Endotoxin and Vitamin C
Part 2 – SIDS and the Shaken Baby Syndrome

Introduction

I have been lucky – or unlucky – in clinical practice in New South Wales to have seen many SIDS cases, mostly Aboriginal children. Working in a hospital, I have seen numerous children die from SIDS before my eyes despite appropriate and timely medical care. I have also seen the rapid positive effects of injected vitamin C administration on these children and the complete cessation of SIDS deaths under my care as a result. Needless to say this is a dramatic and formative event in a medical career and I have devoted most of my time and energy since to understanding what happened. Thousands of hours of research, chance meetings and the invaluable work of many other researchers and colleagues have led me to a deeper appreciation and understanding of the pathophysiological changes in SIDS; the roles of toxins and toxin signalling, the complexities of the immune system and cytokines, and of course some of the effects and mechanisms of vitamin C and other antioxidants.

The potential association of various bacterial toxins or other toxins with SIDS and Shaken Baby Syndrome (SBS) is now a hot topic and in some arenas has developed from theory to investigation to fact just in the last few years. Toxin signalling is now well established as a major factor in the pathophysiological changes seen in many SIDS cases. Some of the changes seen in SIDS cases are also seen in SBS so it is not unreasonable to assume, at least in some cases, that toxin signalling plays a role in the events that lead to the death of the infant. While the role of toxin signalling is fairly well established in SIDS cases, there is no research at all on this in SBS cases. Worse, the pathology required to make these sorts of determinations is simply not done at presentation or on autopsy, leaving the field neglected and wide open for speculation.

1. Clinical awakening

In 1957 I commenced work as the only medical practitioner in the more-or-less isolated Australian town of Collarenebri, 500 miles (805 km) north-west of Sydney. There were about 750 Caucasian individuals in the town, 200 Aborigines in the "native reserve", and 500 graziers in the surrounding district. Within a very short time I was faced with one of the highest infant death rates in the world. Most were Aborigines, but a sizable number were Caucasian. I recall adding up the number of deaths and comparing statistics with figures from Africa and India. In Collarenebri, the rates were higher. One of the figures that has stuck in my head from this time was that more than half of the graves in the Aboriginal cemetery were infant graves.

Over a period of about 10 years I saw approximately 20 infants die from these strange deaths, some Caucasians but mostly Aboriginals. Most infants died before the age of one year. Some died later – up to the age of 5 years. The deaths were difficult to explain. Some could be classified, according to accepted criteria at the time, as sudden infant deaths (SIDS). Others suddenly went into shock and died. Some suddenly became unconscious and died. A few became excessively irritable, as if they had meningitis (which was not so) and died. In all cases autopsies performed by myself failed to explain the deaths. The autopsies were standard – chest, abdomen and cranium and routinely I sent specimens to Sydney for analysis. Routinely I received normal reports.

In many of the cases, although macroscopically the livers appeared to be normal, histologists reported the existence of *'steatosis'*. When I asked what this signified I was told that it was a *'normal'* finding, and nothing to be concerned about – something that I never accepted.

As time went by I observed, in a few cases, liver tenderness before death, and macroscopic liver changes during autopsies. There were pale areas, surrounded by what vaguely appeared to be irregular regions of redness. I was told by the pathologists in Sydney that it was nothing to be concerned about. Persistent questions resulted in a statement that what I was observing was due to autopsy changes. When I tried to detail the fact that before death there was liver tenderness nobody would listen to me. Understandably frustrated and in an endeavour to settle this argument I commenced one autopsy within a few minutes of death – not a pleasant experience. The liver changes were there so I was satisfied that the liver changes were not post mortem changes.

At that stage I decided to go back to square one and look at features that were apparent in Aboriginal infants but in not in Caucasians. Some were malnourished, although I later found that this was due to illnesses and not food deprivation. Hygiene and environments certainly looked bad – but not in every case. Outstanding on examinations were the *'running noses'* that persisted up to and past early school-age. Associated was an extraordinary incidence of otitis media requiring frequent courses of

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antibiotics. Diarrhoea was common. Bowel motions sometimes had a particularly characteristic and terrible odour. This was considered to be a *'normal'* feature of Aboriginal infants. Misery was obvious and contrasted with the happiness displayed by most Caucasian infants.

