Overcoming the Intracellular Synthesis Impasse of Glutathione – the “Master Antioxidant” of the Immune System.

The unique and vital delivery role of Cystine/Cysteine coupling and the importance of the sulfhydryl (SH) in detoxifying oxyradicals to preserve cell, gene, and immune health.

AMERICAN CHEMICAL SOCIETY LECTURE

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National Conference of the American Chemical Society
August 21, 2007
Overcoming the Intracellular Synthesis Impasse of Glutathione – the “Master Antioxidant” of the Immune System.

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Today, one reads a great deal of information about antioxidants and oxyradicals in laymen’s periodicals and in professional journals. I want to go to the heart of an important aspect of this crucial issue—Glutathione.

I - Some History of Glutathione. Some preconditions that highlight the body’s constant need for Glutathione synthesis and replenishment.

1. **History.** Since its discovery in 1888, Glutathione’s importance has been established in over 60,000 peerreviewed articles; its vital and diverse multiple functions have been established, but Glutathione’s bodily synthesis for optimal restoration had been a daunting challenge and elusive goal.

2. **Functions.** Over the years, it has been determined that there are at least 15 vital bodily functions and needs for Glutathione. The Sulfhydryl group on the L-Cysteine moiety plays the most crucial role in the performance of these functions.

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2 Presented at the National Conference of the American Chemical Society, August 21, 2007, Boston, MA. © 2007 Albert Crum, M.D.


4 See also Ladas & Parry “Remarks” dated February 23, 2007. © 2007 Albert B. Crum, M.D.
3. **Daily Need.** The daily need for Glutathione maintenance is heightened in an industrial society with our body’s contact with pollutants, food preservatives, stress, the aging process, the constant need for antioxidant defense, etc.

4. **Turnover Rate.** Turnover rate of Glutathione: Glutathione is completely turned over in the body in 1.5 days (every day and a half). This highlights the need for continuous replacement. Extensive scientific research\(^5\) indicates that with environmental pressures, physical “wear and tear,” high levels of oxyradicals, and the short half-life of Glutathione, the body needs continuous Glutathione replenishment.

5. **No Importation as Intact, Whole Molecule.** Glutathione, as a whole molecule, cannot be taken up by the cell. “There is no evidence that intact Glutathione can be taken up by mammals in cells.” Among other\(^6\) factors, this membrane resistance to importation is a point in the direction of bodily replenishment via intracellular synthesis.

6. **Oral Glutathione Replenishment Handicaps Over the Years.**\(^7\) Oral Glutathione as a whole molecule is metabolized in the gastrointestinal tract by trypsin and pepsin into Glutathione’s constituent amino acids. However, once these amino acids are released in the gastrointestinal tract, they cannot be re-united extracellularly into Glutathione. The hyperactive, highly oxidizable L-Cysteine is then basically on its own. Alone, outside the cell, the L-Cysteine,

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\(^7\) See also Lades & Parry “Remarks” pages 10-11.
perhaps the most important moiety of the Glutathione molecule when it is synthesized into and becomes part of the Glutathione molecule, behaves like an errant child who rushes into the street the minute you let go of its hand and it is “on its own.” The processes that achieve Glutathione synthesis require special conditions that are only present within the cell.

This has been a frequently pursued method. It would be asked: why not just take oral Glutathione—the tripeptide itself? The Glutathione molecule is metabolized by pepsin and trypsin in the gastrointestinal tract, and its three constituent amino acids are released in this digestive process.

Consequently, the released L-Cysteine is not only somewhat toxic, but it cannot be re-assimilated back into the crucially needed Glutathione molecule on an extracellular basis. The two cytosolic, ATP-dependent enzymes which are essential for the amino acids to re-assimilate and form Glutathione are only present within the cell (intracellularly).

However, Dr. Dean P. Jones of Emory University, has shown that Glutathione has local value in the protection of the gastrointestinal mucosa. In addition, some whole (intact) Glutathione does get into the blood stream. Nevertheless, this is not the way the Glutathione synthesis system has evolved. It evolved from well-established synthesis mechanisms with specific enzymes and other specialized elements for Glutathione production and replenishment—all of which are only present intracellularly.

