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The Sunderland Protocol: A logical sequencing of biomedical interventions for the treatment of autism and related disorders.

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We have previously presented and discussed the [theoretical basis](#) underlying many biomedical interventions applied in the treatment of autism (Shattock *et al*, 1990, 1991). These are based largely upon the pioneering work of [Dohan](#) (1966; 1988), [Panksepp](#) (1979; 1987) and [Reichelt](#) (1981) closely followed by Cade (1990). There is some evidence for the effectiveness of some of these interventions but for others the evidence is still anecdotal and untested (and, in some cases, probably un-testable). In most cases, the interventions have

been introduced to patients in a haphazard or random sequence as the parent (or carer) has become aware of a particular therapy through word of mouth, magazine or newspaper article or discussion on the Internet.

In some cases, professionals have suggested a huge range of supplements be initiated and to these more and more are added as time goes by. Parents and carers are normally neither trained in these matters nor in the technicalities of chemical nomenclature. Our worst instant was a girl who was taking approximately 70 "nutritional" supplements; further analysis actually revealed her multi-vitamin tablets contained Vitamin B6 to which she was also being given both [vitamin B6](#) separately and Pyridoxine tablets (which are B6). It is perfectly understandable that parents should want to try everything to help their children but it is also desirable to know which of these elements help a particular child and which do not. It is possible of course, that one or more supplements may make a particular child worse. It is not possible to generalise in this area because all children with autism are different from each other and from their asymptomatic peers. In order to avoid over-medication we suggest the following protocol, which should permit the assessment of each intervention for each individual child. Each element should be treated with the same respect as any other biomedical intervention be it medication which is specifically prescribed or part of a continuing therapy. These interventions do not, in the main, utilise powerful drugs yet we would recommend that they be treated with the same respect and used in a time limited, experimental fashion with all due precautions taken.

If they are found not to be effective, they should, for the time being at least, be abandoned. Failed therapies can always be revisited later on when, perhaps, different developmental issues have arisen and the metabolic or physiological status may have altered as a result of other interventions or age. Likewise, we seek a therapeutic advantage by using such interventions; if the negative effects are too significant it may be difficult to justify continuation. It is difficult to justify a very intensive or restrictive therapy unless substantial benefits are obvious. These interventions must also be seen in the context of an overall treatment plan involving elements of education and social or behavioural training. Such interventions are not a substitute for such educational and psychological strategies but rather they are designed to help make the participant more receptive to the educative procedures.

Figure 1: The Sunderland Protocol (Shattock & Whiteley, 2000).

Stage	Action	Comments
1	Casein-free diet	For an initial period of 3-4 weeks
2	Gluten-free diet	For an initial period of 3-6 months
3	Removal of other offending foods	Identification via food diaries or allergy-testing (IgE, IgG); possible foods include: corn, soya, tomatoes, aubergines, beef.
4	Testing for deficiencies & use of balanced supplementation as appropriate	Vitamins, minerals, amino-acid supplementation possibly including: zinc , calcium , magnesium , molybdenum , vitamins A, C, B1, B3, B6, B12 (supplementation needs to be balanced).
5	Testing & removal of parasitic organisms	Yeasts, worms, protozoa (particularly if the child is prone to pica behaviour). Supplementation with probiotics and beneficial yeasts .
6	Sulphation issues	Use of Epsom salts (external), MSM
7	Promote enzyme activity	Betaine HCL (TMG)
8	Supplementing fatty acids	Fish oil (Cod liver oil), EPO , Flax seed oil
9	Supplementing L-Glutamine	Aid GI function
10	Enzyme supplementation	Bromelain , other commercial compounds
11	5-Hydroxytryptophan (5-HTP)	Optional
12	Pigment-free diet	Optional
13	Salicylate-free diet	Optional
14	Megadose B6 & Mg	Optional
15	Dimethylglycine (DMG)	Optional
16	Secretin	Optional

We advocate introducing one intervention at a time and assessing the therapeutic advantage for each individual child. Consideration should then be given to its continuation or discontinuation. Rather like ancient Gaul, our protocol is divided into three parts. Using a martial metaphor - we are fighting a battle and we should be seeking to establish peace. There are three stages in the establishment of a viable and permanent peace.

- A. Ceasefire;**
- B. Assessment of problems and search for common ground;**
- C. Reconstruction processes.**

We envisage the resolution of these problems in precisely the same way.

