

FOOD IDIOSYNCRASIES: BEETROOT AND ASPARAGUS

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ABSTRACT:

Anecdotal observations scattered throughout the literature have often provided clues to underlying variations in humans' ability to handle dietary chemicals. Beetroot, the red root of the garden beet used extensively as a food source, is known to produce red urine in some people following its ingestion, whereas others appear to be able to eat the vegetable with impunity. Asparagus, a vegetable whose young shoots have been eaten as a delicacy since the times

of the Roman Empire, has been associated with the production of a malodorous urine smelling like rotten cabbage. Those who produce this odor assume that everyone does, and those who do not produce it have no idea of its potential olfactory consequences. These two examples, where the population appears divided in its ability to process food products or more precisely the chemicals contained within them, are reviewed in detail in this article.

In investigating the normal functioning of the human body, and perhaps more pressingly to gather information about an affliction in order to attempt a cure, body fluids have provided a means of accessing the internal workings. Initially, much attention was paid to the manner of noxious exhalations, to the characteristics of the urine, and to a lesser extent, the feces. With improvement in sterile procedures the safe sampling of blood flourished, and many useful parameters can now be quickly and routinely measured. More recently, noninvasive approaches have been able to image the body from a distance, while microanalysis of the genetic fluid, the sequencing of DNA both nuclear and mitochondrial, heralds a new level of understanding.

However, in an age when there was less data, observers were forced to carefully ruminate over every piece of information gathered, and some interesting findings emerged. In a popular text constructed in the middle of the 19th century, the authors state that the rapid development of zoo-chemical analysis (biochemistry) had greatly aided the medical practitioner and that it "has taught us that the urine is a collection of the products of the decomposition of the animal structures, and that from the study of the urine we may hope to obtain positive conclusions concerning the nature of the organic processes going on in the diseased, as well as the healthy, body" (Neubauer and Vogel, 1863).

This article examines two apparent idiosyncratic reactions to food: a colored urine after eating beetroot (*Beta vulgaris*) and an odorous urine after eating asparagus (*Asparagus officinalis*).

Beetroot

The Color of Urine. Of all the colors possible, the production of red urine is particularly distressing as it is associated with the loss of blood. Many referrals to the hospital for suspect hematuria, particularly among young children, fortunately albeit embarrassingly, have

been found to be benign. A passage from the early literature confirms that such misjudgments are not new and states the point quite clearly:

"The urine frequently presents the various odours and colors of vegetable matters which are taken into the stomach; and the examiner must be on his guard against being deceived by such appearances. Thus, I have known a patient on the point of being treated for hematuria, when the urine (by a mere chance) falling under my observation, I discovered the red coloration to proceed from the presence of a vegetable matter. On inquiry, the patient stated that he had been eating a salad, of which beetroot was an ingredient, during the last eight or ten days of his medical friend's visits" (Rees, 1836).

Beetroot is a biennial plant that develops a fleshy taproot during the first season, with branched leafy stems bearing small green flowers and brown fruits emerging during the second growing season. The vegetable is cultivated as an annual and, although the fresh young leaves may be eaten as salad, it is the root that is normally used as human food. These sweetly flavored roots can be stewed, boiled, baked, or pickled, and in Eastern Europe they are popular in a classic soup called borsch(t). Long has it been known and accepted amid folklore that some individuals readily excrete a red urine following beetroot ingestion, whereas others appear resistant to this event. Research published in 1956 reported that a small proportion of a test population (10/104, 9.6%) produced red urine, and family investigations suggested that the characteristic was controlled by a single autosomal recessive gene (Allison and McWhirter, 1956). Such a sweeping statement based on little data has not gone without criticism (Penrose, 1957; Saldanha, 1962). Several studies within the literature undertaken on healthy individuals have reported that anywhere between none and virtually all of their subjects have produced red urine after eating beetroot (0/9, 0%, Zindler and Colovos, 1950; 10/104, 9.6% Allison and McWhirter, 1956; 129/338, 38.2%, Saldanha et al., 1960; 8/58, 13.8%, Watson et al., 1963; 243/244, 100%, Forrai et al., 1968; 47/51, 92.2%, Forrai et al., 1971). Other investigations involving the mathematical analysis of data obtained from 99 pairs of twins (58 monozygotic, 41 dizygotic) failed to show any obvious hereditary pattern, although the authors suggested that some circumstances

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pointed to the effect of genetic factors (Forrai et al., 1982). Pedigree studies have also cast doubt on beeturia being controlled by a single gene (Saldanha, 1962). This is problematic in attempting to assign a simple genetic model to the situation.