7. **Altered Forms have Risk.** If an altered, synthetic form of Glutathione could subvert the cell membrane, it would likely not be optimal and certainly not be physiological, and the process of bypassing the highly evolved Glutathione feedback inhibition or shut-down mechanism could have consequences: α-glutamylcysteinyltransferase (vital enzyme in the shutdown
ã-glutamylcysteinesynthetase (vital enzyme in the shutdown and regulatory mechanism of Glutathione resides only within the cell, and it monitors and regulates Glutathione synthesis.)

8. **Intravenous Administration.** This method is the injection of glutathione directly into the blood stream itself. It is reported that many wealthy individuals pay thousands of dollars just to have Glutathione intravenous (IV) injections so as to bypass the biodegradation and electric charge impasse of the GI tract. This route of administration to increase bodily glutathione can be dramatically but only temporarily effective. Further, the higher plasma concentration of Glutathione does not get imported into the cells, where most of Glutathione’s work is performed. In addition, it has proved to be expensive, short-lived, and impractical. Intravenous administration of Glutathione is also considered “non-physiologic.” This means that the Glutathione is given as a “bolus” and not secreted from a cell on an “as needed” basis. Being secreted “as needed” in response to bodily needs is considered “physiologic.”

9. **Large Molecule Administration, e.g., Whey, Colostrum.** This is a concept that underlies a comparison between Immune Formulation 200® (Patent #6,592,908 B1/RE39734)\(^8\) and Immune Formulation 100™ (Patent #6,667,063 B2)\(^9\) : There are constituent vital amino acids in colostrum and undenatured whey for the synthesis of Glutathione. However, providing for one’s bodily needs, especially under adverse or stressful circumstances would require consuming large quantities of such products. Supply and administration present formidable problems. The large molecule products are also very fragile. They can be readily denatured by heat, agitation (stirring), pH, and salt concentration, and they are more biodegradable (shortened shelf life). The free form amino acids

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\(^8\) Patent Owner, Albert Crum, M.D.

\(^9\) Patent Owner Albert Crum, M.D.
have important different properties when they are in free form, as compared to their properties when they are constituents of larger protein or other molecules. Further, with amino acids in free form, it is not as if a protein has to be broken down (catabolized) in order to gain access to the desired specific amino acids. For all practical purposes, once the free form amino acids are in the gastrointestinal tract, they can be in the blood stream. In other words, it is as if they have been pre-digested. Having a supply of Immune Formulation 200® with the co-factor selenium available (a concentrated form of all the three amino acids together with the co-factor starter absolutely required that enables the intracellular synthesis of Glutathione) largely eliminates the vulnerable biodegradable problems confronting larger molecules. If one is dependent solely upon one’s food source to provide the selenium co-factor, supplying the body’s required selenium can be variable, because it is based on the selenium content in the soil where the food is grown. Once Glutathione is formed intracellularly, it still needs that “starter” as a co-factor provided by selenium, just like the best automobile in the world still needs a starter.

10. **Nasal/Mucosae.** The shortcomings in the principle of whole molecule administration apply here also. Short term, local advantage can definitely be helpful to patients in need of an immune boost, but again, it is temporary and nonphysiologic, because it does not adjust itself on an “as needed” basis continuously for use by the body.

Glutathione is a powerful molecule, and its numerous and varied capabilities need to be respected in our effort to replenish it. We do not know the immune or other consequences of bypassing this highly evolved and sensitive “shutdown” mechanism. The vital Glutathione regulatory shutdown mechanism is only present intracellularly, where, importantly, Glutathione synthesis also takes place.
II - Certain Chemical and Physiological intracellular events and conditions, that needed to be considered in the projected synthesis resolutions. Intracellular conditions favor Glutathione synthesis.

