# Cysteine/Glutathione Deficiency: A Significant and Treatable Corollary of Disease

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## 20.1 Introduction

Life-threatening hepatotoxicity in the setting of acetaminophen (APAP) overdose is due to depletion of glutathione (GSH), a vital cysteine-containing tripeptide that protects cells and organs against oxidant injury. GSH depletion can occur when supplies of cysteine are inadequate to maintain GSH homeostasis in the face of the increased GSH consumption. Thus, rapid administration of N-Acetylcysteine (NAC), which is converted to cysteine by first-pass metabolism and provides the cysteine necessary to replenish the depleted GSH, is the standard of care for preventing injury in APAP overdose.

GSH deficiency has also been recognized in a variety of apparently unrelated clinical conditions and diseases. NAC has been widely tested in randomized placebo-controlled trials (RPCTs) for efficacy in these diseases and conditions. In this chapter, we systematically review reports from early trials of NAC, which collectively suggest that GSH deficiency may be a common occurrence and that NAC may be a useful therapeutic adjunct for treating or preventing the development of this deficiency.

## 20.2 Methods

Publications included in this systematic literature review describe results from RPCT testing NAC for efficacy in a variety of disease settings. Publications were located by searching with the keywords "placebo AND N-Acetylcysteine AND NOT animal" as well as "placebo AND N-Acetylcysteine AND human, AND NOT animal." We searched PubMed, the NLM database, the FDA website, Cochrane Database, Google, and subsequent material through 2006 and the references lists of all placebo- and non-placebo-controlled trials that we review here. This search identified nearly 2000 relevant publications. Within these, we identified 102 RPCTs that met the strict criteria for inclusion that we set for this review, i.e., publications reporting results from RPCT in which at least 10 subjects were used to test the efficacy of NAC administered without other drugs. Findings reported for these trials are summarized in tabular form (Online Tables 20.2 and 20.3) and discussed in the text. Trials excluded are listed in Online Table 20.1. Clinical studies relevant to the findings here but not conducted under strictly controlled conditions are found in Online Table 20.4.

## 20.3 Results

### 20.3.1 Glutathione (GSH)

Rapid administration of NAC is the standard of care for preventing hepatic injury in APAP overdose. The administered NAC is converted by first-pass metabolism to cysteine, which is needed to replenish the cysteine-containing intracellular tripeptide (L-γ-glutamyl-L-cysteinyl-glycine), commonly known as GSH. GSH is depleted

during detoxification of excessive amounts of APAP. If it is not rapidly replenished, severe hepatic injury ensues.

In addition to this well-known use of NAC, at least 102 RPCTs conducted over 25 years have examined the effects of NAC treatment in respiratory, cardiovascular, endocrine, and infectious and other disease settings. Of these, 72 reported beneficial effects (Keays et al. 1991; Jackson et al. 1984; Ardissino et al. 1997; Andersen et al. 1995; Altomare et al. 1996; Aylward et al. 1980; Akerlund et al. 1996; Adair et al. 2001; Bromley et al. 1995; Badaloo et al. 2002; Boesgaard et al. 1992; Brocard et al. 1980; Bernard et al. 1997; Breitkreutz et al. 2000b; Bowles and Goral 1985; Diaz-Sandoval et al. 2002; Drager et al. 2004; De Mattia et al. 1998a, b; Dueholm et al. 1992; De Backer et al. 1996; De Flora et al. 1997; De Rosa et al. 2000; Estensen et al. 1999; Eren et al. 2003; Efrati et al. 2003; Evald et al. 1989; Fischer et al. 2004; Fulghesu et al. 2002; Ferrari 1980; Boman et al. 1983; Grassi 1980; Grassi and Morandini 1976; Horowitz et al. 1988a, b; Hansen et al. 1994; Heinig et al. 1985; Hauer et al. 2003; Herzenberg et al. 1997; Kay et al. 2003; Kasielski and Nowak 2001; McGavin 1985; MacNeill et al. 2003; Olivieri et al. 1985; Ovesen et al. 2000; Pace et al. 2003; Parr and Huitson 1987; Reinhart et al. 1995; Ratjen et al. 1985; Rasmussen and Glennow 1988; Rank et al. 2000; Shyu et al. 2002; Scholze et al. 2004; Spies et al. 1994, 1996; Spapen et al. 1998; Spada et al. 2002; Suter et al. 1994; Svendsen et al. 1989; Stafanger et al. 1988; Stafanger and Koch 1989; Tepel et al. 2000, 2003; Tepel and Zidek 2001; Tossios et al. 2003; Todisco et al. 1985; Verstraeten 1979; Van Schooten et al. 2002; Walters et al. 1986; Watt et al. 2002; Wiklund et al. 1996; Yalcin et al. 2002). Collectively, these findings suggest that cysteine/GSH deficiency contributes to the pathophysiology of a wide range of diseases and that treatment of this deficiency may be important in these diseases.