Stage A

The "Ceasefire" experience and theoretical considerations based upon the *opioid excess theory of autism* suggest that the first stage in the "treatment" of autism must be the removal of the sources of these peptides. We are not suggesting that this is anything like the whole story but it would seem to be an appropriate first step. Since the source of the bullets will almost always include casein and gluten these should be removed from the diet. It may be that parents, carers, professionals or subjects themselves have had some form of analysis performed to detect these substances. The best-known tests are the urinary peptide profiles but there are other methods. Although these tests can provide much useful information when used in conjunction with clinical data, it may be worth considering excluding these products from the diet in any case. We have come across subjects with autism who do not show abnormal levels of urinary peptides (or *trans*-indolyl-3-acryloylglycine, IAG) - in fact their urinary peptide profiles appear to be, to all intents normal, yet the subject exhibits florid symptoms of autism. We have come across subjects like this who still respond to the removal of casein and gluten from the diet. It could be that the subjects are breaking down the peptides into abnormal components that are not detected in our systems. It could be that although the urinary levels are normal, the quantities crossing the blood brain barrier and reaching the [CNS](#) are high. Perhaps this is a consequence of abnormal permeability of the barrier caused by infection natural or induced. We have also come across cases, fortunately very few, where the problems appear to have been triggered by [hypoxia](#) or anoxia at or around birth. In these cases, there may have been damage to the brain including the developing cerebellum. Those areas still functioning may, as a consequence, be affected by even the normal levels of peptides, which may be derived from food via the blood. Whatever the mechanisms involved or the results of biomedical tests, we would suggest that consideration should be given, first of all, to the removal of dietary milk of all sorts.

1. Casein Removal

The effects of removing dairy produce are usually seen quite rapidly. Depending upon the age of the participant, our best guess suggests that it could be 2-3 days (in young children) or 10-14 days in adults when effects, if they are going to occur, are normally seen. We suggest that a three-week trial is appropriate in the first instance. Lucarelli (1995) felt that approximately one two-thirds of participants in their trial showed benefits from this intervention taken alone and, although we have no firm data to support this view, our experience would suggest that this is probably correct. Of course, there could be a period where side effects are seen but by the end of the third week the situation should be clear.

Any withdrawal effects are of comparatively short duration but can be quite severe especially in young or small children. This is another reason why we prefer to separate the removal of the two elements, gluten and casein, during this protocol.

We have also observed that many higher functioning children have voluntarily removed dairy produce from their diet prior to any suggestion of casein withdrawal. Since the relevant peaks found in urinary profiles disappear quite rapidly following casein removal, it is highly likely that subjects will be in a position to detect the difference that abstinence from dairy produce makes. Many people with Asperger Syndrome, for example, complain of being confused or having difficulty in concentrating when drinking milk. Many such people shun milk but will rationalise this avoidance in terms of "*hating milk*" or finding it "*slimy*". On the other hand, some children are clearly addicted to milk and will drink what are generally considered to be very large quantities. A three-year-old child, for example, who drinks 5 pints of milk a day, is by no means untypical of this group. Cultures based upon Western European principles are brought up with the idea that milk is a wonderful and indispensable element of diet. Health visitors, nurses, dietitians and orthodox medical practitioners are not easily convinced that [bovine](#) milk is not designed for human beings and that its consumption is, in some cases, inappropriate and undesirable. It has been recorded that there is an increased incidence of autism amongst the immigrant population in Sweden (Gillberg, 1996) when compared to the indigenous population. There are a number of possible theoretical explanations but one must involve the utilisation of diets for which subjects are not genetically equipped in terms of enzyme complement or metabolic processing ability. The absence of lactase enzymes in some subjects of African origins and the disappearance of enzymes, which break

down casein from subjects of Chinese origin in their early teens, are examples of such phenomena.

We have been very impressed by the number of parents, who have taken the initiative, to remove dairy produce from the diet. Clearly, these parents have intuitively realised that something is wrong with their child's reaction to milk. Projectile vomiting of (cow) milk; eczema, particularly behind the knees and in the crook of the elbow; strange white bumps under the skin; an early history of ear discharges and infections possibly requiring the fitting of grommets (tubes); very early onset of constipation and/or diarrhoea and respiratory disorders resembling asthma may all be taken as signs of a problem with casein.

A "review" of the situation after three weeks of casein removal is appropriate. Clearly, in those situations where improvements are apparent this intervention may be continued. Where improvements are not seen it is difficult to justify the continued removal; but most parents feel that the difficulties inherent in this form of intervention are not so severe that they cannot continue with it. This must be a matter of personal choice. Since the removal of dairy produce is comparatively simple, it serves also to provide parents with the opportunity to prepare themselves for the rigours of gluten removal. Of course, there are many people who prefer to remove both gluten and casein simultaneously and that is fine but we would still strongly advocate separating the elements particularly where children under 4 years of age are involved because of the potential severity of the withdrawal effects. However, we would still suggest a test of the role of milk be performed soon after the implementation of such a diet (casein challenge).