Investigations, of a sort, were carried out. Faecal samples were collected according to instructions and transported to the government laboratory in Sydney. All reports were *'normal'* – no parasites. Previous experience in a coastal area had demonstrated a huge problem with parasites. I thought that, perhaps because the climate was different, inland Aborigines were not affected. This was a serious error. Years later I found that parasites were extremely common everywhere amongst Aboriginal infants and children – but rarely identified in their Caucasian playmates. Apparently, it was necessary to examine specimens in a fresh state. It never occurred to me to look for toxic strains of bacteria (because I had never heard of or about them). For similar reasons I ignored food malabsorption (after all, this was nearly fifty years ago).

Some blood tests were carried out. These revealed a degree of what was reported as *'iron deficiency anaemia'*. I was advised to give oral iron supplements. This did not solve the problem and I was advised to give iron by intramuscular injection. Responses to these were often alarming. Instead of achieving a hoped-for improvement I was forced to abandon the treatment.

Many more infants died.

In 1962 I noticed that a feature displayed by infants who later died was an abnormal number of *'minor'* infections – mainly otitis media and gastrointestinal disorders. This coincided with the arrival in the city of Tamworth, 250 miles away, where the base hospital for the area was situated, of Dr Douglas Harbison – the first specialist physician in the north-west of New South Wales. It soon became apparent that Douglas was a man with considerable ability, so I decided to send to him an Aboriginal boy who was going through the stage of multiple minor infections. I had reached a stage when I could go no further. It was time to seek help, and at long last I could turn to someone who appeared to have the qualifications and common sense required to provide this. Douglas must have had very keen vision because he observed that some of the hair roots were surrounded by extremely minute haemorrhages. There was, he thought, only one condition that could cause this – and that was **scurvy.** An injection of Vitamin C was administered and a few days later the boy was sent back to Collarenebri.

When I read the letter that accompanied him I was mystified. How could it be scurvy? I had been supplementing that little fellow with more than the recommended daily allowances of Vitamin C for months – as part of a routine. *'Everyone'* knew that a few milligrams of Vitamin C, administered, orally, daily, would prevent scurvy. I had not bothered to tell Douglas abut this because I did not consider it to be important. So, I thought, Douglas had made his first mistake. But something bothered me. Clinically, the boy looked better – much better. For many nights this bothered me. I was restless, concerned, and filled with questions. Eventually I had to give up – or almost give up, because the issue remained in the back of my brain and never went away.

In 1965, disillusioned by my failure and lured by the temptation of instant riches I decided to abandon medicine and become an opal miner in the area surrounding Coober Pedy in Central Australia. For a while I revelled in the life-style and the joy of feeling physically fit. Then I became involved in an event that left me physically and mentally injured. One night, in an endeavour to escape from it all I drove out, alone, into the desert, and when tiredness overcame me I stopped and went to sleep. When morning came I found that I was near a camp of semi-tribal Aborigines. For the first time in my life I was able to talk and associate with these people. It was a reversal in roles. I was no longer the carer. They were caring for me. One of the older women was particularly impressive. She was dirty and unkempt. Her hair had grown wild, she squinted through eyes that were covered with flies and were badly inflamed (trachoma). But I sensed her love for the children. What she told me one day has become imprinted in my mind – because it changed everything. I cannot write it in the manner that she spoke, but it amounts to this, 'Before white men came our children did not get sick'.

That night I lay under the stars and began to think. I recalled what Dr Harbison had written about the little boy I sent him. Then a series of *'maybes'* crossed my mind. I do not know how I came to follow a particular pathway because I had never read about it. It was as if someone was forcing me towards the only possible explanation that could exist. There could be no other way.

It amounted to this. *When these children get sick they need vast amounts of Vitamin C. When they get sick they need blood levels of Vitamin C that cannot be achieved by oral doses. It needs to be given by injection.*

The idea was totally persuasive. I decided to return to medicine and try its effectiveness. But there was one problem. I needed to find a practice where I could treat Aboriginal children. For a few months I was unsuccessful. Then one day, while staying with my mother in Sydney, I received a phone call from Collarenebri. *'Our doctor has left. Will you come back?'*

It was like asking me to accept a million dollars! And it was now December 1967 – about 10 years after I first arrived in Collarenebri. Whoever was in control of my future must have been in a hurry because, before I had time to unpack my bags, the phone rang. An astute grazier living on a property 40 miles from town was concerned because an Aboriginal infant (I will call her 'Mary') belonging to his house helper *'has meningitis'*.

This had to be *'it'*. I had seen it so many times before, and only once (in a Caucasian infant) did it prove to be meningitis. My decision was to administer an injection of Vitamin C, and if there were no signs of improvement within 20 minutes I would do a lumbar puncture. One possible complication of scurvy was the reason for this. Scurvy can involve a coagulation/bleeding disorder. If scurvy existed the trauma when a lumbar puncture was performed could cause a haemorrhage, an expanding blood clot, and spinal paralysis.