It has also been suggested that beeturia is linked with food allergies and malabsorption syndromes, with a higher incidence of beeturia being found among those with iron deficiency anemia and patients receiving treatment for pernicious anemia (Zindler and Colovos, 1950; Watson et al., 1963; Tunnessen et al., 1969). Only in 1999 was it suggested that beeturia could be used as a simple screening test for hemochromatosis (Sotos, 1999). However, such an association has been contested following the failure to demonstrate a correlation between serum iron levels in schoolboys, half of whom were anemic, and beeturia (Forrai et al., 1971). Nevertheless, these may be situations wherein pathological changes in gut permeability enhance pigment absorption and subsequent excretion into the urine.

A more detailed investigation demonstrated that a quarter of the urine samples collected from 86 volunteers after beetroot ingestion were subjectively (visually) detected as positive, with an additional group being objectively confirmed positive by spectrophotometry as the power of resolution increased. This simple observation has enabled the conclusion that the creation of separate 'excretor' and 'nonexcretor' categories (a polymorphism) within this continuous spread of excretion, although convenient, was subjective and artificial. Nonexcretors simply produce too little pigment to be visible to the unaided eye (Pearcy et al., 1992; Mitchell, 1996). This was corroborated by an elegant study wherein urine samples from 100 subjects who had previously ingested 60 mg of beetroot pigment were examined by high-pressure liquid chromatography and all were shown to contain small amounts of pigment, but in many the concentrations were too low for them to appear red (Watts et al., 1993).

Data from eight individuals who undertook a repeat study within 1 week showed that the beeturia was reproducible, but four subjects who ingested the same quantity of beetroot on five separate occasions spaced over several months showed variation ranging from good to poor excretion (Pearcy et al., 1992). Such problems of biological repeatability have been mentioned before (Watson et al., 1963; Forrai et al., 1968). Extrapolating from these observations, it was surmised that within any population study a spread of excretion capacities will always be found, but during repeat investigations the characteristics of any one particular individual within a group may change (Pearcy et al., 1992). This is not expected for an event predominantly under genetic control. Furthermore, by varying the amount of beetroot consumed during a single meal, it has been alluded that this may be, and probably is, a dose-dependent phenomenon. Furthermore, the type of beetroot (variety, preparation, source) used influenced the outcome; susceptible individuals who gave an intense coloration with one variety gave virtually normal urine with another (Pearcy et al., 1992; Watts et al., 1993). It is known that the times of planting and harvesting greatly influence the pigment content of the crop and that concentrated beetroot extract is added to certain brands to enhance the coloration of their finished products (Shannon, 1972). Clearly, such factors amid others are probably sufficient to account for the gross variation in frequencies reported within the literature.

Chemical Origins of the Coloration. The major pigments in beetroot that impart the deep red coloration are known collectively as betacyanins. These pigments contain as their chromophore the resonant polymethylene cyanine grouping within the aglycone betanidin (and isobetanidin, its epimer at the C-15 position), which is usually conjugated with glucose (Harmer, 1980). Yellow colorants (betaxanthines) are also present. These pigments are known to behave as redox acid/base indicators and are structurally unstable at the extremes of

pH, loosing their color in alkaline conditions and undergoing irreversible decomposition (red to yellow) in acid solution. Optimal stability exists between pH 4 to 5 (von Elbe et al., 1974; Huang and von Elbe, 1987; Watts et al., 1993; Eastwood and Nyhlin, 1995). If pigment is present, therefore, the resulting color intensity is dependent upon the urinary pH. The red coloration also increased on exposure to sunlight due to pigment rearrangement (Watts et al., 1993) but decreased on storage (Eastwood and Nyhlin, 1995), and repeated freeze-thaw cycles were shown to increase the rate of color loss (Pearcy et al., 1992).

Chromatographic examination of such vermeil urine demonstrated that the red coloration was due to unchanged beetroot pigments (R. M. Pearcy, unpublished data; Watts et al., 1993). This indicates that once absorbed the pigments were not metabolized but rapidly excreted via the kidneys, and this conjecture has been supported by evidence from rats wherein intravenous or intraperitoneal injection of beetroot extracts demonstrated a high renal clearance (Krantz et al., 1980; Watts et al., 1993; Eastwood and Nyhlin, 1995). Also, there exists an anecdotal report of a volunteer, known not to produce red urine after ingesting betanin, who was shown to excrete rufescent urine when betanin was injected intravenously (Watson et al., 1963).

A Reasonable Explanation? These reports forecast, therefore, that the key to the beeturia phenomenon must lie in factors affecting the quantity of pigment entering the systemic circulation, factors influencing the amount of pigment present in the gut and its subsequent absorption.