When we carefully study the various methods of Glutathione replenishment and the highly specialized cytosolic mechanisms that Nature has developed, it would seem that Nature has evolutionarily designated intracellular synthesis at the site of choice to handle the body’s Glutathione replacement.

It could be helpful now to look at the intracellular conditions which are necessary for cytosolic synthesis of Glutathione, plus certain evolutionary reasons which indicate why Glutathione replenishment is favored by these unique and specialized intracellular conditions.

It would appear reasonable that an optimal process to solve the Glutathione replenishment enigma would be to study the routes that Nature has perfected in its evolutionary adaptation over millions of years.

1. Overview: Why the Intracellular Milieu proved Sine Qua Non for Glutathione Synthesis: To help solve the Glutathione replenishment supply and synthesis issue, it seemed essential to ask why Nature would evolve the intracellular conditions so carefully adapted to Glutathione synthesis, if those conditions did not have functional purposes. Within each cell, the synthesis mechanism is so perfected, with so many finely tuned critical elements, that such highly evolved mechanisms must have specific purposes. If we visit a finely tooled manufacturing operation with its magnificent plant, outstanding equipment, highly trained expert workers, and an assembly line of Perfect Products, it would not be counterintuitive to deduct that the “set-up” we were observing had specific functions that it fulfilled to near perfection.
2. **Unique Enzymes with Substrate Specificity** \(^{10}\). Enzyme Role is Specific.

We must ask: why would Nature have evolved intracellular enzymes with such substrate specificity that they act only on the particular molecules and the specialized chemical bonds of those components needed for the assembly of Glutathione? These specific enzymes are only located in the cytosol or the protoplasm within each cell. Enzymes, in general, by their role are specific to a certain molecule and to certain covalent bonds. The following enzymes are specific to the molecular substrate for Glutathione synthesis (and the specific covalent bonds involved in that synthesis):

i. \(\alpha\)-glutamylcysteine synthetase (Shaw)

ii. Glutathione Synthetase (Shaw)

iii. \(\alpha\)-glutamyltranspeptidase (acts on L-Cystine)\(^{11}\)

iv. Thiotransferase (acts on L-Cystine)\(^{12}\)

v. \(\alpha\)-glutamyltransferase degrades Glutathione.\(^{13}\)

One must ask: "Why would Nature evolve the enzymology to be so perfected with such specific enzymes, e.g., glutamyl cysteine synthetase, glutathione synthetase, \(\alpha\)-glutamyltranspeptidase, and thiotransferase, if the intracellular mechanism were meant to be bypassed, by injecting a bolus of the whole Glutathione molecule or by other means that would bypass the careful intracellular monitoring of the shut-down regulatory mechanism?"\(^{14,15}\) To repeat,

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\(^{10}\) Packer, page 376.

\(^{11}\) Mandelker, Figure 4, page 84.

\(^{12}\) Wu et al, Figure I, page 490.

\(^{13}\) Packer, page 14.

\(^{14}\) To view the highly tuned mechanisms in place that are specific for Glutathione synthesis, see Figure 1. “Pathway for GSH synthesis and degradation” in *Glutathione in the Nervous System*, Ed. Christopher A. Shaw. Washington, DC, Taylor & Francis, © 1998, Page 6.

\(^{15}\) There are times, for example, when a person is NPO (nothing by mouth), when IV (intravenous) administration may be indicated.
these enzymes are only specific for the substrate molecules and the chemical bonds which are the components of Glutathione synthesis. These specific enzymes are only present within the cell.

3. **Ubiquitousness of Cellular Synthesis; Principle of Diversity:** Why would Nature evolve the vital Glutathione synthesis to be ubiquitous (every cell in the body) and so diverse (including liver cells, bowel cells, nerve cells, skin cells, et al), if the intracellular synthesis mechanism were meant to be bypassed or to be handled without regard for the existing, highly evolved synthesis structures?

The body has approximately 300,000,000,000,000 (300 trillion cells);¹⁶ Established research indicates that Glutathione synthesis takes place in every cell.