But the head nurse at the hospital did not understand this. She had never met me before and was justifiably concerned. With meningitis one does not *'mess about'*. Progress can be alarming and even a slight delay in administering the appropriate antibiotic can be fatal. However, I was in control. Into one buttock went an injection of Vitamin C - 100 mg, which was how much there was in the ampoules available to me. There were no guidelines concerning dosage, so I repeated the injection – many times.

Within a very short time Mary was normal. I had performed a miracle! From then on all sick (depending on how I defined *'sick'*) infants received, in addition to conventional treatment, injections of Vitamin C. *There were no more strange deaths, and no more SIDS deaths*.

It should not be necessary for me to state that one must be clinically astute and not miss, for example, conditions such as true bacterial meningitis that may need to be treated with specific antibiotics in addition to Vitamin C injections.

I did not need to study thousands of cases or do extensive double blind cross over trials. I knew with this one case that I had *'discovered'* something of extreme importance. High blood levels of Vitamin C could *'cure'* some potentially fatal conditions. Oral doses could not.

I use italics for the word *'discovered'* because, some years later, I was put in touch with overseas physicians who had beaten me to the post by many years – and published what they observed. From then on it was a steep learning curve. Dramatic *'cures'* preceded understanding of the mechanisms involved.

Specialists in various fields, particularly biochemistry, clarified many issues for me. In the 1970s I met a vet, Dr. Barry Reisinger, who told me about the effects of endotoxin in calves and cattle. This was for me one of those spectacular "aha" moments and the penny really dropped hard. It suddenly became obvious to me that a lot of the pathological events in the sick children I had seen could be explained by endotoxin. Nowadays with the Internet, there is a treasure house of knowledge on endotoxin. This in some ways became a hazard because one can easily get lost in details and arrive at false conclusions. That is why clinical observations and clinical experiences are fundamental and so important. *Any* sort of theory offered *must* explain why vitamin C had such a dramatic impact on these children.

The events of the 1950s – 1960s are now fading into time. Hospital records of the children I treated in this period have since been destroyed, so there is no going back to examine records of vital statistics etc. in these cases. At the time I was the only doctor in the area and I was faced with an urgent and confusing situation. I did not have the benefit of hindsight to realise that I should have kept for myself very accurate and detailed records of all these cases before and after I started using vitamin C. I also did not have the benefit of knowing what I know now about toxin signalling and the immune system to even have known what to look for or measure in these cases.

I also used injectable vitamin C in many adult cases at Collarenebri. Over the years numerous very drunken Aboriginal patients were brought to my care for a "detox". Some of these patients were aggressive and all were extremely inebriated. The vitamin C was given i.v. and three typical events occurred. If the patient was aggressive, as soon as the i.v. of vitamin C started they would calm down – dramatically. Very rapidly the patient would become completely sober - typically they would feel so much better after a few minutes that they would pull out the line themselves and leave the clinic. The most striking effect of the IVC was that if the administration rate was increased past a certain point, the patient would become unconscious and display signs that looked like a morphine overdose. If the administration

rate was then slowed down, the patient would instantly regain consciousness. This occurred repeatedly *purely as a result of the rate of administration*, not the total amount of vitamin C given.

Needless to say that the clinical experiences with Aboriginal children and adults using vitamin C have affected me profoundly and defined the path of my medical career. I had quite simply never imagined, seen or heard of anything like it, and these experiences have caused me to support and champion the use of IVC in clinical practice ever since.

2. SIDS – The Emergence of the "Endotoxin" Theory

Barry Reisinger completely electrified me with news of endotoxin in the 1970s. It was just plainly obvious to me that this had to have something to do with the SIDS cases and other sudden death cases I had seen. A detailed treatment of endotoxin has already preceded this article, so I will not go into that detail again, however much of the synthesis of this information simply was not available in the 1970s and to most medical professionals the association of SIDS with endotoxin seemed patently absurd. This is definitely not the case now. In the 1970s there was no evidence because, quite simply, the research had not been done.

I know now that the scope of bacterial and other toxins implicated in SIDS is **large** and encompasses many agents other than endotoxin (LPS). Many of these toxins do indeed initiate LPS signalling even without the presence of LPS, and other pathways of cytokine response not related to LPS signalling may also be involved. Other toxins and host factors may also synergise with LPS to produce greatly amplified signals. The complexities and interactions are horrendous and in truth the core of the material I have collected and researched over the last decades relates to LPS. LPS is certainly one of the most potent initiators of immune response and without doubt the most extensively studied. Collectively, I tend to be in the habit of referring to all of these agents as "endotoxin".

