation of FMO3. In addition, it appears that there may be combinations of intragenic polymorphisms within FMO3 that determine a modified and less severe form of the condition (Akerman et al., 1999a; Zschocke et al., 1999). These advances should now make it possible to diagnose the disorder at the molecular level as well as identifying carriers.

**2. Acquired Form.** There are at least three cases known of individuals with clinical and biochemically diagnosed fish malodor syndrome (Ruocco et al., 1989; S. C. Mitchell and R. L. Smith, unpublished data) where the condition appeared to emerge in adult life. There was no previous history in childhood and there was no familial background to the disorder. What appeared common to the three cases was evidence of hepatitis, possibly viral, in adult life and this may have been responsible for precipitation of the condition possibly by insertion of viral DNA into the genome thereby affecting normal expression of the human FMO3 gene.

**3. Transient Childhood Forms.** A preterm infant (29-weeks old) who developed a fish odor while being fed a choline-containing food supplement has been described (Blumenthal et al., 1980). When the choline supplement was withdrawn the odor disappeared, and it failed to reappear at 8 months of age when the supplement was reinstated. When the supplement was given to three other preterm infants of similar weights and ages, one of these developed a fish odor. The authors attributed the fish odor associated with the choline-containing supplement to the immaturity of the *N*-oxidase enzyme. Since then, other cases of pediatric fish malodor syndrome have been described (Mayatapek and Kohlmuller, 1998). During early childhood a transient or mild form of trimethylaminuria may occur. Molecular analyses in some cases can reveal compound heterozygosity for several mutations. Recent studies suggest that both severe and variant mild trimethylaminuria is much more common than hitherto recognized (Zschocke et al., 1999).

**4. Transient Form Associated with Menstruation.** Several of our female patients told us anecdotally of how their fishy odor seemed to intensify with the onset of menstruation (Ayesh et al., 1993). A subsequent study of a single female fish malodor patient showed that her trimethylaminuric condition deepened just before the onset of menstruation and that this biochemical feature related closely to her own subjective description (Zhang et al., 1996b). 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 (S. C. Mitchell and R. L. Smith, unpublished data). Although this may be an interesting phenomenon in its own right, particularly with respect to possible hormone modulation of flavin monooxygenase activity, it is also of diagnostic importance because a sample taken at this time and analyzed for trimethylamine and trimethylamine *N*-oxide might lead

TABLE 5

*Point mutations of human FMO3 associated with fish malodor syndrome*

Position	Mutation
61	Asn → Ser <sup>a</sup>
82	Met → Thr <sup>a</sup>
153	Pro → Lev <sup>a</sup>
158	Glu → Lys
180	Gly → Val
257	Val → Met
305	Glu → X <sup>a</sup>
434	Met → Iso <sup>a</sup>
492	Arg → Trp <sup>a</sup>
661	Met → Iso <sup>a</sup>

<sup>a</sup> Inactivates FMO3.

to an incorrect diagnosis of inherited (primary genetic) fish malodor syndrome whereas the condition may only be transitory.

**5. Precursor Overload.** A few cases of a transient form of the fish malodor syndrome have been attributed to precursor overload thereby saturating the existing levels of flavin monooxygenase. Trimethylamine is mostly derived from dietary precursors such as choline, carnitine, and trimethylamine *N*-oxide through enterobacterial metabolism. Exposure to unusually high levels of such precursors may hasten a fish malodor syndrome especially if the individual is a haplotype for certain mutations. Large oral therapeutic doses of choline (8–20 g/day) have been used to treat Huntington's chorea, and although there was some improvement in the clinical picture, patients complained of a striking fish-like odor, which was attributable to the generation of excessive amounts of trimethylamine that exceeded their enzyme's capacity to oxidize it to the non-offensive *N*-oxide (Growdan et al., 1977). It is noteworthy that the precursors of trimethylamine, choline and lecithin, sometimes recommended in quite high doses in health foods, food supplements, and alternative diets could lead to the problems outlined above.