2. Gluten Removal

As previously stated, gluten removal requires the removal of the proteins ([prolamins](#)) from a number of cereals; especially wheat, barley, rye and oats ([oats](#) remains under investigation due to slight structural differences in proteins). Given the modern Western diet and its dependence upon cereals this is not an easy task; but most do seem to accomplish it without undue difficulty. The peaks in the urinary profiles which we (correctly or incorrectly) ascribe to gluten persist for much longer than the casomorphins. In our trial (Whiteley *et al*, 1999) there had only been a 26% reduction in urinary levels of specific compounds (thought to be related to gluten) after a 5-month period. This is possibly explicable in terms of such compounds being stored in body tissues (assuming full compliance with the diet). If the body is incapable of breaking these peptides down which it

has absorbed it must do something with those it produces during digestion. It cannot break them down and the mechanisms for dumping them in the urine are (we speculate) swamped by the sheer quantity of the materials. As in other instances, the body has little option but to store them probably in fat tissues. When dietary sources are removed these stores are depleted as rapidly as possible but as the child/person becomes older, the quantities stored will, in absolute terms, be larger and the time required for their removal will be correspondingly longer.

For this reason, it is very rare for gluten to have been spotted as causing offence in the way that milk frequently has either by the parent or by the person primarily affected. There is almost always a degree of craving for gluten products and we are aware of only few with autism spectrum disorders who have refused gluten-containing products in the same way that milk and dairy produce is avoided. It is strange that we are so hooked onto what is essentially the seed from an obscure type of grass. It could be that this production of opioid substances is an element in its acceptance as a staple diet throughout so much of the world.

Although it can and does happen, gluten removal does not normally result in immediate, dramatic effects. Except in very young children, where results are seen more rapidly, we normally expect to see changes in 3-4 weeks so we suggest that people consider removal for a period of three months. After this time it is appropriate to review progress. We are aware of a number of cases where dramatic improvements have occurred 7-9 months after initiating the diet and in one case (Reichelt – Personal communication) these improvements became apparent after two years of rigid dietary intervention (obviously we cannot discount other effects in such a long time frame). As previously stated, the disappearance of the compounds related to gluten appears to be more gradual than with the casein-derived peptides. Therefore, the withdrawal effects tend to be somewhat milder in severity but rather more prolonged particularly in adults.

The Norwegian studies have been going on for the longest period of time (Knivsberg *et al*, 1995). They have always proposed removal of gluten as well as casein. Interestingly, they observed a phenomenon that we had also noted in participants who used this approach where the casein and gluten are removed simultaneously. There is an initial rapid withdrawal period and improvement. This tends to be followed by a period where not much happens at all and parents often begin to wonder if their initial improvement observations were a result of self-delusion. After a further period of time, other improvements appear, sometimes

after a second set of withdrawal symptoms. We believe that this biphasic pattern is due to the sequential effects of casein and then gluten removal from the diet.

Stage B "Assessment of Problems"

We believe that these peptides and related compounds are the agents (bullets) directly responsible for the causation of the symptoms in a proportion of cases, but there may be other compounds, which can also have a serious impact upon the total picture. In some cases, gluten and casein appear to be the sole elements but in other cases it is clear that other factors are involved. The relative involvement of these compounds (from gluten and casein) is very large and will subsequently obscure other potentially important factors. It is only after the main sources of the bullets, gluten and casein, are removed from the diet that the smoke will clear sufficiently to allow us to detect other potential causative elements which may be of dietary origin.

Keeping a Food Diary

It is a good idea to keep a food diary in any case before, during (and after?) any intervention. This is important because after the gluten and casein have been removed from the diet, only now are we able to determine the potential role of other dietary factors. It is note-worthy that new members to the Spanish autistic society, APNA (*Asociacion de Padres de Ninos Autistas*) has, for some years, provided its members with just such a diary in which they can record daily food intake as well as behavioural and performance estimates. Many parents have used these diaries and noted that the consumption of a particular food is often associated with deterioration in behaviour, sleep patterns or performance. Without accurate record keeping it is unlikely that these culprits would have been identified. Responses to these other foods tend to be idiosyncratic or personal but some foods are commonly found to cause particular problems to groups of people. Eggs, tomatoes, avocados, aubergines, red peppers, soya, and corn (maize) are common agents whereas beef, pork, rice and potato are very occasionally implicated. If a particular food is suspected it should be removed from the diet for a trial period of, perhaps, two weeks and the effects noted. We concede that this is still a very hit and miss procedure but is all that is available to us at this time. There are, however, often clues to be picked up by observing the subject. It is well known that children with autism are "faddy" eaters and will often have only a restricted range of foods that they will accept. If a child has a

problem with a food he or she will tend to either avoid it assiduously or become more or less addicted to it. The situation mirrors that seen in adults with a history of abusing alcohol. They either continue to abuse it or they avoid it like the plague. When the main culprits are removed from the diet (presumably gluten and casein) the parent or carer must be alert to the possibility of a switch to other foods with potentially harmful effects. On a number of occasions, we have known children who detest milk yet have suddenly developed a craving for it once the gluten has been removed from the diet.

