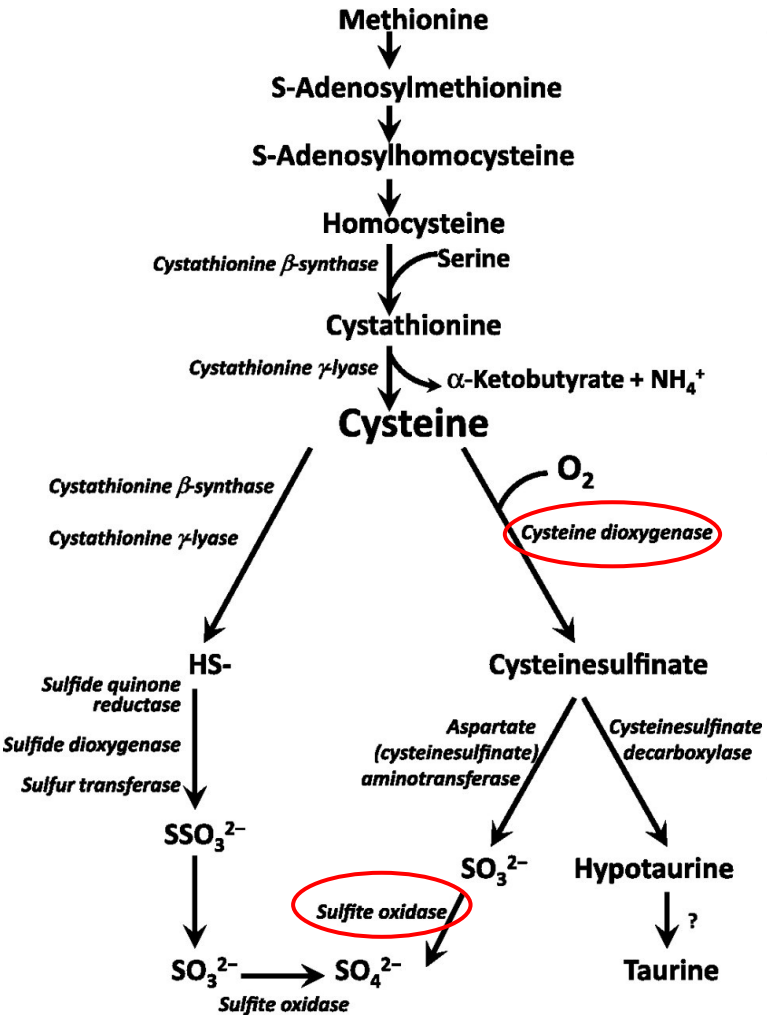
Sulphation, Detoxification and ASD

Sulphur is the sixth most abundant mineral in breast milk (colostrum has three times more than mature milk) and the third most abundant mineral determined by percentage of total body weight in an adult. Compounds containing sulphur are found in all body cells and are indispensable for life. The primary sulphur-containing compounds of interest in humans include (but not limited to): methionine, cysteine, homocysteine, S-adenosylmethionine (SAMe), taurine, glutathione (GSH), metallothionein, and inorganic sulphate. In addition, sulphur is needed for a number of chemical reactions involved in the metabolism of drugs, steroids, and xenobiotics.

The extracellular sulphate pool in humans is among the smallest of animal species and is readily depleted by consumption of a low protein diet or by drugs.

Sulphate is produced in the body by oxidation of the dietary proteins, methionine or cysteine (both sulphur containing amino acids), which probably provides ~ 80% of the sulphate required in man.



The first stage in genetating sulphate from protein, involves the enzyme **cysteine dioxygenase (CDO)**; cysteinesulphinate is formed and undergoes fission to provide sulphite (SO_3^{2-}) ions which are then further oxidised to sulphate (SO_4^{2-}) ions by the enzyme **sulphite oxidase (SOX)**. Obviously, if CDO or SOX have reduced activity, the provision of sulphate will also be decreased.

The CDO protein is found in the nervous system, particularly in the cerebellum and the Purkinje neurons; these are known to be abnormal in patients with ASD. CDO activity is variable in human populations and there are sub-sets with lower activity (~ 30% of the population) or null activity (~ 3% of the population). The null sub-type is heavily over represented in chronic disease states with an auto-immune component such as rheumatoid arthritis; in general auto-immune problems are more common in the family background of autistic children.