Principle: when a function is vitally important, Nature does not rely solely upon one system, but to insure survival of the species, Nature diversifies. Nature has placed this level of importance on the maintenance and replenishment of Glutathione. An everyday example: when Nature wants to insure a plant’s survival, it evolves mechanisms to have its seeds blown to the wind for maximum diversification of seeding places for maximum perpetuation.

4. **Selective Advantage and Protection by the Finely-Tuned Enzyme “Shut-Down”/Regulatory Mechanism:** Why would Nature evolve the Glutathione synthesis shut-down regulatory mechanism to be so perfected, if this mechanism were not meant to be functionally utilized?¹⁷ Bodily mechanisms are regulated by chemical balance. No system, no matter how vital and valuable, is allowed to proceed in an unregulated manner. Glutathione is no exception.

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¹⁷ Ibid. Shaw at page 6, Figure 1.
5. **Energy: an Enzymatic Equation cannot Proceed without an Optimal Energy Source ("Source" Meaning Pre-Energized Molecules and/or ATP).**

Having the needed energy available is essential for a synthesis equation to proceed. ATP, needed to fuel the enzymatic reactions of Glutathione, is produced and released by intracellular mitochondria.

**1st Stage:**
- enzyme: ã-glutamyl cysteine synthetases
- L-Glutamic Acid

\[ \text{L-Glutamic Acid } \rightarrow + \text{ATP } + \text{L-Cysteine } \rightarrow \text{L-ã-glutamyl-L-Cysteine} + \text{ADP } + \text{P} \]

**2nd Stage:**
- Glutathione Synthetase enzyme
- ã-glutamyl cysteine + ATP + Glycine

\[ \text{L-ã-glutamyl-L-Cysteine + ADP } + \text{P} \rightarrow \text{GLUTATHIONE} \]

6. **Mitochondria’s Intracellular Presence: Essential Role in ATP Production.**

Cytosolic Mitochondria is the supplier of the ATP, and it is the source that provides the power for chemical reactions in Glutathione synthesis. It is present only within the cell.

7. **Order of Linkage or Assembly:** Only after Stage I is completed as illustrated in #5 above, does another enzyme for Stage II come into action. Thus, Nature is indicating that a selective advantage is favored by order of sequence and the enzymes that come into play at each linkage. The synthesis enzymes do not come into action in response just to any linkage order. Once State I is completed and L-ã-glutamyl-L-Cysteine is formed, that dipeptide has different properties from the two individual or free form amino acids. That dipeptide molecule can then become the substrate for the unique enzyme, Glutathione synthetase, which can carry that dipeptide (two amino acids) to Stage II.
Principle: Specific peptide bonds are formed intracellularly which serve the purpose of stability, allowing the next stage (Stage II) of the Glutathione synthesis to proceed. The first stage captures the hyperactive cysteine and secures it in a bonded linkage.

Each linkage is unique and has different properties from the free form amino acids or the peptides preceding it.

8. **Glutathione Exportation from Cell: Meaning and Significance.** Glutathione is synthesized, replenished and stored in the cell, various sources say 90% or greater. The extracellular percent of Glutathione in plasma is small.

Glutathione is exported from the cell to the plasma on an “as needed” basis. However, its main retention and storage is within the cell, where most of its vital 15 or more essential functions are carried out.

The exportation is one way. The Glutathione molecule, as such, cannot be imported into the cell. “There is no evidence that intact glutathione can be taken up by mammalian cells.”

Nature favors movement of Glutathione from the intracellular site of its synthesis (where it is also retained and stored) to exportation extracellularly into blood plasma.

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18 Packer, page 103.
9. **No Natural Glutathione Importation into Mammalian Cells: Meaning and Significance.** “There is no evidence that intact Glutathione can be taken up by mammalian cells.” Similar statements are found elsewhere in the literature.  

Principle: this is consistent with Nature’s system in that Nature favors Glutathione’s being synthetized intracellularly where it can be monitored and carefully regulated. Further, the inner cellular milieu is where Glutathione performs most of its vital functions.