The first of a series of papers detailing research into the potential connection between toxins and SIDS appeared in the mid 1980s with the emergence of the "Common bacterial toxins" hypothesis forwarded by J.A Morris et al[1]. Put simply, this hypothesis goes that "…common toxins produced by bacteria growing in the respiratory tract following a viral infection are a cause of SIDS." … "Viral infections of the respiratory tract disturb the normal bacterial flora and lead to an increased nasopharyngeal carriage of *Staphylococcus pyogenes* and gram negative bacilli. Many of these bacteria are known to produce potentially lethal toxins. Thus it is proposed that bacterial toxins absorbed from the upper respiratory tract are a possible cause of SIDS. A central assumption of the hypothesis is that the putative toxins, produced by bacteria of the normal microbial flora, are common. Infants normally meet them in early life and develop immunity to them, but if a first encounter with a particular toxin producing organism coincides with a viral infection then the bacteria may overgrow in the nasopharynx and produce toxin induced sudden death before immunity develops."

This was a big step in the right direction. One of the key successes about the initial work of J.A. Morris is that with mathematical modelling he successfully predicted the typical age incidence of SIDS. Typically SIDS infants die within the first three months of life with peaks at two and three months. This was most definitely NOT the case with the majority of Aboriginal and other children who died or were treated by me in the Collarenebri district. Most died or were presented to me before one year old, but the majority were older that three months. It is debatable then whether some of these cases should really be called SIDS, but in reality there simply wasn't anything else to call them at the time. They died suddenly and without explanation, right in front of me. Some were classified as SIDS, some were not. Without exception, all of the children had chronic streaming noses and most of them had diarrhoea – plenty of opportunity for toxins to translocate across inflamed and compromised membranes into the circulation.

In 1996 a paper by Sayers et al[2] published in the Journal of Clinical Pathology reported on the lethal synergy between bacteria, associated with SIDS, on chick embryos. I have paraphrased a fair bit of this paper to give some idea of the complexity of the toxins involved: "Extracellular toxins of 13 isolates of Staphylococcus from SIDS victims and matched healthy infants were tested for lethal toxicity in chick embryos with and without standard endotoxin (used at 1.00 ng/embryo). Endotoxin and toxins from staphylococci were used at dilutions with negligible toxicity. Simultaneous injection of nonlethal levels of endotoxin and toxins from 11 of the 13 staphylococci isolates tested produced lethal toxicity that was 111 to 613% greater than expected by an additive effect alone." … "The results presented herein show that Gram negative endotoxin and extracellular toxins from staphylococci act synergistically to produce a lethal effect in chick embryos. Eleven of the 13 staphylococcal isolates tested stimulated a lethal synergistic effect with endotoxin. Of these 11 isolates, four produced SEC (staphylococcal enterotoxin C), two produced SED (staphylococcal enterotoxin D), two produced TSST-1 (toxic shock syndrome toxin-1) and

four did not produce any detectable enterotoxins or TSST-1. These results suggest that the presence of any particular enterotoxin or TSST-1 is not an absolute requirement for lethal synergy to occur between staphylococci and endotoxin."… "Staphylococci produce other extracellular toxins including exfoliating toxins (A and B), pyrogenic exotoxins (A, B and C), and leukocidin which also may be involved…Enterobacteria also produce a wide range of toxins other than endotoxin; these include haemolysins, vero-cell cytotoxin and proteases, which could also act synergistically with staphylococci."… "The physiological effects of endotoxin are varied. Gram positive toxins (including TSST-1, SEA, SEB and SEC) can potentiate the activity of endogenous endotoxin by priming or activating macrophages. Endotoxin activity can also be potentiated by other antigens including influenza virus A; it is also reported that SIDS victims are more likely to have depleted antibodies to endotoxin core (lipid A) than normal healthy controls."

This is a big step forward but still the tip of the iceberg in the bacterial toxin story – it gets much more complicated than this. What is fairly clear now however, and reproduced in other research, is that endotoxin (LPS) has synergistic and dramatically amplified effects with other toxins.