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Changing the way we think about treating autism.

We now know that inflammatory cytokines (immune mediators) such as TNF-α, which are at relatively high levels in many autistic children and in auto-immune diseases, can reduce expression of CDO and SOX and therefore reduce the supply of sulphate for conjugation with drugs and biological compounds. Expression of both CDO and SOX has been inhibited experimentally at the minute levels of 0.1 ng/ml TNF-α, concentrations which could easily occur in the body during an infection.

The importance of sulphate in the body

⇒ Sulphate is essential for many biological processes.

⇒ Sulphate is needed for formation of proteins in joints; low levels of sulfate are found in plasma and synovial fluid from patients with rheumatoid arthritis.

⇒ Sulphate is needed to start the cascade of digestive enzymes released from the pancreas. Without proteases, lipases and amylases, food is not digested efficiently.

⇒ Sulphate is essential in forming the mucin proteins which line the gut walls. These have 2 main functions- they stop the gut contents from 'sticking' and they block transport of toxins from the gut to the bloodstream. Low plasma sulphate has been found in patients with irritable bowel disease.

⇒ Sulphate is necessary for formation of brain tissue. Before birth, the functional units of the brain, 'neurons', are laid down on a network of sulphated carbohydrate chains.

⇒ Reduced sulphation can lead to faulty neuronal connections and later dysfunction.

⇒ Sulphation is a major pathway in detoxifying drugs and environmental contaminants.

⇒ Sulphate is not easily absorbed across the gut wall. Recent research has shown that it can be absorbed across the skin. It is also formed in the body by oxidation of the amino acids **cysteine** and **methionine**. However, this pathway is often sub-optimal and many people benefit from sulphate supplementation.

ASD individuals generally have low sulphate levels, typically about 10-15% that of age matched controls tested.

It is interesting that autistic children who are challenged with a paediatric dose of paracetamol are less able to form its sulphated derivative than controls of the same age. This may explain why some children with autism are reported to respond badly to paracetamol and to other drugs; obviously toxic effects are more likely if clearance is impaired by reduced metabolism to water-soluble derivatives that can be excreted in the urine. Sulphate is also required for the phenol-sulphotransferase enzyme to help detoxify phenols and amines from the body. Many ASD children have problems processing phenolic compounds [see separate article on Phenol Sulphotransferase (PST) Pathway].

Sulphation and the Brain

Sulphation is a major inactivation pathway for neurotransmitters, such as dopamine. Usually, when neurotransmitters are released in the central nervous system, they act at receptor sites and are then inactivated by sulphation, other enzymes or are carried by transporter proteins back into the initiating neuron. Poor sulphation will lead to a neurotransmitter imbalance and raised serum and CSF levels of dopamine. Elevated urinary levels of dopamine metabolites have been reported in ASD children. In rats, high dopamine concentrations are associated with stereotyped and repetitive behaviour, not unlike that seen in ASD. Other neurotransmitters, such as noradrenalin, also control behaviour and affect mood, so that changes in their levels can have obvious effects as well. Sulphation also affects the synthesis of brain tissue. Sulphated polysaccharides and glycosaminoglycans are critically important in the development of the foetal and neonatal brains. Infections in pregnancy, have the potential to reduce sulphate levels and affect brain development in the foetus. However, this is just speculation at this time.

Sulphation in the Gastrointestinal Tract

Sulphation also affects the function of proteins. Mucin proteins, which form the mucus layer lining the gastrointestinal tract, are sulphated glyco-proteins which control adhesion and absorption of nutrients. If the sulphate residues are lost, this leads to a protein which has a more globular structure and provides less protection for the tissues from the intestinal contents as there are 'gaps' between the proteins (intestinal permeability). Reduced sulphation ability has been linked with gut dysfunction in irritable bowel disease and lower levels of sulphation in ASD children probably explains why gut permeability is increased in ASD. Sulphation of mucins increases resistance to colonisation by pathogenic microorganisms.