Seroussi (2000) has described how corn was unmasked as a problem food for her child only after the very strict removal of the gluten and casein from the diet. Usually, when the offending foods are removed, the child's diet will expand to take in things they had previously ignored. If the diet remains restricted, this can be a clue (but not a certainty) that an offending food is still forming a part of the diet. The same result is seen when a child is inadvertently reintroduced to one of these offending foods. Perhaps, for example, the content of a particular brand of baked beans is changed without notice, by the introduction of gluten. The child's behaviour may change but also his tendency towards a restricted diet may well reappear. We would stress, yet again, that removal of staple elements of the diet are likely to result in reduced intake of vitamins and minerals and other essential nutrients. A good, balanced, supplement system should be instituted. This is best done with the active input of a knowledgeable professional who is sympathetic to and understanding of these approaches. Without appropriate levels of these essential nutrient elements the normal metabolic processes of digestion and absorption will be severely impaired in any case.

3. Testing

It is at this time that further testing may be appropriate. There is no doubt that many of our children have abnormal levels of minerals, vitamins and other materials in their systems. However, the true position is often obscured by the presence of the smokescreen resulting from gluten and casein consumption. It is only now, after the removal of these offending dietary protein sources, that meaningful testing can be performed. On a number of occasions, parents have sent us the results of vitamin and mineral status determinations (on hair or blood) taken before and after gluten and casein removal. The 'before' results had been very abnormal indeed; the results following exclusion of the offending proteins conversely show normal (or near-normal) patterns. We have interpreted this as an indication that intestinal function has been partially restored by the

removal of these elements; that dietary vitamins and minerals are now being absorbed as they should but there may, of course, be other mechanisms involved.

We always suggest that anybody initiating a restrictive diet should take care to ensure an adequate intake of minerals and vitamins and for this reason we advocate the involvement of a qualified dietitian or equivalent. We suggest a balanced multi-vitamin and multi-mineral supplement just to ensure adequate levels. There are certain patterns, which are common. Some children are very low on calcium and magnesium and the remedy is obvious. Others are high in toxic substances such as aluminium. The addition of supplementary zinc is said to remediate this situation. Zinc supplementation is, in any case, probably desirable since so many normal metabolic reactions require it. There are no rigorous scientific studies that demonstrate effectiveness in ameliorating the symptoms of autism but there are numerous anecdotal reports that support its effectiveness. Waring (2000) has reported that the addition of trace amounts of Molybdenum has dramatic effects in correcting abnormalities in sulphate and sulphite levels (other problems with [low iron / ferretin levels](#) may also need addressing under medical supervision).

We have also observed that classical allergies will frequently "disappear" when gluten and casein are removed from the diet. At the same time, certain underlying and genuine allergies are revealed. For this reason, we believe that the most appropriate time for testing for allergies is after the removal of the main offending foods. If allergies are suspected such interventions are worthy of consideration. We have come across numerous individuals who were tested, using VEGA (skin conductance) type tests, before initiating any interventions. These tests usually result in 30 or 40 different products showing up as positive but subsequent to gluten and casein removal these numbers have been dramatically reduced. In some cases, children have been deprived of foods where the "allergies" which were detected before the other interventions are of no clinical relevance.

Hospital-based laboratories tend to test blood for antibody levels ([IgE](#) in particular) to indicate "allergy" towards particular foodstuffs. In the UK at least, the results of these tests are not necessarily communicated in full to parents. Traditionally they are rated at somewhere between 0 and 4 (4 being the highest). Levels of 0 and 1 are pretty common and are usually ignored whereas higher numbers should be taken more seriously. It must be understood that these levels are no more than a snapshot at a particular time and it may be appropriate to consider removal of offending food on a trial basis at some time in the future.

We believe that the relevance of these, genuine, allergies has been grossly underestimated in the past and that research should be directed towards these areas. Avoidance of the allergen is the obvious therapy but there may be other alternatives. [Enzyme Potentiated Desensitisation](#) (EPD) techniques are employed by a limited number of practitioners who feel that it is effective. It has not been subjected to rigorous evaluation and practitioners in the US have attracted censure for utilising it. We do feel that there are considerable potential benefits and, in any case, the claims of practitioners are very modest.

4. Yeasts

For many years a close association between autism spectrum disorders and abnormal gut bacteria or the presence of parasitic yeasts has been noticed and reported; yet the nature of this relationship remains uncertain. The fact that two conditions co-exist does not necessarily imply that the one must necessarily cause the other. The cause and the effect could be the other way around but there could also be an underlying mechanism, which causes both these phenomena. For some years, we took the view that yeasts, such as [Candida](#), became established as a result of a depressed immune system (which may itself, be consequent upon the actions of the food derived opioid peptides and related compounds). This colonisation by such yeasts may be enhanced by the inappropriate use of antibiotics early in the development of the child. For example, it is well known that many children with autism spectrum disorders suffer from ear infections (usually referred to as [otitis media](#)). It is possible that these may be at least initially consequent upon problems caused by milk yet they are treated by antibiotics. These powerful antibiotics are used routinely and with great regularity in children. Sure enough they kill bacteria even though their role in the causation of the ear problems may be minimal. Unfortunately, they will also eradicate other bacteria in the intestines; this will permit the right conditions for the development of yeasts and other organisms much more akin to fungi. If yeasts are present they could increase the permeability of the intestinal wall especially where sulphate levels are low. Shaw has made a particular study of yeast related phenomena and has postulated a number of mechanisms by which products of yeast growth could have more direct influence and we must refer the interested reader to his work (Shaw 1998) for further information. Recently (Shaw 2000), has also suggested that yeasts may be responsible for the production of compounds, which may form complexes with the enzymes (such as Di-Peptyl Peptidase IV), which would, under normal circumstances, break down

the food derived opioid peptides. There is certainly logicity and reasonableness about this idea but strong supportive experimental evidence is still awaited.