A good review of the bacterial toxin ideas related to SIDS was published by Blood-Siegfried[3] in 2000. She states: "Although one of the defining characteristics of SIDS is the absence of symptoms, at least 70% of all infants who die of SIDS have been reported to have a mild viral infection before death. In many cases, parents have consulted a health care provider in the preceding weeks, reporting symptoms in their child of an upper respiratory tract illness including rhinitis, pharyngitis, and cough." … "At autopsy, most of these infants are found to have combined infections with two or more bacteria and/or viruses." … "There is significant correlation between endotoxin levels in the blood and signs of inflammation in SIDS. It is well accepted that high levels of endotoxin are known to cause septic shock and death. Maternal IgG levels decline slowly between 2 and 6 months. Valdes-Dapena and Hummeler showed that gamma globulin levels were the same in infants who had died of SIDS and control infants who had died of other causes, i.e. trauma. However, in SIDS, infants have low levels of IgG specific to Lipid A, the component of endotoxin that stimulates an inflammatory response. Antibody to Lipid A could help prevent a fatal response to endotoxin." … "Many of the Gram positive bacteria found at autopsy in SIDS are toxigenic and produce super antigens. In the absence of endotoxaemia, an organism such as *Staphylococcus aureus* could induce the same sort of abnormalities as in septic shock." She goes on to say: "It is clear from observations in animal models that a synergistic insult can cause a SIDS-like death. Extrapolating this to the human population is much more difficult. It is generally thought that some infants may overreact immunologically because of predisposing factors and/or underlying host vulnerability, succumbing to an otherwise nonpathologic event. Trying to pinpoint a particular toxin or group of toxins has been non-productive."

3. SIDS Gets More Complicated

The research implicating bacterial toxins in SIDS is expanding and continues today. A review published in FEMS Immunology and medical Microbiology in 2004 by Goldwater[4] covers a lot of ground and gives comprehensive insight into the typical pathological changes seen in SIDS and unequivocally associates most of these with toxins. Goldwater asserts that a single cause of SIDS is most likely because of the consistent pathological findings at SIDS autopsies. The "single cause" is most likely to be common or related cytokine pathways that are stimulated by a variety of toxins. What is paramount in SIDS cases is that for whatever reason, the host response is overwhelming. These reasons will vary from infant to infant and of course the genetic susceptibility[5] to various toxins and their combinations will also vary from infant to infant.

Goldwater has proposed another toxin, soluble curlin antigen as a significant initiator of the pathological changes seen in SIDS. He states: "One of the newer candidate ''toxins'' is soluble curlin antigen (CsgA), the subunit of curli fimbria, which are colonisation/adherence factors common to most Enterobacteriaceae. Curlin could be accompanied by other toxins absorbed through the gut and reach the circulation via the portal system, which takes it to the liver. Fatty change, for which toxaemia is a cause, is found in the livers of some SIDS babies. A second and possibly more important route for curlin or toxin absorption would be via the lymphatic system and the thoracic duct. Curlin protein or toxin would be delivered via the duct to the innominate vein to the right side of the heart. The first organ exposed to curlin would be the lungs followed by the heart and the thymus. Bacterial toxins/products could perturb basement membranes of small blood vessels leading to the small haemorrhages (petechiae) and fluid-laden organs seen in SIDS. Curlin binds to fibronectin and this could precipitate damage to capillary basement membranes and perturb the clotting system. The distribution of petechiae is distinctive and could be explained by the fact that intrathoracic organs would be the first exposed or that these organs are replete with hypothetical toxin receptors possibly fibronectin.

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…. The pathological findings in SIDS include liquid (unclotted) blood within the chambers of the heart and elevated cross-linked fibrin degradation products also seen in toxaemia/sepsis. In this context, curlin protein represents contact-phase bacterial components which can activate the pro-inflammatory pathway involving reactions with fibrinogen and fibronectin which can lead to depletion of coagulation factors resulting in a hypocoagulability state. The finding of an empty bladder in most SIDS cases suggests decreased renal perfusion (toxaemic shock) during the last sleep. This proposed hypotension could be explained by induction of pro-inflammatory cytokines by curlin protein with subsequent release of bradykinin and/or nitric oxide."

As research is progressing in this area, and as more funding inevitably becomes available, it is inevitable that the complexities of toxins and their interactions in SIDS will increase. This will in time, hopefully give us a clearer picture of what is really happening in all the pathological changes associated with SIDS. Whether it is endotoxin, particular synergies with endotoxin, curlin, endotoxin and curlin – or something else altogether will hopefully be uncovered by research in time. Most likely it will be different combinations of these factors in different infants, in combination with genetics and environment (exposure to viruses etc.), i.e. not at all a simple explanation. The potential of this is obvious - to develop therapies and strategies to prevent SIDS, or at least significantly reduce its incidence.