Experiments in rats have suggested that the stomach is the main site responsible for the decolorization of beetroot. It is known that the mean fasting acidity of the human stomach is about pH 2, and in these conditions rapid decomposition of the pigment occurs (Dressman et al., 1990; Watts et al., 1993). As these latter authors have adeptly commented, "if the acid-catalyzed degradation of beetroot pigments in the stomach is a major determinant of their fate in man, the occurrence of beeturia may be more common in individuals who, after eating beetroot, show a slow decrease in stomach pH to fasting levels coupled with a rapid rate of gastric emptying". (Watts et al., 1993). This hypothesis has recently been supported by a report of an elderly man who to his knowledge had never produced red urine following beetroot ingestion but suddenly displayed erythruia during the time he had been taking a course of ranitidine, the histamine H₂-receptor antagonist, for reflux esophagitis (Mitchell, 1996).

In addition to being decolorized by hydrochloric acid, beetroot pigments also become achromatic in the presence of ferric ions and rat colonic bacterial preparations but not with saliva, pancreatic, or mucosal enzymes (Eastwood and Nyhlin, 1995). These workers reported that the oral ingestion of beetroot pigment together with oxalic acid can produce beeturia in previous nonexcretors and suggested that oxalic acid and ascorbic acid, both found in beetroot, could act as protective factors limiting the degradation of pigment in stomach acid. This combination (beetroot pigment plus oxalic acid) produced a bright red ileostomy effluent but did not produce beeturia in ileostomy patients, indicating that pigment absorption occurs mainly in the colon. They concluded, adding to the "stomach acid hypothesis", that coingestion of oxalic acid is able to protect the pigment during its travel to the colon; otherwise, the pigment is decolorized in nonbeeturic individuals by nonenzymatic processes in the stomach and colon (Eastwood and Nyhlin, 1995).

Although many other investigations could be undertaken, there is at present sufficient evidence to proffer that beeturia is more a function of an individual's physiological constitution and not a phenomenon under direct polymorphic genetic control as originally implied.

Asparagus

Pointers From History. Whether or not asparagus was known in the ancient Egyptian world, or earlier, is unclear. Mythological mention of the vegetable occurs during the perilous walk of Theseus via the Saronic Gulf wearing his father's sword and sandals to claim the heirdom of the Athenian throne. At the Isthmus of Corinth he was accosted by the marauder Sinis but managed to outwit and kill him. He then discovered the brigand's daughter, Perigune, hiding in a dense clump of asparagus, vowing never to burn or uproot the plant if it would only protect her. Alas, to no avail. She bore Theseus a son, Melanippus, whose descendants, the Ionians inhabiting Caria, protected the plant by severe laws out of respect for their ancestors. Asparagus is also mentioned in the writings of such Greek scholars as Antiphon (480–411 B.C.), Theopompus (380–? B.C.), and Theophrastes (372–287 B.C.), but cultivated asparagus seems to have been unknown, and all of these may have been referring to a wild plant of another species.

However, the Romans at the time of Cato the Elder (234–149 B.C.) were well acquainted with asparagus, and detailed instructions for its cultivation are given in Cato's surviving treatise, *On Agriculture (De Agri Cultura)*. Other authors, including Dioscorides (ca. 40–90 A.D.) in his *De Materia Medica*, Pliny the Elder (23–79 A.D.) in his epic *Historia Naturalis*, and Apiculus (*De Re Coquinaria*—sometimes credited to Caelius) and Columella (*De Re Rustica*), who both lived under the rule of Tiberius (14–37 A.D.) during the early part of the first century, also described the plant and its cultivation, and it appears that their asparagus was the same as we enjoy today.

Even though asparagus was well known in England by the 10th century A.D. a resurgence in interest occurred throughout Europe during the 1500s. John Gerard(e) (1545–1612), who wrote in 1597, was the first English author to mention asparagus, deriving the name from the Latin "*asparagi*" which he translated to signify "the first sprig or sprout of every plant, especially when it be tender". Meager, in his *English Gardener*, informs us that in his time (1670) the London markets were well supplied with forced asparagus, and Louis XIV (the Sun King) (1638–1715) popularized asparagus among the French nation when he built Versailles. By the late 1600s herbalists and horticulturists had made asparagus familiar all over Europe (M'Intosh, 1855; Hedrick, 1919).

Despite its long usage over 2000 years, it appears that it wasn't until the turn of the 18th century that reports linking its ingestion with the production of odorous urine began to emerge. John Arbuthnot (1667–1735), a Scottish mathematician and physician to Queen Anne, noted in a book on foods first published in 1731 that "asparagus. . . affects the urine with a foetid smell (especially if cut when they are white) and therefore have been suspected by some physicians as not friendly to the kidneys; when they are older, and begin to ramify, they lose this quality; but then they are not so agreeable" (Arbuthnot, 1735). Samuel Johnson (1709–1784), in the first edition of his *Dictionary of the English Language* (1755), quotes Arbuthnot's passage, although Charles Knight (1791–1873) in his *English Cyclopaedia* (1859) does not mention the odiferous property; perhaps it was not yet common (Johnson, 1755; Knight, 1859). However, by 1866, Pierre Larousse in the *Grand Dictionnaire Universel* assures us that "tout le monde connaît l'odeur fétide qu'elle communique à l'urine" (Larousse, 1866).