Various synthetic or electronic alterations may bypass or overcome the natural resistance of the cell membrane, but this is not physiological. We do not know if there is a risk to bypassing the natural process of Glutathione synthesis, with its carefully monitored and evolutionarily perfected shut down and self-regulatory mechanism.

10. **Reduction and pH Conditions of the Intracellular Milieu:** The intracellular cytosolic environment favors the reductive release of L-Cysteine from L-Cystine.

The reducing intracellular environment also attenuates the hyperactivity and oxidizability and toxicity of L-Cysteine. This favors L-Cysteine’s incorporation into the 1st stage of Glutathione synthesis. Why would the intracellular cytosolic milieu favor a reducing environment and a pH of ~7.35, if that reducing environment did not also favor Glutathione synthesis and maintaining the stored intracellular Glutathione in its reduced or latent state? This internal reducing environmental condition is another indication that favors Glutathione’s powerful latency’s being preserved and Glutathione’s replenishment’s being achieved on

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18 Packer, page 103.
19 Packer, page 103.
20 Shaw, page 348.
21 Mandelker, page 84.
an intracellular basis. This hypothesis is supported by research data that documents greater than 98% of the intracellular Glutathione’s being maintained in its reduced or latent form. Intracellular Glutathione is then exported extracellularly on a physiological or “as needed” basis.

11. **Metabolic Turnover Rate:** Various sources document that Glutathione in general has a short half life. The entire bodily turnover rate takes place in 1.5 days.

“Interestingly, among extra-hepatic cells the erythrocyte has a relatively high turnover rate for GSH. For example, the whole blood fraction synthesis rate of GSH in healthy adult subjects is 65%/day (reference 6), which means that all the GSH is completely replaced in 1.5 days.”

“There is a constant turnover of GSH in the body, with the liver occupying a central position in this dynamic flux; turnover of GSH in normal liver, estimated in rodents and humans, approximately 20% per hour (Reference 72).”

Principle: this rapid turnover points to the need for protection of Glutathione production in the widest possible range by maximizing cell diversity per Nature’s interest in species survival. Following Nature’s evolutionary selective advantage, when a single molecule has so many vital functions and has such a short half-life and high turnover rate, a species could not be protected unless synthesis was maximized throughout the entire organism—best estimate, 300 trillion cells! The

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23 Mandelker, L, page 88.

24 Mandelker, L., pages 88 [page 154 references 78 and 79].

25 Wu et al. Page 490.

26 Mandelker, page 84.
storage and residual site is also where Glutathione performs most of its 15 functions and where it has its “headquarters.”

12. **Location and Storage of Glutathione:** Most of Glutathione (85% to 90%) is present in and performs its functions in the cytosol, with a portion of intracellular Glutathione functioning in organelles (including the mitochondria, nuclear matrix, DNA, and peroxisomes). The portion that is present in the plasma is a small fraction.

13. **Internal Environmental Protection from Hydrolysis by Peptidases and Proteases during Intracellular Storage.**

14. **Thermodynamic Laws in Glutathione Synthesis.** The intracellular enzymatic environment is thermodynamically favorable to the anabolism of free form amino acids into Glutathione with the production of water and heat.

15. **Sulfhydryl Criteria for Maintenance of Latency (Storage) and Functionality Favored by Intracellular Milieu.** The sulfhydryl radical is highly functional for immune protection. It is oxidized (oxidizes or detoxifies oxyradicals) but it must be kept in a reduced or latent state in order not to “burn out” before it functions. It must be maintained in a reducing environment in order to preserve its latency or potency. After the sulfhydryl performs its detoxifying function, the sulfhydryl can be directed back to its reduced state. It functions by being oxidized (losing its hydrogens or electrons). Then, it restabilizes itself by regaining the hydrogens in the intracellular reducing environment. The reducing environment favors and facilitates redox recycling of the sulfhydryl moiety.