It is potentially possible of course to develop drugs to interfere with specific toxins and of course to develop antibodies by vaccination. Research into the toxin association with SIDS has advanced to a point where it may become realistic for pharmaceutical companies to pursue this. This sounds all very enthusiastic to me – to date similar attempts to develop drugs to interfere with septic shock have not been successful despite multi million dollar input into several research arms from several companies. I see no reason at present why such attempts would succeed for SIDS prevention drugs since essentially the same mechanisms of pathological change are involved. Frankly the interactions, complexities and levels of feedback and control of the immune system are too complex to be able to easily develop an effective and safe drug.

An excellent case in point is the development of "knockout" mice which do not activate NF-κB after reperfusion following intestinal ischaemia[6]. NF-κB is involved deeply in the escalation of cytokine responses triggered by reperfusion injury. NF-κB enters the nucleus and expresses genes for cytokines. It is proposed then, as a pharmacological principle, that blocking NF-κB activation or blocking its access to the nucleus will attenuate cytokine responses and prevent systemic inflammatory responses typically seen with reperfusion. When tested in these knockout mice NF-κB certainly did not activate – the animals, after intestinal reperfusion, did not get systemic inflammatory responses. However their intestinal mucosa developed severe damage from apoptosis, because, as it turns out, NF-κB is crucial for the control of cell death signalling including cell death signalling in cancer cells.

Endotoxin (LPS), as a mediator of NF-κB activation, is *normal* and *necessary* in low concentrations to maintain normal NF-κB signalling. You simply CANNOT get rid of LPS or NF-κB completely without causing severe problems elsewhere.

4. Vitamin C is Completely Missing from the SIDS/Toxin literature

It is obvious to me that a realistic discussion about the role of vitamin C in all of this toxin research is utterly absent. I can guarantee you that vitamin C can be administered regularly in high doses (many grams) and it does not interfere AT ALL with **normal** levels of NF-κB and cytokine function. This is obvious because despite millions of IVC doses over decades, even with 60-100g doses, there are no reports of anything like these problems.

I can also guarantee you that on many occasions, the progression of SIDS has been stopped before my own eyes after administration of IVC to the infant.

It is now appreciated by many that toxin signalling – whatever the toxins or combinations of toxins are - is responsible for the rapid and escalating pathology seen in SIDS. Realistically at present nothing else can account for the rapidity of onset and progression to death seen in SIDS, and nothing else at present can account for the host of pathological changes seen in SIDS. Certainly for endotoxin (LPS), a tremendous amount is now known about how vitamin C interferes with and attenuates LPS signalling. Much of this is discussed in detail in the previous article. In short, vitamin C attenuates the expression of iNOS, brings under control *excessive* activity of NF-κB, maintains intracellular GSH levels and directly quenches ROS and RNS produced in phagocytes. Vitamin C also supports cytochrome function in the liver, maintains GSH levels and protection of the liver from endogenous radicals, blunts LPS signalling and in general maintains liver function. The upshot of this of course is unimpaired detoxification of LPS and other toxins and release of them into the bile.

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One of the things that frequently astounded me about vitamin C is its rapidity of action. Literally a child could go from screaming, unconscious or a full-blown "meningitis" presentation to *normal* in the space of 20-30 minutes. Sometimes it took a few hours. It was *always* fast. It is tempting to think of vitamin C as a miracle drug in this respect which rapidly interferes with toxin signalling. In reality the scenario emerging from all the research into vitamin C transport into cells and intracellular vitamin C concentrations is that the signalling cascades get out of control when vitamin C is significantly *absent* from cells (particularly macrophages, neutrophils etc.). If vitamin C is low in cells, then LPS signalling is dramatically amplified. It only takes a little bit, or otherwise normal amount of LPS to really get the ball rolling. In neutrophils maintaining intracellular vitamin C saturation maintains GSH levels, minimises rises in superoxide radical concentration, normalises NF-κB translocation to the nucleus and nitric oxide formation and limits the production of peroxynitrites. In short, maintaining vitamin C concentrations in neutrophils etc. minimises escalation of signalling cascades.

There is ample research that demonstrates that vitamin C levels are depleted in sepsis/LPS signalling. Very obviously, given the discussion above, a depleted vitamin C level leads to escalation of the problem. The pharmacological goal with vitamin C therapy then is to *at least* restore intracellular vitamin C levels to normal. In the face of LPS signalling, it turns out that it would be next to impossible to do this with oral vitamin C. To rapidly restore intracellular vitamin C levels it should be administered by intramuscular or intravenous injection.