It is coincidental that the odor-producing phenomenon was not observed until the use of sulfur, sulfate, and organic sulfur materials as fertilizers to improve asparagus flavor had become prevalent from the late 17th century onwards. It is probable, therefore, that the urine odor was associated with a sulfur-containing component of asparagus.

During this century it has been conclusively demonstrated that onions and garlic grown in the presence of low levels of sulfur have a very weak flavor and lose lachrymatory properties; increased flavor strength, typical of the Alliums, is associated with higher levels of sulfur compounds, mainly sulfate, within the soil (Platenius, 1941; Kumar and Sahay, 1954; Freeman and Mossadeghi, 1970, 1971).

The Emergence of Variation. Although there have been a few anecdotal intimations that not every individual exhibits odorous urine following asparagus ingestion (Mitchell, 1989), it was not until 1956 and the publication of Allison and McWhirter's paper that the two discrete categories of "excretor" and "non-excretor" were first applied. This is understandable. Those who produce the odor assume, politely, that everyone does and those who do not produce it have no idea of the olfactory consequences. There is no reason as to why these two opposing factions should converse on this subject. A brief discourse with one's colleagues will confirm such differences and verify this state of affairs.

Studies have found that in the United Kingdom about half of the population produced the odor [46/115, 40%, 95% confidence interval (CI)¹ 31–49%, Allison and McWhirter, 1956; 346/800, 43%, 95% CI 40–47%, Mitchell et al., 1987], whereas the frequency was greater in Americans (15/19, 79%, 95% CI 61–97%, Sugarman and Neelon, 1985). This phenomenon was present in both male and female subjects, and limited pedigree information suggested that the odor-producing trait was characteristic of, and compatible with, being inherited in an autosomal-dominant fashion, with the heterozygous state giving rise to an affected phenotype (Allison and McWhirter, 1956; Mitchell et al., 1987). In McKusick's tome on Mendelian inheritance, a personal communication to the editor from W. K. Maas explains that a nonexcretor may become an excretor during pregnancy, the unborn child presumed to be an excretor (and also, I assume, the father) (McKusick, 1983).

Additionally, six subjects who ingested asparagus each month for a year were shown to give the same result (four odorous, two nonodorous) with each repeat challenge. Also, anecdotally, five subjects had reported long-term possession of this odorous trait, the time between first noticing this characteristic and laboratory confirmation ranging from 46 to 77 years—a lifetime (Mitchell et al., 1987).

Complications and Anosmia. However, the situation appears to be more complicated. Three studies have reverted to the former stance and claimed that all individuals excrete odorous urine following asparagus ingestion. One study on a French population is reported in a short letter and states that all 103 subjects examined excreted graveolent urine, perhaps indicating a genuine ethnic difference (Richer et al., 1989). In the two other studies, undertaken on Israeli and Chinese subjects, the authors suggest, but appear not to have proven conclusively, that the ability to excrete pungent substances in the urine after eating asparagus was a universal characteristic. Unknowingly, I may be instigating an injustice against these works and recommend that interested readers refer directly to these publications (Lison et al., 1980; Hoffenberg, 1983).

All investigations in the literature have been subjective, the urine being smelled by individuals (sometimes a panel of individuals) who had been previously shown to be able to positively smell and identify asparagus-related odorous urines. However, with subjective assessment, apprehension always exists concerning the results. The separation of the characteristic asparagus-related odor from the background odors of the urine, which may vary enormously between individuals, presents complications. Strict control samples from each subject are imperative. Indeed, even the odor associated with the phenomenon

¹ Abbreviation used is: CI, confidence interval.

apparently lends itself to different subjective description; “rotten or boiling cabbage” are the usual phrases used within Europe but “vegetable soup” has also been put forward in the Israeli study. Until an objective method of assessment of the odor can be achieved and strict criteria for sample handling and analysis presented (and accepted), the problems of individual opinion will remain (Mitchell, 1989). Objective urine analysis has been attempted. Of three volunteers who had eaten asparagus, one voided a urine that displayed four additional component peaks when examined by gas chromatography, whereas the other two subjects failed to produce profiles that differed from those obtained under control conditions (Gearhart et al., 1977). Such studies need to be extended.