Whether these mechanisms may or may not pertain, it is clear that many parents believe that they see benefits from treating these yeast infections. Unfortunately there are no published data to support their observations but the numbers reporting behavioural improvements from the use of the anti-fungal product [Nystatin](#) suggest that these reports should be taken seriously. It has been suggested that the Nystatin may be acting by some other mechanism, for example by making the intestinal wall less permeable or other more direct actions on the CNS.

Yeasts thrive on sugar ([sucrose](#) and others) so many parents have attempted to control yeast infections by limiting or removing dietary sugars completely. Additionally, some parents have gone further than this and removed and foodstuff containing yeasts at all. Other parents have attempted to control yeast infections by supplementing the diet with tablets or medications containing high levels of the beneficial bacteria, which are normally found in the gut. *Acidophilus* or *bifidi* containing products are used for this purpose along with natural "yeasticides" such as grape-seed oil, garlic and supplements such as [saccharomyces boulardii](#).

There are a number of tests for yeast infections. These may involve examination of the stools (for direct evidence of infections); the blood (for antibodies or antibody-antigen complexes) or urine (for yeast metabolites absorbed from the intestines). Each test has its strengths and none is without its weaknesses. Many parents feel that it is simpler to assume infection and just go ahead with treatment in terms of supplements. Nystatin is however a prescription-only medicine and as such it is unlikely that physicians will be persuaded to prescribe such a product without prior testing or other good reason.

5. Other intestinal parasites

Life for intestinal parasites is not always simple; survival depends not only on obtaining nourishment but also on being able to survive the body's defence mechanisms. The production of substances, which will depress the host's immune system, would greatly enhance the survival chances of any organism. Only a very "foolish" parasite would produce chemicals that would injure its host for its own chances of survival would depend upon the survival of the host organism. Opioid peptides are perfect for this task; they would depress the host's immune system but would not, under normal circumstances, be absorbed. However, we know that

some people with autism spectrum disorders do have a tendency to excessively permeable intestines leading to an accumulation of problems.

Some worms and [protozoal](#) organisms (such as [giardia](#)) are thought to produce these compounds and we suspect, although it is not proven, that bacteria could utilise the same mechanisms. No one seriously believes that "*worms cause autism*" but they could exacerbate the situation especially in our subjects who may be especially prone to these types of infestation as a result of their already depressed immune system and frequent [pica](#) behaviours. One theory for the existence of the unusual [dermorphin](#) type compounds, referred to previously, suggests that they are derived from bacteria (perhaps anaerobic bacteria such as [Clostridia](#)) who seek to increase their chances of survival by this means. Although there is as yet no evidence to support the possibility, it could be that viruses or even *Candida* could be utilising similar mechanisms. In any case, it would seem important to normalise intestinal flora as much as possible by using appropriate medication regimes.

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Gluten Free Diets (again)

The nature of the intestinal microflora will be very much dependent upon the nature of the food consumed. A restricted diet, such as that selected by many people with autism would favour particular bacteria at the expense of others. For example, a diet with a high wheat diet would tend to favour Clostridia organisms; whereas they would be almost absent if rice were to be the sole dietary carbohydrate source. Clearly these are areas that require detailed investigation.

Stage C. The Reconstruction Phase

The ultimate aim of all these interventions must be to make it possible to eat a diet as near as possible to normal. If, for example, we can reduce the levels of potentially harmful peptides in the intestines or decrease the permeability of the intestinal wall and/or the blood brain barrier (BBB) we can minimise the risk of harm. This is the aim of the elements of the "*Reconstruction Phase*".

6. Sulphotransferase and Phenolic Foods

Interest in these aspects came about as a result of parental observation and study. Parents observed that particular foods appeared to result in the appearance of bad behaviours in their children. These foods such as apple juice,

citrus fruits, chocolate and paracetamol were precisely those that were known to precipitate migraine attacks in susceptible individuals. The parents also noted the according high incidence of migraines within the families of people with autism. They noted that certain enzymes tended to be functioning sub-optimally in migraine and wondered if the same situation pertained in autism. They coerced Rosemary Waring, a well-known researcher into these aspects, into testing a group of children with autism. The results were published some years back (1997) and have been replicated and extended in dramatic fashion by Alberti (1999) and recently by Waring herself (2000a).