GSH is a central component of the oxidative-reductive (redox) apparatus of every cell. One of its key functions is to combine with, and thereby inactivate (detoxify), reactive oxygen species (ROS), other oxidative molecules, and certain drugs, exogenous chemicals, and toxins. Because GSH is depleted in these reactions, it must continually be replenished to maintain cell and organ viability and to support normal cellular functions. Drug intoxications resulting in severe GSH depletion, notably APAP overdose, cause extensive hepatic injury if treatment to replenish GSH is not initiated before GSH stores are depleted to below-critical protective levels.

Synthesis of GSH requires cysteine, a conditionally essential amino acid that must be obtained from dietary sources or by conversion of dietary methionine via the cystathionase pathway. If the supply of cysteine is adequate, normal GSH levels are maintained. In contrast, if supplies of cysteine are inadequate to maintain GSH homeostasis in the face of increased GSH consumption, GSH depletion occurs.

GSH depletion impacts a wide variety of cellular processes, ranging from DNA synthesis and gene expression to sugar metabolism and lactate production. The pleiotropic activity of this key intracellular molecule, which arose very early in evolution, derives from its participation in the energy economy and the synthetic

and catabolic activities of virtually all cells. In higher animals, it also participates in regulating the expression or activity of extracellular molecules, including many of the cytokines and adhesion molecules implicated in inflammatory reactions and other disease processes.

Acute GSH depletion causes severe—often fatal—oxidative and/or alkylation injury. This injury can be prevented (e.g., in APAP overdose) by rapid treatment with NAC, an efficient nontoxic source of cysteine, which is able to replenish hepatocellular GSH. Chronic or slowly arising GSH deficiency due to administration of GSH-depleting drugs, or to diseases and conditions that deplete GSH, can be similarly debilitating (Taniguchi et al. 1989).

In this chapter, we first review evidence for a cysteine/GSH deficiency in a variety of disease settings and consider the biochemical mechanisms through which this deficiency, and its correction, can impact disease processes. We then consider findings from a large series of RPCT in which the effectiveness of NAC treatment has been investigated and discuss this in terms of cysteine/GSH replenishment.

### 20.3.2 GSH Deficiency and Disease

A role for GSH deficiency in the clinical manifestations of a broad spectrum of diseases and conditions is suggested either by the direct documentation of low GSH levels in these conditions or by the demonstration of significant improvement in patient condition following NAC administration. Over 70 RPCTs demonstrate beneficial effects of NAC treatment (Online Table 20.2) (Keays et al. 1991; Bromley et al. 1995; Estensen et al. 1999; Reinhart et al. 1995; Ardissino et al. 1997; Badaloo et al. 2002; Boesgaard et al. 1992; Horowitz et al. 1988a, b; Spies et al. 1996, 1994; Svendsen et al. 1989; Andersen et al. 1995; Eren et al. 2003; Fischer et al. 2004; Tossios et al. 2003; Altomare et al. 1996; Diaz-Sandoval et al. 2002; Drager et al. 2004; Efrati et al. 2003; Kay et al. 2003; MacNeill et al. 2003; Shyu et al. 2002; Tepel et al. 2000, 2003; Tepel and Zidek 2001; De Mattia et al. 1998a, b; Fulghesu et al. 2002; Pace et al. 2003; Ratjen et al. 1985; Stafanger et al. 1988; Stafanger and Koch 1989; Scholze et al. 2004; Wiklund et al. 1996; Aylward et al. 1980; Boman et al. 1983; Brocard et al. 1980; Dueholm et al. 1992; Evald et al. 1989; Ferrari 1980; Ferrari and Spinelli 1980; Grassi 1980; Grassi and Morandini 1976; Hansen et al. 1994; Heinig et al. 1985; Jackson et al. 1984; McGavin 1985; Parr and Huitson 1987; Rasmussen and Glennow 1988; Kasielski and Nowak 2001; Verstraeten 1979; Olivieri et al. 1985; Van Schooten et al. 2002; Todisco et al. 1985; Bernard et al. 1997; De Backer et al. 1996; Suter et al. 1994; Rank et al. 2000; Spapen et al. 1998; De Flora et al. 1997; Akerlund et al. 1996; Breitkreutz et al. 2000b; De Rosa et al. 2000; Herzenberg et al. 1997; Spada et al. 2002; Watt et al. 2002; Adair et al. 2001; Hauer et al. 2003; Ovesen et al. 2000; Walters et al. 1986; Yalcin et al. 2002; Bowles and Goral 1985) in diseases and conditions that include systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), chronic lung disease (CLD), chronic obstructive pulmonary disease (COPD), neurodegenerative disease, cardiovascular disease, alcoholism, infectious disease (e.g., HIV-1