What is evident is that there also appears to exist a specific hyposmia (hyposphresia) or anosmia, wherein certain individuals are unable to smell the odor even from the most fetid urines. The frequency of this condition within a population is high (277/307, 90%, 95% CI 87–94%, in an Israeli group, Lison et al., 1980; 74/98, 76%, 95% CI 67–84%, in a Chinese group, Hoffenberg, 1983), suggesting that a great number of people are unable to detect the asparagus-related odor. This predicament was shared equally between male and female subjects and did not appear to be age related. A later American study suggested that both phenomena coexist. These authors concluded that “some people are excretors while others are nonexcretors; some people are perceivers (able to smell the odor) while others are nonperceivers” (Sugarman and Neelon, 1985). Clearly, this complicated issue requires further detailed investigation.

Chemical Nature of the Odor and its Source. The mephitic nature of these asparagus-related odorous urines was (and still is) markedly reminiscent of certain pungent sulfur-containing compounds and, accordingly, the offensive substance was initially identified as methanethiol following its precipitation as silver and mercury mercaptides. The actual techniques used for this isolation, however, were lengthy and harsh and undoubtedly degraded other sulfur compounds, if present, into methanethiol (Nencki, 1891; Crouzel, 1893; Gautier, 1923; Allison and McWhirter, 1956). Nonetheless, a French text states that this disagreeable odor disappeared upon the addition of sublimate (mercuric chloride) to the urine (Ronchère, 1912). More recent studies have suggested that there are at least three major sulfur-containing components in the urine (Gearhart et al., 1977), and two of these have been identified as *S*-methylthioacrylate and its methanethiol addition product, *S*-methyl-3-(methylthio)thiopropionate (White, 1975). Smaller amounts of other sulfur compounds have also been detected in noisome urine, including dimethyl trisulfide, tetrahydrothiophene, and an unidentified substance containing two sulfur atoms (White, 1975).

However, the isolation of sulfur-containing compounds from the urine after asparagus ingestion is no indication that they themselves contribute to the odor, as they may be insufficiently volatile. Furthermore, the methods commonly used for handling urine, which involved continuous solvent extraction and heating to well above body temperature, may have induced chemical alterations within the urine such as to create an artifactual aroma for investigation. Although the urinary components derived from asparagus may play a role as intermediary precursors, and it is important to be aware of their identity, if they are nonvolatile and do not appear in the vapor phase then they cannot contribute to the odor.

Examination of the head-space volatiles above urine samples revealed the presence of six discrete compounds in individuals who were known to produce asparagus-related odor, whereas these were either absent or detectable in only minute amounts in urine from subjects who did not manifest the odor. These chemicals, confirmed by gas chromatography-mass spectrometry, were identified as meth-

anethiol, dimethyl sulfide, dimethyl disulfide, bis(methylthio)methane, dimethyl sulfoxide, and dimethyl sulfone. These compounds were given off from odorous urine in concentrations of up to several thousand times greater than normal. When assessed subjectively the most pungent compounds were methanethiol and dimethyl sulfide, which probably constituted most of the odor, with the sulfur-oxidized products, dimethyl sulfoxide and dimethyl sulfone, modifying the smell to impart a “sweet” aroma. These compound acted together in “reconstituted asparagus urine” to give the typical asparagus-related bouquet (Waring et al., 1987).

Such small molecules when presented to the mammalian metabolic system would be extensively degraded to carbon dioxide and inorganic sulfate, with only negligible amounts passing through the body unchanged, presumably being removed via the lungs with the expired air (Canellakis and Tarver, 1953; Distefano and Borgstedt, 1964; Mitchell and Waring, 1985–86). Furthermore, these volatile compounds would be liberated during the process of cooking before they could be ingested with the vegetable (Tressl et al., 1977a,b; Fenwick and Hanley, 1985). Consequently, it is probable that the sulfur compounds found in the odorous urine head-space are derived from a precursor molecule (or molecules) during passage through the human body or indirectly from metabolically generated intermediates that are unstable and subsequently decompose within the urine.

S-Methylmethionine sulfonium salt (α -aminodimethyl- γ -butyrotetin) was previously thought to be a candidate for this precursor (Challenger, 1959). However, it appears to have been excluded by observations that it undergoes thermal decomposition (on cooking) to liberate methanethiol and dimethyl sulfide, which are essential components of the flavor and smell of many cooked vegetables including asparagus and cabbage (Challenger and Hayward, 1954; Freytag and Ney, 1968; Ney and Freytag, 1972, 1982). The precursor of the urinary odor must be stable to the processes of food preparation and unique to asparagus, as similar vegetables such as cabbage and parsley do not display this phenomenon (White, 1975).