The gastrointestinal hormones gastrin and cholecystokinin, which are involved in the digestive process are both activated by sulphation. In the activation pathway, gastrin is sulphated and, with hydrochloric acid from the stomach, causes release of cholecystokinin, which also requires sulphation. This acts with the hormone secretin on pancreatic tissue to induce the secretion of a range of proteolytic enzymes. Without adequate sulphation to trigger the release of pancreatic enzymes, the complete digestion of proteins to their amino acid building blocks cannot take place adequately and be absorbed. So that peptides (larger protein fragments), are left behind in the gastrointestinal tract and undergo putrefaction by intestinal bacteria. At the same time, the reduced levels of pancreatic enzymes alter the digestibility of starch-based foods and allow increased fermentation by pathogenic bacteria while the decreased ability to digest fats promotes formation of foul-smelling fatty stools which contain undigested fats.

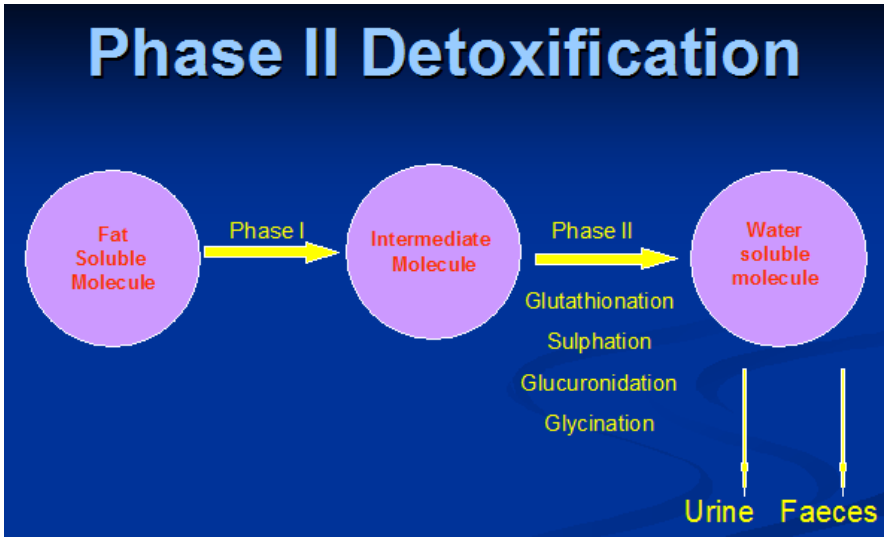
Some partially digested proteins which cross the gut wall, particularly those derived from casein and gluten, have been found to be neuroactive with effects on the brain where they act on opioid receptors, affecting behaviour, mood and responses to physical stimuli such as pain.

Sulphotransferase Enzymes

Not only is there an impaired level of sulphate in ASD, there is also often a corresponding lack of sulphotransferase activity. These are the enzymes which carry out sulphation of a wide range of substrates. Sulphotransferase activity is known to be altered in some dysfunctional states, for example in patients with migraine. The increased blood levels of amines/phenols with neurotransmitter activity are thought to 'trigger' migraine headaches in those who are already susceptible. Many children with autism, particularly those with gastrointestinal problems, have a family background of migraine, and in a small pilot study, Dr Waring found that some children with autism also had reduced sulphotransferase activity. It would be expected that these children would react badly to foods containing phenols, catecholamines or flavonoids and this response may underlie the benefits of the Feingold (low-phenol) diet and provide an explanation for the dietary intolerances which can be found in autism. (See separate article on the Phenol Sulphotransferase (PST) Pathway)

It is interesting that the sulphated cholecystokinin hormone has receptors in the brain as well as the gut and is required for release of the peptide hormone **oxytocin**. Children with autism have reportedly lower levels of oxytocin and as this hormone is responsible for social behaviour, any deficiency may contribute to the social deficits in ASD. Read more on the hormone oxytocin in the article Oxytocin and Cholesterol.

Sulphation and Detoxification



Sulphation is one of a number of liver detoxification pathways, specifically phase II detoxification. The sulphation system is important in detoxifying several drugs, food additives and especially toxins from intestinal bacteria and the environment. Sulphation also detoxifies some normal body chemicals helping to eliminate steroid hormones (e.g. oestrogen), thyroid hormones and neurotransmitters. This process is catalysed by the superfamily of enzymes called – sulfortransferases (SULTs).