infection and chronic hepatitis), hepatic and renal failure, diabetes, malnutrition, and certain autoimmune diseases.

The mechanisms that underlie the development of GSH deficiency in disease are reasonably well understood, at least in some instances. A wide variety of inflammatory and metabolic stimuli common during active disease increase the production of intracellular oxidants. In addition, neutrophils and other cells present at sites of inflammation release oxidants (reactive oxygen and nitrogen intermediates) that enter other cells and add to the internal oxidant burden. GSH provides the main defense against toxic oxidative intermediates by reducing and thereby inactivating them. However, in so doing, GSH is oxidized to GSH disulfide (GSSG). GSSG is then either rapidly reduced to GSH by GSSG reductase and NADPH or is excreted from the cell and only in part recovered from the circulation.

Factors that may contribute to GSH deficiency include GSH losses that occur when GSH is enzymatically conjugated to exogenous chemicals (drugs, dietary components, and toxins) and excreted from the cell as GSH or acetylcysteine mercapturates (conjugates). In addition, disease processes may decrease the cellular uptake or synthesis of cysteine or cystine, increase GSH efflux (Abrams et al. 1995), or increase the loss of cysteine/GSH sulfur due to accelerated oxidation to the final oxidized forms (sulfate and taurine) (Hortin et al. 1994; Breitkreutz et al. 2000a). Because a balance between cysteine supply and GSH utilization must be maintained, if oxidant production or levels of substrate for GSH conjugation are high and cysteine supplies for GSH replenishment become limiting, severe GSH deficiency may occur.

Importantly, there are significant potential iatrogenic contributions to GSH depletion. Inadvertent treatment with higher doses of APAP than patients can tolerate is perhaps the most common. This can be particularly dangerous for patients with conditions in which GSH depletion tends to occur as a consequence of the disease process or following treatment with drugs that are detoxified by GSH. In addition, long-term maintenance on parenteral nutrition may result in GSH depletion since parenteral nutrition formulations are not necessarily designed to provide adequate cysteine equivalents to meet the metabolic needs of diseased patients. In the absence of adequate attention to maintenance of adequate cysteine supplies, physicians and other caregivers can inadvertently contribute to GSH deficiency.

Patient behavior may also result in the development of GSH deficiency. Chronic over-consumption of alcohol is well known to deplete GSH in certain tissues, particularly the liver, and thus to render patients susceptible to APAP toxicity at doses well below those that cause toxicity in healthy individuals. Indeed, the FDA has issued a warning to this effect (www.fda.gov/ohrms/dockets/ac/02/briefing/3882b1.htm). However, chronic consumption of APAP or other GSH-depleting drugs, even well below toxic dose levels, can gradually deplete GSH to the point where these drugs elicit toxicity. Such practices become more dangerous if patients are malnourished or are GSH deficient for other reasons.

In summary, GSH deficiency occurs more frequently than previously suspected. GSH is readily replenished by de novo synthesis as long as sufficient supplies of cysteine are available, either directly from dietary sources or indirectly by conversion of dietary methionine. However, failure to obtain sufficient dietary cysteine to

replace that lost when GSH is oxidized or conjugated to drugs or exogenous chemicals results in a deficiency in cysteine and/or GSH that may necessitate pharmacological intervention.