It would seem that the sulphotransferase systems are functioning at sub-optimality in people with autism. There are a number of consequences including effects upon the metabolism of classical neurotransmitters; impaired breakdown and metabolism of the [bile](#) pigments bilirubin and biliverdin; impaired action of the hormone [CCK](#) which would result in decreased secretion of bile from the gall bladder and biliary tract into the intestines. This could, once again, result in low uptake of certain vitamins and other nutrients from the intestines; reduced activity of [gastrin](#) in the stomach (and subsequent reduced secretion of stomach acid, mucus and [pepsin](#) in the stomach and perhaps reduced production of [secretin](#) and absorption of other vitamins further downstream).

Perhaps of even greater importance is the effect on intestinal permeability. The intestines are lined with a slimy layer of mucoproteins. This layer, as well as containing important [immunoglobulins](#) (specifically of the IgA class), provides lubrication and protection for the intestinal wall as food passes down the alimentary canal. These mucoproteins must be sulphated if they are to be continuous, protective and effective. If they are not sulphated, the proteins clump together and leave exposed intestinal material and so the transport of peptides into the tissues will be encouraged.

The role of sulphation may well be one of the pivotal factors in the causation of autism yet it is poorly understood and has received scant attention. The role of sulphate in the immune system, in the effectiveness of hormones and in maintaining the integrity of intestinal function, kidney function and detoxification systems is deserving of much greater attention than it currently receives. Owens (1998) has drawn the attention to the importance of sulphation issues in chemical bodies called GAGs ([Glycosaminoglycans](#)), which have huge implications for many functions including brain development. Processes involving inflammation, such as that which would result from infections that may be acquired naturally or from introduction through vaccine programmes, will result in stripping of the sulphate containing GAGs from the intestinal wall. Owens has

suggested that these GAGs will form the main reservoir of sulphates held in the body. Therefore, any lingering inflammatory process will result in sulphate depletion. Waring (2000b) has also presented data indicating that the conversion of sulphite to sulphate is severely inhibited after immunisation of adult students against hepatitis B.

Sulphate ions are only poorly absorbed from foodstuffs but may well be absorbed through the skin. That is the rationale for the use of a cupful of [Epsom Salts \(Magnesium Sulphate\)](#) in the bathwater of children with autism. Some parents are experimenting with home made "[trans-dermal patches](#)" containing crystals of Magnesium Sulphate. The intention is that small amounts of the salt are absorbed through the skin on a continuous basis. Alternatively, [Methyl-Sulphonyl-Methane](#) (MSM) may be given orally in an attempt to elevate blood sulphate levels. Efficacy has not, however, been demonstrated in terms of appropriate clinical trials but the body of anecdotal evidence is impressive.

7. Betaine (Trimethylglycine) Hydrochloride

As with the enzymes, referred to above, [Trimethylglycine \(TMG\)](#) has been used for many years in the treatment of hyperactivity even though the mode of action has remained unclear. This compound will, by slowly releasing hydrochloric acid, increase the acidity of the stomach contents. There is soft evidence that some people with autism have insufficient acid in the stomach ([achlorhydria](#)) and that, as a consequence, the stomach enzymes act inefficiently to break down the proteins. It may also be of relevance to consider that secretin is produced in the intestines as a consequence of acid in the stomach. Thus, if there is insufficient acid there could be reduced levels of secretin produced.

As with Dimethylglycine (DMG), it is possible that any activity is dependent upon totally different mechanisms. The role of DMG and TMG in [cysteine](#) metabolism is very well known. Alternatively, these compounds could, conceivably, have direct neurotransmission effects or act as a source of glycine, which is always in demand within the body. It is our opinion that this compound has little, if any potential for harm and given its long history of use should be considered at this juncture.

8. Fatty Acids (Fats and Oils)

There is a popular misconception that fats act as nothing more than storage systems for energy or as packing material. Only recently has it become

acknowledged that fats have a very significant role in the metabolism and development of the body. There exists a clear need for a greater understanding of the role of fatty acid metabolism in the maintenance of membrane permeability throughout the body. There are [intriguing data](#) being produced but, as yet, there is no total consensus on which elements are of relevance and which are not. At this point we hesitate to make definitive statements about which interventions are appropriate and we must suggest that those interested in the topic obtain advice elsewhere until the position clarifies. Although definitive evidence has yet to be presented, it would appear that there are [abnormalities in the fatty acid](#) content in the circulating bloodstream as well as in the bound forms and there is no agreement as to whether circulating levels accurately reflect the situation in membranes. Given the instability of these membranes and the fact that analyses are rarely performed immediately after collection there must still be some doubt about the reliability of any but the most carefully collected data.

Many have extolled the benefits of flaxseed oil; of cod liver oil; of olive leaf oil and many others but for a variety of reasons. Evidence is accumulating that any intervention should involve a balanced approach of (what are termed) [Omega 3](#) and Omega 6 acids rather than gross overloading of one form (an approximate ratio of 4:1 omega 3: omega 6 seems to provide the optimum performance).