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27 Wu et al, Texas A & M, page 489.
28 Ibid. Article References 1 through 10.
29 Wu et al, page 489.
16. “Home Field Advantage:” Reasons for Redox’s (Re-Cycling) Potentiality being Favored by Intracellular Milieu. As an alligator would pull its prey into the water, where the alligator has the advantage, the sulfhydryl of Glutathione attacks or “pulls its prey” (its prey actually being a cell predator that creates oxidative stress) into its reducing environment, where the Glutathione has the home field advantage. If its “prey” (whatever event has attracted the attention of Glutathione) is confronted in a reducing environment, the Glutathione has an army of back-up, and it can recycle after being “spent.” The toxins are at the disadvantage in a reducing environment, just as an alligator’s prey is at a disadvantage in water.

17. Ribosome—Resides in Intracellular Environment—Role in Peptide Bonding/Linkage Specificity. Ribosomes carry out genetic instructions given to it by messenger RNA (mRNA). This process determines the linkage or assembly sequence of the amino acids in the formation of Glutathione.

18. Rough Endothelium Reticulum (RER) Reside in Intracellular Environment. Ribosomes are located on the RER.


Specific Raw materials must be present
L-Glutamic Acid, L-Glutamine
L-Cysteine (as L-Cystine)
Glycine
Selenium (as selenomethionine) as a co-factor.

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30 Bishop, page 145.

31 AC handwritten note says “quote Biology of Life.” NC needs “Biology of Life.”
20. **Substrate Concentration of Components in Synthesis Equation: Equation Balance is Vital for Optimal Enzyme Performance.** Inclusion of all of the vital components needed for the glutathione synthesis equation to go forward, including the co-factor selenium.

In summary, the other procedures for Glutathione synthesis by focusing mainly on L-Cysteine elevation (and not simultaneously providing for L-Glutamine and Glycine elevation) cannot chemically produce the best results for increasing Glutathione levels in the body for the following two reasons: 1) Stability: without simultaneously having sufficient levels of L-Glutamine and Glycine to keep the LCysteine stable, the maximum utilization and synthesis cannot take place, and 2) the Equation: if the two other amino acids are not present or are present in deficient quantities, the equation for Glutathione synthesis cannot optimally proceed.

Implications of this invention are most important. This method of Glutathione synthesis is reliable, safe, and physiological. Originally, I foresaw the Cystine/Cysteine interactive reversibility. I did not feel L-Cystine was inert and inactive, notwithstanding it was oxidized. This invention foresaw L-Cystine as being the primary systemic carrier of LCysteine, hence this coupling’s being the reason why LCystine could function as the primary carrier of L-Cysteine. This patent 6,592,908B1/RE39734, is also an economic way for replacement of bodily Glutathione. Scientists at RCMI\(^{32}\) and the scientists at the Culinary Institute of America feel this invention can provide low-cost immune support to a large part of the world. Scientists at RCMI have been studying the effect of these patents for replenishment of Glutathione on our immune system function. Based on

\(^{32}\)RCMI (Research Centers in Minority Institutions) is a consortium of 18 medical schools. Representative schools are Drew University for Medicine and Science.
Patent # 6,592,908 B1/RE39734, RCMI has committed research funds of $10,500,000.00 annually to conduct additional clinical trials.

For at least the previous twenty reasons, it appears that, in Nature’s ingenuity, the intracellular route is favored as the method of choice for Glutathione synthesis and replenishment and the enzymatic regulatory mechanism.

III - Synthesis Challenge and Overview. Patent 6,667,063B2 (the co-factor issue) and path to 6,592,908B1/RE39734 (elemental state).

Among the synthesis challenges, the most difficult one, since the discovery of Glutathione in 1888 boils down to L-Cysteine. L-Cysteine presents a paradox. L-Cysteine is the most functional, but also the most active and a toxic molecule, when uncombined or separate from the Glutathione molecule (or other proteins). In order to accomplish Glutathione replenishment, all the raw materials for its synthesis must first achieve intracellular status and reach a specific end-stage ratio. Over the 36 years, L-Cysteine delivery has presented the greatest challenge and the greatest enigmatic problem.