### 20.3.3 Dietary Sources of Cysteine

Cysteine utilized in the body is derived from dietary cysteine and methionine, sulfur-containing amino acids (SAAs) that are largely obtained from digested protein. Since mammals obtain cysteine both directly from the diet and by degradation of dietary methionine, the normal cysteine requirement can be satisfied from dietary sources. However, as indicated above, an additional source of cysteine may be required when cysteine loss (e.g., via GSH loss) outstrips the usual dietary supply.

Requirements for SAAs in humans are based upon nitrogen and SAA balance studies conducted with healthy individuals. The average American diet contains about 100 g of protein daily, greater than half of which is animal protein with a relatively high content of SAAs. The recommended daily allowance (RDA) for SAAs for an adult male is about 1 g (200 mg of methionine and an additional 810 mg of methionine that can be replaced by an equivalent amount of cysteine). A healthy, well-fed person will often consume greater than twice the SAA RDA. However, poor appetite and/or a tendency to select fresh food with low SAA content or bioavailability (Hitchins et al. 1989) or processed food depleted of SAAs (Volkin and Klibanov 1987; Schnackenberg et al. 2009; Briganti et al. 2008) can result in cysteine deficiency even in otherwise healthy people. Furthermore, as evidence here indicates, the need for SAAs can be substantially increased in many disease states.

The limited ability of the body to store amino acids is an additional problem. The human liver does contain a reservoir of cysteine (about 1 g) that is largely present in GSH. Since this amount approximates the daily SAA requirement, it provides only a short-term source to maintain a stable cysteine supply despite intermittent methionine and cysteine consumption. Under conditions of excessive cysteine requirements or deficient cysteine/methionine consumption, GSH is released from skeletal muscle and other tissues to supply cysteine. This results in decreased antioxidant and detoxification functions throughout the body. Consequently, even short-term inadequate intake of SAAs can pose a risk to individuals who may consume adequate amounts most of the time (Larsen and Fuller 1996; Shriner and Goetz 1992).

### 20.3.4 Mechanisms that May Mediate the Clinical Effects of Cysteine/GSH Deficiency

GSH has multiple roles in cells, ranging from neutralization of ROS to acting as a coenzyme in a variety of metabolic processes. The widespread participation of GSH in biochemical reactions of importance to cell growth, differentiation, and function offers mechanistic insights into how interfering with GSH homeostasis could influence the course of varied disease processes. A full discussion of the preclinical data

bearing on these issues is beyond the scope of this review. However, to provide a mechanistic context for the clinical findings we discuss, we have summarized some of the key processes regulated by GSH in the following section.

#### 20.3.4.1 Oxidative Reactions

In its best-known role, GSH participates in enzyme-mediated reactions to neutralize ROS, preventing the accumulation of ROS damage to DNA, proteins, and lipids. Glutathione peroxidases play a key role in this process by catalyzing the reaction of GSH with peroxides, including hydrogen peroxide and lipid peroxides. Thus, decreasing GSH can sharply augment oxidative damage and result in cell death or loss of function.

#### 20.3.4.2 DNA Synthesis

Low GSH availability can impair DNA synthesis since GSH acts (via thioredoxin) as a coenzyme for ribonucleotide reductase, an enzyme required for the synthesis of DNA (Holmgren 1985, 1989; Zhong et al. 2000a).

#### 20.3.4.3 Gene Expression and Signal Transduction

GSH has been shown to regulate or influence the expression of several genes, notably inflammatory genes under the control of transcription factor nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), even in settings where there is no marked overproduction of ROS. In addition, GSH has been shown to regulate T-cell signaling by controlling phosphorylation of phospholipase C γ 1 (PLCg1), which is required to stimulate the calcium flux that occurs early in the T-cell receptor-signaling cascade (Kanner et al. 1992a, b, c; Kanner and Ledbetter 1992; Flescher et al. 1994). Importantly, GSH has also been shown to regulate the expression of vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells, one of the early features in the pathogenesis of atherosclerosis and other inflammatory diseases (Ahmad et al. 2002; De Mattia et al. 1998a, b; Marui et al. 1993; Schmidt et al. 1995; Weigand et al. 2001).