9. Amino-Acids

There are number of disorders, which can result directly from amino-acid irregularities. [Histidinaemia](#), [PKU](#), [Homocysteinuria](#) and others could be involved in the causation of symptoms. Tests to rule out these gross problems should be performed routinely. There is considerably anecdotal evidence that certain amino acids are beneficial to people with autism. Supportive evidence tends to be lacking but supplementation could be considered and, in any case, their use is unlikely to cause any harm. [L-Glutamine](#) has found favour amongst many parents even though the precise mode of action is unknown. It is used routinely in medicine to encourage growth of gastrointestinal villi and thereby improve absorption from the intestines. It has been suggested that glutamine levels, in the blood, are low in people with autism in any case so supplementation may be no bad thing.

[5-Hydroxy Tryptophan \(5HTP\)](#) is a metabolite of the amino-acid tryptophan and is used in the formation of the transmitter substance serotonin. It may be that serotonin levels, in the areas where it is required, are low and that

supplementation with 5HTP is helpful. Many people feel that this is the case although, once again, evidence of efficacy in autism is lacking.

10. Supplementary Enzymes

If the peptides in the gut are not being broken down adequately, this could be a result of insufficient levels of peptidase enzymes. For many years, parents of children with hyperactivity have been utilising enzymes (orally) to ameliorate the problems. Many such products are on the market. Some of the plant-derived enzymes are particularly effective and we are aware of many parents who feel that the enzyme from pineapples, [bromelain](#) produces beneficial results. Bromelain has a particular advantage over so me of the other naturally occurring enzymes as it is known to break down the tyrosine-glycine links which are crucial to the opioid activity of so many of these biologically active peptides. Many of these products contain another enzyme "papain" which is also plant derived. However, we have come across a few instances where it appears that an allergy to this compound exists. A product especially designed for people with autism (SerenAid) is now commercially available. It contains peptidase enzymes from a variety of sources and has been specially formulated to function in the acid medium of the stomach. the peptides will be broken down here and will not be available for absorption lower down in the intestines. The manufacturers do not claim SerenAid to be a stand-alone product but it would appear to be useful as an adjunct to other dietary interventions. Many parents use it regularly, with meals. No results from formal trials have so far been published.

Stage D - Additional Interventions

The following interventions have been placed in this comparatively late position in the protocol for a variety of reasons. The use of diets devoid of colour or salicylates, although supportable on theoretical grounds and by experimentation in vitro (Waring 1999) is not easy to maintain and parents initiating these comparatively restrictive regimes do not find it easy to justify their actions to orthodox health professionals. Similarly the use of secretin must still, at this stage, be seen as experimental rather than routine. As the newer and purer versions of the product become available and evidence of safety and efficacy appears this situation may well change. Even the use of high doses of Vitamin B6 is frowned upon as there are theoretical risks associated with its use. The use of DMG would not attract such criticism but since we do not know the

reasons for any effectiveness we were unable to allocate a rational place in our protocol.

11. 5-HTP (5-HydroxyTryptophan)

The mechanism we have proposed involves a pivotal role for indole-3-acrylic Acid (IAcrA) which is an unusual metabolite of the amino-acid tryptophan and the immediate precursor of *trans*-indolyl-3-acryloylglycine (IAG) which we have reported as being present in abnormally high quantities in the urine of people with autism. We have suggested that this distortion of the normal pathways in favour of this route may be a consequence of partial inhibition of the enzyme tryptophan hydroxylase. This is the enzyme responsible for the conversion of tryptophan to 5-hydroxytryptophan (5-HTP), which is then converted to [5-hydroxytryptamine](#) (serotonin or 5-HT). Thus, an inhibition of the enzyme tryptophan hydroxylase would result in an increase of the potentially harmful IAcrA and a reduction in available serotonin throughout the body. The obvious remedy would be to provide supplementary tryptophan but there are two problems with this. Firstly, if the enzyme activity is diminished as we propose, the tryptophan will be converted to IAcrA, which is undesirable. Secondly, tryptophan is now only available as a prescription medicine in most of the world. This banning of over the counter sales of tryptophan is unusual and controversial given the history of the product but, in any case, the use of 5-HTP would be more appropriate. Once again, the only reports of usefulness are anecdotal but its use is both logical and unlikely to result in side effects.

12. Phenol (Pigment) Free Diet

It would seem that this sub-optimality of sulphotransferase activity is a function of low plasma sulphate levels rather than of deficits in the actual enzyme. Thus, any foodstuff requiring or using up sulphate ions during its metabolism will make the situation worse. These foodstuffs will include apple juice, citrus fruit juices, chocolate and paracetamol. In fact, any chemicals with a high proportion of phenolic groupings will have this effect and enhance the problems referred to above. Many colouring materials, whether of natural or synthetic origin, possess phenolic groupings. For this reason, some practitioners recommend the removal of all pigmented foods from the diet. Of course, the earliest dietary interventions to gain publicity (Feingold Diets) were heavily dependent upon the removal of synthetic colorants especially those given E numbers. Some of the negative publicity for these products may result from a

feeling of distaste for these unnecessary additions to our food but for some people they are of significance. Except in a very few isolated instances we have not seen great changes in people with autism when pigmented materials are removed unless other elements are removed as described above. There are those (perhaps the majority) in whom these foodstuffs, including paracetamol (acetaminophen), seem to make no difference at all but there are individuals who would be well advised to avoid such products. Once again, it is a question of assessing the effects on each individual.