Reasons: although it is the most functional moiety of Glutathione, with its Sulphydryl group, the L-Cysteine component is the most difficult to attain intracellular status. This is owing to the fact that, alone, it is so highly active; it gets diverted by interacting with other compounds; it is highly oxidizable; when alone, it can be toxic to neighboring cells and other molecules, i.e., it is especially neurotoxic, and it can also interact with and disrupt certain neurotransmitters.

Challenges Encountered:
1. Cysteine toxicity/cysteine oxidizability and instability.
2. Handicap of Larger Protein Molecules.
3. Need for Co-Factor Availability.
5. Equation Balance/Substrate Concentration.
IV - Steps to Resolution

1. Cystine

Now that we see that Nature points to the internal milieu of each cell as the Glutathione synthesis site, we are faced with the challenge of safely transporting the elusive, highly active, readily oxidizable, and toxic L-Cysteine into the cell, where it is essential in the 1 Stage of Glutathione synthesis.\(^{33}\)

Why did Nature evolve the coupling of Cysteine/Cystine to be so interactive, interrelated, readily interchangeable and reversible, if there were not an important function(s) being served by that coupling? Reasons why the disulfide bond, hence L-Cystine, may have been overlooked. Durability of the S-S can be misleading. One might be tempted to underestimate the versatility and diversity of Nature. When one looks at a few (#8) examples of the disulfide bond, one is tempted to think in terms of permanence and irreversibility, i.e., that the double-bond is static and hence non-functional.

Look at some examples of S-S durability.

- The hair (S-S) in Egyptian tombs that has lasted thousands of years.
- The vulcanization of rubber.
- The S-S bonds in antibodies.
- The S-S bonds between protamines in sperm.
- The stability provided by the S-S bond in protein folding.
- “These disulfide (S-S) bridges generate a ring that greatly limits molecular shape.” This provides durability and strength and resistance to lysis.
- The bond’s resistance to hydrolysis, and the vigorous digestive enzymes, pepsin and trypsin.

• Once the sulfhydryl has been oxidized, it may appear as if it’s life is over, finished! However, Nature is amazing. It functions on a menu of diversity, alternatives, backup systems, and options (potentialities) held in reserve. In Nature’s plan, a substance can be toxic under one set of parameters and can be life-saving and vital in another range or circumstance.

The versatility, interchangeability, and reversibility of the L-Cystine thiol covalent bond that links the L-Cysteine molecules to L-Cystine has possible quantum dynamic significance and implications in terms of its interactivity and maintenance of various states. In an associative way, one could be reminded of quantum wave-particle interactivity. While in the interactive coupled state, the toxicity and hyperactivity and individual features of L-Cysteine are held in abeyance or “suspension.” The individual traits of the molecule are overridden by the coupling.

Summary of Attributes of the Disulfide Bond and, hence L-Cystine: Using L-Cystine is consistent with a system that Nature has evolved and favored and on which I based my rationale for Patents US 6,667,063 B2 (2003), US 6,592,908 B1 (2003), and US RE39734 (2007). Its benefits are as follows:


A. The features of the unique and vital-for-life disulfide bond, including the redox potential of the disulfide bond:

• Electron transfers.
• Interchangeability
• Interactivity
• Cycling
• Reversible switch
B. The fact that L-Cystine is stable but not inert. I like to refer to L-Cystine as “a sleeper;” however, it is readily awakened!

C. L-Cystine has a melting point of 260° C. and can withstand high temperatures. One can utilize Immune Formulation 200® to increase bodily Glutathione, via orally ingestable food.

D. The L-Cystine double bond (disulfide) can resist pepsin and trypsin digestive enzymes in the gastrointestinal system. Thus, L-Cysteines are not released until L-Cystine enters the cell.

E. L-Cystine can safely carry 2 Cysteines and only release them intracellularly via the cell membrane in the presence of the needed and vital cytosolic enzymes.