#### 20.3.4.4 Enzymes and Protein Functions

GSH regulates the activity of enzymes and other intracellular molecules by post-translational modifications (glutathionylations) that control the oxidation state of protein-SH groups. When intracellular GSH is at its normal level for a particular cell type in a healthy individual, most of the free protein thiol groups are reduced, i.e., are present as protein-SH. In contrast, when GSH levels are low and/or GSSG levels are increased, GSH is reversibly coupled to many free thiols to create mixed disulfides (protein-S-S-G) (Ghezzi et al. 2002). These *S*-glutathionylated proteins, which may be functionally altered, then persist as such until GSH levels return to normal.

By controlling the activities of a series of enzymes and other intracellular proteins, glutathionylation can rapidly and reversibly alter the metabolic status of cells in response to changes in the redox environment. For example, glutathionylation

has been shown to regulate actin polymerization (Wang et al. 2001), to inhibit the activity of several key enzymes (including glyceraldehyde-3-phosphate dehydrogenase, carbonic anhydrase, and protein tyrosine phosphatase), and to activate or stabilize other enzymes (including HIV-1 protease and the NF-κB transcription factor (Pineda-Molina et al. 2001)). Nitrosylation of protein thiols has similarly been shown to increase under oxidative conditions (Galli et al. 2002; Choudhary and Dudley 2002; Estevez and Jordan 2002; Yang et al. 2002) and to alter functions of key enzymes (Arnelle and Stamler 1995) and other molecules (Gow et al. 2002; Marshall et al. 2002). Thus, both glutathionylation and nitrosylation are of central importance to mechanisms through which cysteine/GSH deficiency may impact cell, and hence organ, function.

As indicated above, these types of posttranslational modifications are highly sensitive to shifts in the intracellular redox balance. They are rapidly initiated when GSH is depleted and rapidly reversed when GSH is replenished. As such, they provide the kind of flexible response to oxidative stress necessary for organisms living in an oxidative environment. However, at the extreme, they may underlie some of the pathologic changes that occur when chronic cysteine/GSH deficiency occurs in disease.

#### 20.3.4.5 Glutaredoxin and Thioredoxin

Glutaredoxin (Grx) and thioredoxin (Trx) belong to the two major oxidoreductase enzyme families, which take electrons from GSH and NADPH respectively (Zhong et al. 2000a; Holmgren 1989; Cotgreave et al. 2002; Nakamura et al. 2001; Vlamis-Gardikas and Holmgren 2002). Trx and Grx interact with proteins to regulate functional activity, both directly and via glutathionylation. Intracellular GSH and GSSG levels play a major role in this regulation. The activity of Grx is directly regulated by the amount of intracellular GSH and GSSG, which controls the status of the Grx active site. The active sites in Trx (Cys-Gly-Pro-Cys) and Grx (Cys-Pro-Tyr-Cys) contain a dithiol that can be oxidized when GSH levels are low (or GSSG levels increase) to form an internal disulfide between the two cysteine residues or a mixed disulfide in which GSH is bound to one or both cysteine residues in the active site.

Formation of the Grx mixed disulfide (Casagrande et al. 2002; Cotgreave et al. 2002; Ghezzi et al. 2002) represents a special case of protein glutathionylation since it arms the Grx for glutathionylation of other proteins. Although Trx can also be glutathionylated (Casagrande et al. 2002), current data indicate that glutathionylation is mainly mediated by the Grx mixed disulfide (Daily et al. 2001; Shenton et al. 2002; Song et al. 2002). Oxidation of Grx and Trx active sites can also regulate Trx or Grx functions mediated by direct binding to key intracellular proteins. For example, under reducing conditions, Trx and Grx protect cells from apoptosis by binding to and inactivating apoptosis signaling kinase I (Song et al. 2002; Saitoh et al. 1998), whereas this binding is blocked, and apoptosis induction proceeds at low GSH levels (and/or high GSSG levels; Arner and Holmgren 2000).