5. Vitamin C Transport and Intracellular Concentrations

As stated in the previous article (Endotoxin and Vitamin C – Part 1) IVC can achieve much higher plasma concentrations than oral vitamin C: "The maximum transient *plasma* concentration achievable with oral administration is approximately 200 micromoles per litre (3.96 mg %), more typically 100 micromoles per litre (1.98 mg %). Note that this is a plasma concentration, *not* an end tissue concentration. Plasma ascorbate concentrations are fairly tightly controlled after oral administration, mostly due to saturation of absorption versus rate of excretion. On the other hand, an intravenous dose of 50 grams of ascorbate can achieve a plasma concentration of approx 13,000 – 14,000 micromoles per litre (257 – 277 mg %)."

It is clear that higher plasma levels can be achieved with IVC. This does NOT mean that the vitamin C will go everywhere to achieve very high intracellular concentrations. The intracellular concentration of vitamin C, like many other molecules, is tightly regulated.

Vitamin C is water soluble, similar in size and structure to glucose, and like glucose does not significantly diffuse across cell membranes. Vitamin C, like glucose, has to be pumped around everywhere and actively transported across cell membranes. For example, the vitamin C concentration in parts of the brain is approximately ten times higher than the normal plasma concentration. To maintain this concentration vitamin C is actively transported against a concentration gradient.

I am not going to go into *great* detail about vitamin C transport, there are excellent reviews available[7]. In a nutshell *reduced* vitamin C (sodium ascorbate) is transported by sodium dependent transporters in the SLC23 family. There are two transporters characterised to date: SVCT1 and SVCT2 (SVCT = sodium dependent vitamin C transporter). SVCT2 is expressed far more widely than SVCT1. Essentially, SVCT1 is expressed in epithelial cells (lining membranes etc.) and is involved with bulk transport (e.g. from the gut to the blood) of reduced vitamin C across the membrane: "Endogenous mRNA for one or both of the SVCT isoforms has been found in most organs. Reverse transcription-polymerase chain reaction (RT-PCR) analysis showed that brain, skeletal muscle, and spleen express predominantly SVCT2, whereas liver and kidney express mainly SVCT1; indeed, quantitative RT-PCR showed that SVCT2 mRNA levels in liver and kidney are less than 5% of SVCT1 levels. SVCT1 is localized mostly in epithelial tissues, whereas SVCT2 has a wider distribution. On the one hand, the high capacity of SVCT1 is appropriate for epithelial cells that transport much more ascorbate than required for their own internal use. On the other hand, the affinities of both SVCT1 and SVCT2 are sufficiently high to enable cells to absorb ascorbate effectively from extracellular fluid where in most tissues except the stomach, eye, and central nervous system the concentration of ascorbate may approximate the 20 80 M (0.4 1.6 mg %) normally found in plasma. [7]

Vitamin C in its oxidised form (dehydroascorbate DHA) is readily transported across most cell membranes by glucose transporters, predominantly GLUT1, GLUT3 and GLUT4. The ability to transport vitamin C this way clearly depends on extracellular DHA availability, the expression and translocation of GLUT transporters to the membrane (impaired in insulin resistance), competition with glucose and saturation of the GLUT transporters. It is emerging from research that many cells do not express SVCT transporters at all, and that their method for acquiring vitamin C is via GLUT transporters. Once

inside the cell, DHA is rapidly reduced to ascorbate by GSH dependent enzymes, however the intracellular reduction of DHA to produce ascorbate is controlled to achieve normal intracellular concentrations of ascorbate.

An excess of glucose, such as occurs during the hyperglycemia of uncontrolled diabetes or surgical stress or sepsis, may competitively block most DHAA (dehydroascorbic acid) uptake through facilitative glucose transporters and thus impair the clearance of DHAA by cells. In addition to direct competition between glucose and DHAA for binding sites on transporters, chronic changes in glucose supply can have noncompetitive effects on the amount of DHAA uptake mediated by glucose transporters. [7]

The transport of reduced vitamin C by the SVCT transporters is saturable and the expression of the receptors and concentration of them on the cell membrane is controlled in part by the intracellular vitamin C concentration of the cell in question. *The lower the intracellular concentration, the better the vitamin C transport, and conversely, the higher the intracellular vitamin C concentration, the lower the rate of transport.*

Having said this, with LPS signaling in place, intracellular ascorbate plummets (it rapidly gets used up) and the cells (including neutrophils) become hungry for vitamin C. *They will rapidly uptake extracellular vitamin C, assuming it is there*. The limiting problems in maintaining intracellular vitamin C concentration in all cells are extracellular availability and the GSH mechanisms used to recycle and reduce DHA to ascorbate in the cell. In LPS signaling, intracellular GSH levels drop dramatically, thus vitamin C recycling drops, so effectively vitamin C must be imported into the cell. *It can t be imported if it is not there.* Giving vitamin C in high dose by injection is the only practical way to ensure extracellular vitamin C is available so that vitamin C can be transported when it is needed. Availability of vitamin C essentially means that intracellular concentrations can be normalized, returning the cell to its normal redox tension and thus inhibiting the escalation of LPS signaling.