Of the many sulfur-containing compounds identified in asparagus only asparagusic acid (1,2-dithiolane-4-carboxylic acid) and its derivatives appear unique (Jansen, 1948; Schotte and Ström, 1956; Yanagawa et al., 1972, 1973; Tressl et al., 1977a,b). The five-membered 1,2-dithiolane ring structure is shared with the ubiquitous lipoic acid (thioctic acid, 1,2-dithiolane-3-valeric acid), and a few related compounds have been isolated from nonfood species such as the tropical mangrove plants (*Rhizophoraceae*) (Kato and Hashimoto, 1980). A marine annelid worm (*Lumbrineris heteropoda*) uses this heterocycle to form nereistoxin (4-*N,N*-dimethylamino-1,2-dithiolane), which is fatal to predatory insects (Sakai and Sato, 1972). Asparagusic acid is known to be active against parasitic nematodes and is considered a major factor in the survival of the plant preventing the entry of invading organisms into the tissues. The compound is present in a relatively high concentration in young growing plants, but this decreases rapidly as the shoots mature and become woody (Takasugi et al., 1975). This is in concordance with Arbuthnot’s astute observation (Arbuthnot, 1735).

Early investigations wherein dihydroasparagusic acid (dithiolisobutyric acid) was given orally to two individuals who subsequently produced no unpleasant urinary odor seemed to exclude the possibility that this compound was responsible (Jansen, 1948). However, since it was not appreciated during this period (not until 1956) that some individuals may not display the odor, it cannot be certain that these two individuals did not reside within the nonexcretor category, thereby invalidating the experiment. A recent study demonstrated that when asparagusic acid was given orally to two subjects known to possess the odor-producing characteristic, graveolent urine was pro-

duced and shown to contain the same volatiles in similar proportions to their asparagus-induced odorous urines. Another individual who did not possess the characteristic did not produce odorous urine after taking asparagusic acid. The authors concluded that asparagusic acid and its derivatives, probably bound in some form within the vegetable, may be the precursors of the urinary odor (Waring et al., 1987).

With regards to metabolism, asparagusic acid may be reduced within the mammalian system to its free thiol form, which could presumably be methylated and then be a substrate for thionase/ β -lyase activity liberating methanethiol (Binkley, 1950). Dimerization of methanethiol would yield dimethyl disulfide, while methylation and subsequent sulfur oxidation would give dimethyl sulfide, sulfoxide, and sulfone. Oxidation at the electron-rich sulfur centers (Foss and Tjomsland, 1958) may form a series of relatively unstable oxygenation products that could rearrange and cleave to provide similar precursor molecules. Such reactions are well documented. However, we cannot necessarily presuppose that this is a metabolic phenomenon with potentially pervasive pharmacological implications, as a simple lack of absorption of asparagusic acid from the gastrointestinal tract would produce a nonexcretor. In addition, many other compounds have been found within asparagus, including unusual cysteine derivatives (Kasai et al., 1981), and although these occur in other vegetables the concentration differences may be sufficient to engender this phenomenon. More detailed work must be undertaken in this area before this age-old curiosity can be finally evaluated and laid to rest.