Typical toxins neutralised include:

- ✓ Steroid hormones (oestrogen, progesterone)
- ✓ Artificial food colourings
- ✓ Aniline (found in dyes, pharmaceuticals, burning of plastics and tobacco)
- ✓ Coumarin, acetaminophen (paracetamol), methyl-dopa (for Parkinson's disease).
- ✓ Terpenes
- ✓ Amines (heterocyclic amines)
- ✓ Hydroxylamines (nylon, some soaps and tanning agents)
- ✓ Phenols
- ✓ Catecholamine's

Regardless of which process sulphation is involved to transform and excrete toxins, sulfation will not take place without the rate limiting compound – ***sulphate***.

Sulphate Transport and *NaSi-1* Gene Mutation

ASD individuals have lower serum sulphate levels compared to normal controls. As sulphate transporter proteins control plasma sulphate levels, research is being undertaken to see if the transporter proteins are defective in ASD individuals. ASD individuals excrete large amounts of sulphate in the urine, compared to non-ASD individuals.

Sulphate transporter genes, such as the NaSi-1 gene, encode a sulphate transporter protein that is ***expressed in the proximal tubule of the kidney.*** When 20 ASD individuals were compared to controls, ***two mutations were found in the gene that changes the function of the NaSi-1 protein.*** One mutation caused complete loss of function of the protein, the other caused a partial loss of function.

In a mouse model where the NaSi-1 gene was inactivated, the mice excreted large amounts of sulphate in their urine and exhibited some behavioral abnormalities and gastrointestinal disturbances, such as soft stools, which parallel symptoms of ASD individuals. Since ASD individuals have 'leaky gut', sulphate loss also occurs through the intestine and it is believed that autistic individuals are losing sulphate through both the kidneys and the intestine, as the NaSi -1 gene is expressed in both organs. ASD individuals usually have a five-fold lower level of serum sulphate compared to control individuals.

Food Sources of Sulphate

Though the absorption of inorganic sulphate (i.e. potassium sulphate and sodium sulphate) in the intestinal tract is inefficient, it still accounts for one-third of the sulphate pool in the human body. Approximately 19% of the body's total sulphate pool comes from the direct ingestion of inorganic sulphate from foods. Much of the sulphate found in foods is added during processing.

The consumption of high protein foods containing sulphur proteins (methionine and cysteine), along with the consumption of inorganic sulphated compounds in both food and beverages, is usually sufficient to meet the body's requirement for sulphate. However, in humans, the serum sulphate level varies dramatically over 24 hours, and is decreased in individuals who are fasting or ingesting high levels of substances that are metabolized by sulphation (such as acetaminophen).

Food (mg/g)	Sulfate Content
Almonds	0.9
Bread (brown)	1.5
Bread (white)	1.3
Broccoli	0.9
Brussel sprouts	0.9
Cabbage	0.8
Cauliflower	0.5
Dates	1.1
Dried apples	4.9
Dried apricots	3.0
Pasta, durum wheat	0.3
Peanuts	0.7
Prunes	1.0
Raisins	1.3
Sunflower seeds	0.6

Table: Sulfate Content of Foods

Beverage (mg/L)	Sulfate Content
Beer	260
Cider	270
Coconut milk	500
Cola	80
Juice, apple	70
Juice, grape	200
Juice, tomato	250
Milk, cow	100
Milk, human	5
Wine, red	380
Wine, white	300

Table: Sulfate Content of Beverages

Increasing Sulphate in the Body

Epsom salt, or magnesium sulphate, has been used by parents for many years to help increase sulphate levels in their ASD children. The Epsom salt is used in the bathwater, releasing the magnesium and sulphate, which is then absorbed through the skin. Parents have found this to be an effective way to boost sulphate levels. If using Epsom salt in a bath is not an option, then a cream made with Epsom salt may be used instead.

Warning!

Only use pharmaceutical grade Epsom salt from a trusted supplier and NOT agricultural Epsom salt, which contains contaminants such as heavy metals.

I have also used the tissue salt, sodium sulphate orally, however it must be kept in mind that if gastrointestinal function is compromised, there may be less than optimal absorption of sulphate. At the local level in the gut, sodium sulphate may be beneficial in increasing sulphate, thereby helping to overcome the sulphate deficit of the mucus lining the gut. Oral sulfate such as glucosamine sulfate may also be effective to some degree in some individuals.