13. Salicylate Free Diet

Ever since the days of the Feingold Diets people have been aware that foods high in salicylates may be problematic for people with autism. Salicylates (such as aspirin) are used medicinally for their anti-inflammatory, antipyretic (temperature lowering) and anti-pain properties. These effects are achieved by blocking the actions of enzymes called COX1 and COX2. These enzymes, as well as causing the production of inflammatory and other responses, are necessary for the production of certain prostaglandins essential for the maintenance of intestinal integrity. Drugs such as aspirin, which inhibit COX1 reactions, will have serious effects on the intestines and lead to greatly enhanced permeability especially in susceptible individuals. Some parents find it advisable to avoid such foods as almonds and others containing salicylates. For others, no such problems exist.

14. Megadose Vitamin B6 and Magnesium

Very high levels (500 - 1000mg/day) of Vitamin B6 (balanced by magnesium another vitamins of the B group) are advocated by some and many claim benefits from such usage. There are theoretical risks involved and attempts have been made, in the US as well as the UK, to limit availability. However, I am unaware of anyone who has ever seen the deleterious effects described in the literature.

15. Di-Methyl Glycine (DMG)

Dimethylglycine (DMG) would appear to be a safe, and in some cases, useful supplement but, once again, the encouraging observations of parents and some professionals have yet to be demonstrated by clinical investigation.

16. Secretin

Although not strictly speaking a dietary intervention, mention must be made of the hormone product secretin. Secretin has received considerable publicity of late. The rationale for its use was its ability to stimulate the pancreas to produce peptidase enzymes (Horvath *et al*, 1998). It could be working in a number of alternative ways. The results of preliminary trials are somewhat equivocal and further clarification is awaited. However, a discussion at this point is beyond the scope of this presentation. Further information about secretin and autism can be found here.

Other Supplements

There exists a plethora of substances which whilst, strictly speaking, are not medicines in the legal sense of the word, do have actions which push the borders between what could be considered as "*nutritional supplements*" and are sold accordingly. For example, Gingko (biloba) has been used extensively for its action in increasing blood flow and, therefore, the supply of oxygen to the brain. Ginger, Liquorice and other herbal products are also being used on account of their effects upon the gastrointestinal tract and may have a place once more information becomes available. Although not food supplements in any sense of the word, the use of chelating agents will have to be considered at some point. For a considerable period of time there have been insistent voices concerned about the potentially seriously harmful effects of mercury in children with autism. Indeed, there are close parallels between the known effects of mercury and the symptoms of autism. Evidence is beginning to emerge which suggests a greatly increased mercury burden in people with autism. This only becomes apparent when chelating agents are employed to remove heavy metals from the body. Research is currently being conducted to test these hypotheses and at this stage we feel it inappropriate to discuss the utilisation of these chelating agents. The potential for side-effects is unacceptably high for self-medication and such treatments should only be attempted under experienced medical supervision. Clearly this is an area that warrants very close attention.

Conclusions

Interventions involving manipulations in diet, in terms of avoiding certain components or taking dietary supplements are being increasingly used for autism spectrum disorders as well as many other conditions. Western cultures are geared

very much towards the use of drugs, often synthetic and very potent, to give symptomatic relief for particular problems which interfere with the quality of life of the affected individual. This approach is acceptable only up to a point. Parents and carers are becoming increasingly interested in the processes which may underlie the symptoms and, where possible, intervening and thereby minimising the presentation of the symptoms. For sure, the predisposition, the fragility, the seeds of the autism will remain but by minimising the triggering factors amelioration of the problems is possible. Many interventions are advocated and, at first sight, they would appear, especially to the non-interested professional, to be a rag-bag of ideas without substance. Most of these interventions have been discovered and developed as a result of serendipity and investigative common-sense. Mechanisms appearing to be reasonable, logical and justifiable have been established. These interventions do integrate and can be utilised to form individualised plans for each individual. They offer the clinician opportunities for intervention which hold promise and for which supportive evidence is accumulating.

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Further details about the *Sunderland Protocol* can be found [here](#).

Selected additional links (added 24 November 2006):

[Vitamin B6 & Magnesium](#) | [Dietary intervention for autism](#) | [Dietary intervention for autism \[2\]](#) | [Gut bacteria in autism](#) | [Tryptophan hydroxylase](#) | [DMG for autism](#) | [Fatty acids for autism](#)