Oral ascorbate dosing cannot achieve this, simply because the extracellular levels reached with oral dosing are too quickly used up. In the developing SIDS cases I saw and treated with the injectable vitamin C, I am assuming now that enough vitamin C was given to produce an extracellular pool of vitamin C that was not extinguished by the requirements of activated neutrophils and macrophages etc. Assuming the situation has not gone too far, these cells rapidly normalize if they can get enough vitamin C.

6. What has this all got to do with the "Shaken Baby Syndrome"?

Well, that is a good question. Thirty years ago people thought I was a crackpot for claiming that SIDS had something to do with endotoxin. It just seemed obvious to me at the time. The gradual unravelling of the involvement of endotoxin and other toxins with SIDS has come from the collection of samples from autopsies, their careful analysis and in particular the foresight to look for and test for the right things. This simply could not have occurred without the collaborative work of many people, both researchers and clinicians, and without a continuous pressure to seek the truth.

In Shaken baby Syndrome (SBS) cases, the presence together of brain swelling, subdural haemorrhage and retinal haemorrhage has in the past been sufficient to convict parents or carers of infant abuse. In most cases the infant has died. There was recently a ruling by the court of appeals in the UK which found that the presence of these three symptoms alone cannot be accepted as proof in themselves of abuse, that other evidence must be examined. The reason for this ruling is that there was considerable doubt in the court's opinion, based on conflicting expert medical testimony, that there could not be other reasons for these presentations.

While of course it is true that infants are abused and violently shaken, there are enough parents or carers who vehemently deny anything but *normal* handling of their baby. Since there are conditions in a SIDS infant or child that can predispose to an increased susceptibility to otherwise normal levels of toxins, to the point of rapid escalation of complications leading to death, it is not unreasonable to assume that similar conditions may lead to an increased susceptibility in other infants. It is quite possible that normal handling of an infant may put in place a chain of events that leads to the child's death.

As in SIDS, the exact combination of agents and events in any particular case will vary considerably. It occurs to me that a very *likely* combination in many SBS cases would be "endotoxin" signalling (like in SIDS) combined with chronic vitamin C depletion in many tissues and cells. Many of the pathological changes typically seen in SBS cases (fractures, bruises, subdural haemorrhage etc.) are also classical features of scurvy. Now, I am not saying that these children have full-blown scurvy (called Barlow's disease in infants) however it is quite possible that some of these changes can be related to chronic vitamin C deficiency.

Imagine a SIDS child who has not quite succumbed to the escalation of SIDS pathology – they are "teetering" on the edge. With some degree of toxin signalling, just

under control (from chronic rhinitis or diarrhoea, or whatever), they are likely to suffer from vitamin C deficiency (toxin signalling dramatically lowers vitamin C levels). Another infection (synergistic toxins) or some undefined stress (like vaccination) might *push them over the edge*. These are the children I saw again and again in clinical practice in Collarenebri. Some of these children had or developed bruising but I did not have reason to suspect child abuse.

Now imagine that one of these infants, teetering on the edge, was picked up and handled slightly roughly, or even normally. A chronic vitamin C deficiency combined with mechanical pressure in the right place, could certainly produce many of the physical injuries seen commonly in SBS cases. Such a point of deviation might determine the escalation of pathological changes towards SBS, rather that SIDS. This is all very hypothetical, but like SIDS and endotoxin thirty years ago, there is a feeling in my gut that there is something in this.

This of course will be resolved, in time, as in SIDS, by timely and appropriate pathology testing and research. Maybe there is nothing in it. At present, NO tests are done at SBS autopsies to determine toxin involvement in various organs, vitamin C levels or coagulation indices. THEY ARE SIMPLY NOT DONE.

There are enough similarities with SIDS, in my mind, that suggest it is timely and prudent to routinely do a SIDS like workup in SBS autopsies. The information collected form this would fairly rapidly determine whether or not the endotoxin/vitamin C hypothesis is worthy of further research. The point, of course, is that if there are underlying pathological abnormalities in some of these children, then many cases of SBS can be prevented. Also, obviously, truly innocent parents and carers may be spared a prison sentence if these data are available.

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