References

- Allison AC and McWhirter KG (1956) Two unifactorial characters for which man is polymorphic. *Nature (Lond)* **178**:748–749.
- Arbuthnot J (1735) *An Essay Concerning the Nature of Aliments*, 3rd ed., pp 64, 261–262, J. Tonson, London.
- Binkley F (1950) Enzymatic cleavage of thioethers. *J Biol Chem* **186**:287–296.
- Canellakis ES and Tarver H (1953) The metabolism of methyl mercaptan in the intact animal. *Arch Biochem Biophys* **42**:446–455.
- Challenger F (1959) *Aspects of the Organic Chemistry of Sulphur*, pp 44–50, Butterworths, London.
- Challenger F and Hayward BJ (1954) The occurrence of a methylsulphonium derivative of methionine (α -aminodimethyl- γ -butyrolactone) in asparagus. *Chem Ind* 729–730.
- Crouzel ME (1893) De l'odeur spéciale communiquée à l'urine par l'ingestion des pointes ou turions d'asperges. *Gaz Hp Toulouse* **B**:193–194.
- Distefano V and Borgstedt HH (1964) Reduction of dimethylsulfoxide to dimethylsulfide in the cat. *Science (Wash DC)* **144**:1137–1138.
- Dressman JB, Berardi RR, Dermentzoglou LC, Russel TL, Schmaltz SP, Barnett JL and Jervelpaa KM (1990) Upper gastrointestinal (GI) pH in young healthy men and women. *Pharmacol Res* **7**:756–761.
- Eastwood MA and Nyhlin H (1995) Beeturia and colonic oxalic acid. *Q J Med* **88**:711–717.
- von Elbe JH, Maing IY and Amundson CH (1974) Color stability of betanin. *J Food Sci* **39**:334–337.
- Fenwick GR and Hanley AB (1985) The genus *Allium*, part 2. *CRC Crit Rev Food Sci Nutr* **22**:273–377.
- Forrai G, Bankovi G and Vágújfalvi D (1982) Beeturia: A genetic trait? *Acta Physiol Acad Sci Hung* **59**:265–282.
- Forrai G, Vágújfalvi D and Bolosky P (1968) Beeturia in childhood. *Acta Paed Acad Sci Hung* **9**:43–51.
- Forrai G, Vágújfalvi D, Lutter J, Benedik E and Soós E (1971) No simple association between betanin excretion and iron deficiency. *Folia Haematol (Liepz)* **117**:424–426.
- Foss O and Tjomsland O (1958) The crystal and molecular structure of 1,2-dithiolane-4-carboxylic acid. *Acta Chem Scand* **12**:1810–1818.
- Freeman GG and Mossadeghi N (1970) Effect of sulfate nutrition on flavor components of onion (*Allium cepa*). *J Sci Food Agric* **21**:610–615.
- Freeman GG and Mossadeghi N (1971) Influence of sulfate nutrition on the flavor components of garlic (*Allium sativum*) and wild onion (*Allium vineale*). *J Sci Food Agric* **22**:330–334.
- Freytag W and Ney KH (1968) Vorkommen und entstehung von dimethylsulfid im spargelaroma. *Z Lebensm Unters Forsch* **137**:293–295.
- Gautier C (1923) Rapidité d'élimination urinaire du méthylmercaptan après ingestion d'asperges. *Compt Rend Soc Biol* **89**:239.
- Gearhart HL, Pierce SK and Payne-Bois D (1977) Volatile organic components in human urine after ingestion of asparagus. *Clin Chem* **23**:1941.
- Harmer RA (1980) Occurrence, chemistry and application of betanin. *Food Chem* **5**:81–90.
- Hedrick UP (1919) *Sturtevant's Notes on Edible Plants: Report of the New York Agricultural Experiment Station for the Year 1919*, (27th Annual Report), vol 2, Pt II, pp 72–73, JB Lyon Company, Albany.
- Hoffenberg L (1983) A note on polymorphism: The ability to smell urinary metabolites of asparagus. *Diastema* **11**:37–38.
- Huang AS and von Elbe JH (1987) Effect of pH on the degradation and regeneration of betanin. *J Food Sci* **52**:1689–1693.
- Jansen EF (1948) The isolation and identification of 2,2'-dithiolisobutyric acid from asparagus. *J Biol Chem* **176**:657–664.
- Johnson S (1755) *A Dictionary of the English Language*, vol 1, W. Strahan, London.
- Kasai T, Hirakuri Y and Sakamura S (1981) Two cysteine derivatives in asparagus shoots. *Phytochem* **20**:2209–2211.
- Kato A and Hashimoto Y (1980) Biologically active 1,2-dithiolane derivatives from mangrove plants and related compounds, in *Natural Sulfur Compounds: Novel Biochemical and Structural Aspects*, (Cavallini D, Gaul GE and Zappia V eds) pp 361–374, Plenum Press, New York.
- Knight C (1859) *The English Cyclopaedia—Arts and Sciences*, vol 1, pp 609–610, Bradbury and Evans, London.
- Krantz C, Monier M and Wahlstrom B (1980) Absorption, excretion, metabolism and cardiovascular effects of beetroot extract in the rat. *Food Cosmet Toxicol* **18**:363–366.
- Kumar K and Sahay RK (1954) Effect of sulfur fertilization on the pungency of onion. *Curr Sci* **24**:368–371.
- Larousse P (1866) *Grand Dictionnaire Universel*, vol 1, p 757, Librairie Classique Larousse et Boyer, Paris.
- Lison M, Blondheim SH and Melmed RN (1980) A polymorphism of the ability to smell urinary metabolites of asparagus. *Br Med J* **282**:1676–1678.