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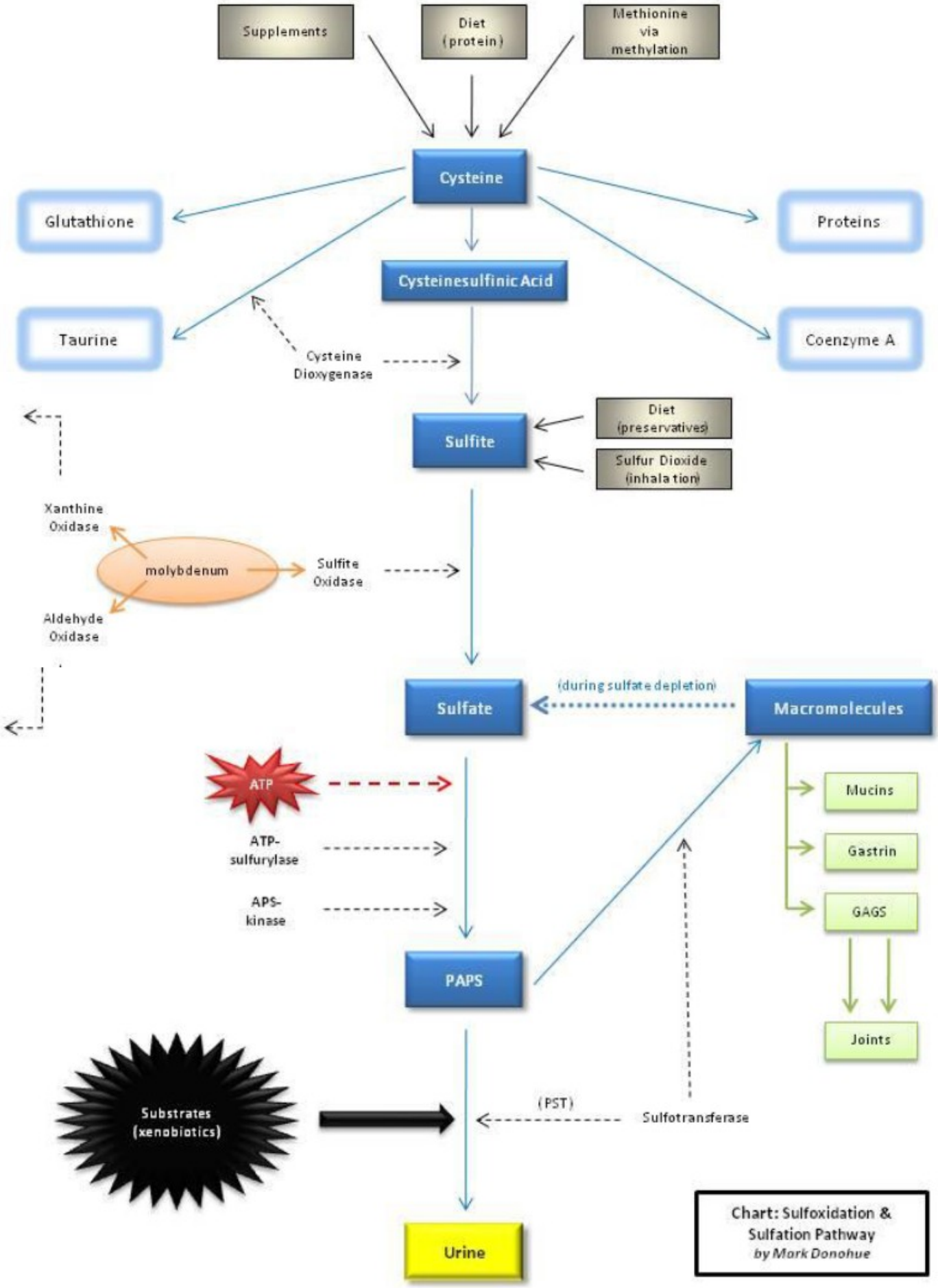
Sulfoxidation and Sulphation Flow Chart



Source: The Detoxification System. Part III: Sulfoxidation and Sulfation by Mark J Donohue