### Clinical Aspects of the Fish Malodor Syndrome

The principle consequences of the fish malodor syndrome appear in the main to be psychosocial in nature although there are some other observations that deserve to be followed up. The psychosocial reactions appear to arise from the excretion of excessive amounts of malodorous trimethylamine in the sweat, breath, urine, and other bodily secretions thereby conferring a powerful and offensive body odor. The latter, as well may be imagined, can be highly destructive to personal, working, and career lives of the affected individuals. Some individuals become socially withdrawn and isolated and may go on to develop mental depression (Todd, 1979; Shelley and Shelley, 1984; Ayesh et al., 1993). The condition can be particularly acute and severe for young children and adolescents who may be subject to ridicule, lose confidence, and even schooling.

It is a moot point as to whether the mental depression that is seen in some cases, but by no means all, is attributable to the debilitating social isolation that some experience or whether it arises from the dysfunctional metabolism of other endogenous substrates. Endogenous amines such as tyramine are substrates for FMO3, which is expressed in the brain (Bhamre and Ravindranath, 1991; Bhamre et al., 1995; Lin and Cashman, 1997). What does seem to come through in the various studies is that the severity of the syndrome is highly variable; in some individuals, it is severe, in others less so and sometimes it seems to be more episodic in nature. Another curious feature is that although some sufferers are cognizant of the smell of their condition others remain unaware (Ayesh et al., 1993).

## Diagnosis

Until recent years, diagnosis was made on the basis of clinical symptoms and biochemical assays of urine samples for either trimethylamine alone or in combination with its *N*-oxide metabolite. An oral challenge test involving the administration of 600 mg of trimethylamine (as its hydrochloride salt) has also been found useful for investigating family pedigrees and identifying carriers of the metabolic disorder. However, with the advent of molecular genotyping and recognition of causative mutations, the primary genetic type in both its homozygous and carrier forms can be readily recognized. However, there could remain difficulties in identifying some of the other forms particularly those arising from various haplotype combinations or nongenetic causation. Basically, one has to recognize that trimethylaminuria/fish malodor syndrome can arise from the interaction of two entities, namely a dysfunctional *N*-oxidation capacity (owing to genetic or nongenetic reasons) and the burden of trimethylamine available to be oxidized. It is important to appreciate that some forms of trimethylaminuria may be transient or episodic in nature and are different from the primary inherited form. Thus, a finding of trimethylaminuria on its own, although of interest, is not necessarily reflective of the inherited fish malodor syndrome, and the fact has to be considered along with other details and possibilities. The cautionary tale here is not to misapply the diagnosis of trimethylaminuria as necessarily that of the inherited fish malodor syndrome, which may require long-term management and counseling.

## Treatment

There has been no systematic evaluation of the various treatments for the fish malodor syndrome. Many of the reports are anecdotal in nature or involve just small groups of patients. Attempts to reduce the intake of precursors of trimethylamine such as carnitine and choline, through dietary management, appear to have been successful in some patients but not in all. It appears likely that dietary management might be most effective in mild to moderate forms of fish odour syndrome arising from particular mutations or haplotypes (Danks et al., 1976; Mitchell, 1996). Occasionally, a short course of neomycin and metronidazole to reduce the activity of the gut microflora and suppress the generation of trimethylamine have been said to be effective in some, but once again, not all cases (Treacy et al., 1995).

Sufferers and their families can derive considerable benefit from counseling if and when this is available. Quite apart from dietary advice, patients can be counseled that events such as menstruation, pyrexia, and stress appear to exacerbate the condition.

As to the future, one may envisage some new approach to treating or managing the condition quite apart from the obvious one of gene therapy with replacement of the human gene for FMO3. Alternative approaches might embrace the following: use of gut absorbents, such as charcoal or ion-exchange resins; modify the gut flora to reduce the bacterial species responsible for the conversion of precursors to trimethylamine; incorporate micro-organisms "engineered" with human FMO3 into the gut flora, to oxidize any trimethylamine released to its non-odorous *N*-oxide; provide riboflavin supplements, a precursor of the FAD cofactor for flavin monooxygenase function, in an attempt to maximize any residual activity; and finally, from the cosmetic point of view, the development of "malodor suppressants" in hygiene products to disguise the offensive smell of trimethylamine.

With greater numbers of patients being discovered with this unfortunate metabolic disorder, it should prove possible to evaluate these and other treatments for their potential effectiveness and application.

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