- McKusick VA (1983) *Mendelian Inheritance in Man*, 6th ed., p 56, Johns Hopkins University Press, Baltimore.
- M'Intosh C (1855) *The Book of the Garden*, vol 2, pp 117–129, William Blackwood and Sons, Edinburgh.
- Mitchell SC (1989) Asparagus and malodorous urine. *Br J Clin Pharmacol* **27**:641–642.
- Mitchell SC (1996) Beeting a crimson retreat: Beeturia. *Lancet* **347**:474–475.
- Mitchell SC and Waring RH (1985–86) The early history of xenobiotic sulphoxidation. *Drug Metab Rev* **16**:255–284.
- Mitchell SC, Waring RH, Land D and Thorpe WV (1987) Odorous urine following asparagus ingestion in man. *Experientia* **43**:382–383.
- Nencki M (1891) Ueber das vorkommen von methylmercaptan im menschlichen harn nach spargelgenuss. *Arch Exp Path Pharmacol* **28**:206–209.
- Neubauer C and Vogel J (1863) *A Guide to the Qualitative and Quantitative Analysis of the Urine*, (translated by W. O. Markham), 4th ed., p 1, The New Sydenham Society, London.
- Ney KH and Freytag W (1972) Dimethylsulfid als wesentliche komponente des spargelaromas weitere untersuchungen der flüchtigen bestandteile des gekochten spargels. *Z Lebensm Unters Forsch* **149**:154–155.
- Ney KH and Freytag W (1982) The origin of dimethylsulphide, the essential component of asparagus flavour (*Asparagus officinalis* L.). *Gordian* **82**:72–77.
- Pearcy RM, Mitchell SC and Smith RL (1992) Beetroot and red urine. *Biochem Soc Trans* **20**:22S.
- Penrose LS (1957) Two new human genes. *Br Med J* **1**:282.
- Platenius H (1941) Factors affecting onion pungency. *J Agric Res* **35**:681–684.
- Rees GO (1836) On the analysis of the blood and urine in health and disease. With directions for the analysis of urinary calculi. *Lancet* **i**:969–971.
- Richer C, Decker N, Belin J, Imbs JL, Montastruc JL and Giudicelli JF (1989) Odorous urine in man after asparagus. *Br J Clin Pharmacol* **27**:640–641.
- Ronchèse A (1912) *Guide Pratique pour l'Analyse des Urines*, p 5, J. B. Baillière et Fils, Paris.
- Sakai M and Sato Y (1972) Metabolic conversion of the nereistoxin-related compounds into nereistoxin as a factor in their insecticidal action, in *Insecticides. Proceedings of the Second International IUPAC Congress on Pesticide Chemistry* (Tahiri AS ed) vol 1, pp 455–467, Gordon and Breach, New York.
- Saldanha PH (1962) On the genetics of betanin excretion. *J Hered* **53**:296–298.
- Saldanha PH, Magalhaes LE and Horta WA (1960) Race differences in the ability to excrete beetroot pigment (betanin). *Nature (Lond)* **187**:806–807.
- Schotte L and Ström H (1956) The preparation of 1,2-dithiolane-4-carboxylic acid. *Acta Chem Scand* **10**:687–688.
- Shannon S (1972) Changes in soluble solids, red pigment content and firmness of table beet cultivars with growing time and season. *J Am Soc Hort Sci* **107**:713–718.
- Sotos JG (1999) Beeturia and iron absorption. *Lancet* **354**:1032.
- Sugarman J and Neelon FA (1985) You're in for a treat: Asparagus. *North Carolina Med J* **46**:332–334.
- Takasugi M, Yachida Y, Anetai M, Masamune T and Kegasawa K (1975) Identification of asparagusic acid as a nematocide occurring naturally in the roots of asparagus. *Chem Lett* 43–44.
- Tressl R, Bahri D, Holzer M and Kossa T (1977a) Formation of flavor components in asparagus. 2. Formation of flavor components in cooked asparagus. *J Agric Food Chem* **25**:459–463.
- Tressl R, Holzer M and Apetz M (1977b) Formation of flavor components in asparagus. 1. Biosynthesis of sulfur-containing acids in asparagus. *J Agric Food Chem* **25**:455–459.
- Tunnessen WW, Smith C and Oski FA (1969) Beeturia, a sign of iron deficiency. *Am J Dis Child* **117**:424–426.
- Waring RH, Mitchell SC and Fenwick GR (1987) The chemical nature of the urinary odour produced by man after asparagus ingestion. *Xenobiotica* **17**:1363–1371.
- Watson WC, Luke RG and Inall JA (1963) Beeturia: Its incidence and a clue to its mechanism. *Br Med J* **ii**:971–973.
- Watts AR, Lennard MS, Mason SL, Tucker GT and Woods HF (1993) Beeturia and the biological fate of beetroot pigments. *Pharmacogenetics* **3**:302–311.
- White RH (1975) Occurrence of S-methyl thioesters in urines of humans after they have eaten asparagus. *Science (Wash DC)* **189**:810–811.
- Yanagawa H, Kato T, Kitahara Y, Takahashi N and Kato Y (1972) Asparagusic acid, dihydroasparagusic acid and S-acetyldihydroasparagusic acid, new plant growth inhibitors in etiolated young *Asparagus officinalis*. *Tetrahedron Lett* 2549–2552.
- Yanagawa H, Kato T, Sagami H and Kitahara Y (1973) A convenient procedure for the synthesis of asparagusic acids. *Synthesis* 607–608.
- Zindler GA and Colovos GC (1950) Anthocyaninuria and beet allergy. *Ann Allergy* **8**:603–617.