F. L-Cystine, as a molecule to carry L-Cysteine, is more stable than the large molecules found in whey and colostrum which are the other rich sources of L-Cystine and L-Cysteine. When individual amino acid molecules are in the gastrointestinal tract, they can, for practical purposes, be considered in the blood stream, where they can be taken up by individual cells.

G. L-Cystine, as an individual molecule, has a low molecular weight. Therefore it has greater versatility and endurance and stability than when it is present in larger peptides or proteins.

H. L-Cystine with its disulfide is a stable molecule which is not readily hydrolyzed. The disulfide bond is adapted to resist hydrolysis and degradation.

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I. L-Cystine is nontoxic.

J. L-Cystine promptly releases L-Cysteine after it enters the cell membrane, where a genetically programmed intracellular ribosome can assist making the appropriate linkage.

K. L-Cystine can enter other cells that are on the front line of immune protection: macrophages and astrocytes, lymphocytes, and neurons.

L. The simple molecule of L-Cystine has greater bioactive advantages over unpasteurized or low pasteurized, undenatured whey or colostrum.

M. L-Cystine molecules can withstand more mechanical agitation than large molecules of whey and colostrum, other rich sources of L-Cystine.

N. L-Cystine can withstand greater pH variations.

O. L-Cystine is not readily biodegradable as are large protein molecules such as whey or colostrum. L-Cystine has a longer “shelf-life.”

P. L-Cystine is Nature’s safe, stable but reversible carrier of two L-Cysteines.

Q. L-Cystine and L-Cysteine have a natural affinity for each other via a covalent bond interactivity.

R. The toxicity, oxidizability, reactivity of L-Cysteine are held in abeyance by its coupling with L-Cystine.

S. L-Cystine’s disulfide bond has evolved to be the ideal LCysteine carrier.
2. **Free Form (Elemental State) Rationale** – such as Vitamin C principle. In this case, by using the free form of the amino acids (i.e., not being a part of the larger protein molecules in colostrum and whey), their elemental properties become available. For example, the constituent elemental amino acids are more soluble and have strong resistance to acidity/pH ranges, agitation, salts, and high temperatures, etc.

3. **Co-Factor Supplementation.** Inclusion of all of the vital components needed for the Glutathione synthesis equation to go forward, i.e., the co-factor selenium.

4. **Derivatives.** The novel use of derivatives and precursors, including esters and anhydrides.

5. **Balance in the equation so reaction can proceed:** Other procedures for Glutathione synthesis by focusing mainly on L-Cysteine elevation (and not simultaneously providing for L-Glutamine and Glycine elevation) cannot chemically produce the best results for increasing Glutathione levels in the body for the following two reasons:

   1) **Stability:** without simultaneously having sufficient levels of L-Glutamine and Glycine to keep the L-Cysteine stable, the maximum utilization and synthesis cannot take place, and
   2) the **Equation:** if the two other amino acids are not present or are present in deficient quantities, the equation for Glutathione synthesis cannot optimally proceed. The equation can be held back by the quantity of the lowest denomination.
Conclusions: This Cystine/Cysteine coupling is special and unique. Subsequent to issuance in 2003 of my Patent US 6,592,908 B1, which focused on the carrier interrelationship between Cystine/Cysteine, recent research has discovered that this coupling also has a signaling function which is so important that it actually redefines oxidative stress.36

On L-Cystine’s entering the cell, the individual LCysteines are released from L-Cystine, where the L-Cysteines can be effectively and efficiently incorporated into the Glutathione synthesis (again, see Diagram of Glutathione synthesis with text from Patent US 6,592,908 B1 by Albert B. Crum, M.D.). When not used in Glutathione synthesis, the LCysteines can be used for protein synthesis, used for other nutritional benefits, or otherwise metabolized and excreted.

To repeat, Glutathione is a powerful molecule. Its numerous capabilities needed to be appreciated in order to elucidate the optimal way to replenish it. This synthesis problem was able to be solved by observing carefully and tracking persistently the systems and the evolutionary routes that Nature had adapted and perfected over millions of years.

End