#### 20.3.4.6 Selenoenzymes

Decreasing GSH increases the intracellular redox potential of the GSH/GSSG redox couple and puts an additional burden on the Trx-Trx reductase system. This may be quite important in patients who have low selenium levels, since human Trx reductases are selenoenzymes with an essential selenocysteine residue in the active site (Arner and Holmgren 2000; Gladyshev et al. 1996a, b; Sandalova et al. 2001; Zhong et al. 2000a, b; Zhong and Holmgren 2000). Cysteine/GSH deficiency in these patients, in whom Trx reductase activity is compromised, may make them particularly susceptible to cell damage under oxidative stress. Thus, cysteine/GSH deficiency can impact cell and organ function through multiple pathways operating at the same or different sites, depending on the underlying mechanisms responsible for depleting GSH. The fact that multiple different pathways are affected explains why the effects of cysteine/GSH deficiency can affect many diseases and why cysteine/GSH deficiency has not been readily recognizable as a single clinical entity in the past.

### 20.3.5 N-Acetylcysteine (NAC) Treatment to Relieve Cysteine/GSH Deficiency

Clinical experience in the treatment of APAP toxicity has established that rapid administration of NAC, an essentially nontoxic cysteine source, restores normal GSH levels in solid tissues and the systemic circulation and thus prevents the potentially lethal consequences of severe cysteine/GSH deficiency induced by APAP overdose. In addition to this well-known role for NAC, NAC treatment has been shown to be clinically beneficial in a wide variety of diseases and conditions. In fact, over 70 RPCTs (Online Table 20.2) have reported beneficial effects of NAC treatment. Collectively, these studies demonstrate that cysteine/GSH deficiency is an important emerging clinical entity and that NAC administration offers an effective method for treating this deficiency.

Although various forms of cysteine and its precursors have been used as nutritional and therapeutic sources of cysteine, NAC is the most widely used and extensively studied. NAC is about ten times more stable than cysteine and much more soluble than the stable cysteine disulfide, cystine. L-2-oxothiazolidine-4-carboxylate (procysteine/OTC) has also been used effectively in some studies (Aaseth and Stoa-Birketvedt 2000) as have GSH and GSH monoethyl ester (Meister et al. 1986). In addition, dietary methionine is an effective source of cysteine, as is *S*-adenosylmethionine (referred to either as SAM or SAM-e) (Castagna et al. 1995). We focus on NAC in this review because NAC is the cysteine source used for correcting cysteine/GSH deficiency in most studies and because NAC is already approved for therapeutic use for treatment of APAP overdose and as a mucolytic agent in cystic fibrosis.

Surprisingly, given the diverse roles that GSH plays in cellular physiology and regulation of enzyme activity and protein function (see above), GSH deficiency has mainly been discussed from a clinical perspective in terms of the loss of

intracellular protection against oxidative stress. Similarly, NAC is principally considered to be an antioxidant rather than a source of cysteine for GSH replenishment. However, while antioxidants such as vitamins E and C can spare GSH under conditions of oxidative stress, GSH loss due to oxidative or detoxifying reactions can only be offset by GSH resynthesis, which requires a cysteine source.

In addition to providing the cysteine necessary to replenish GSH, NAC administration improves the cysteine supply for protein synthesis and metabolic purposes. When administered intravenously, it also appears for a short period of time at high levels in blood and can react directly with oxidants and nitric oxide derivatives. However, when administered orally (as in most of the studies), it is rapidly converted by first-pass metabolism to cysteine, which is either incorporated into GSH in the liver or released into the blood in a regulated manner. Thus, orally administered NAC appears in the circulation only transiently and at only minimal levels. Hence, it is effective largely via its ability to increase cysteine supplies and thereby facilitate the GSH replenishment.

In the sections that follow, we discuss examples of RPCTs (Online Table 20.2) which have examined the outcomes of NAC therapy in various medical disorders. We also discuss selected findings from observational studies (Online Table 20.3) that further illuminate clinical aspects of cysteine/GSH deficiency.

#### 20.3.5.1 Acetaminophen Toxicity

APAP overdose is a well-known cause of fulminant hepatic failure. In fact, APAP overdose and idiosyncratic drug reactions have now replaced viral hepatitis as the most frequent causes of acute liver failure in the United States (Ostapowicz and Lee 2000). The toxicity of APAP is due to depletion of GSH in hepatocytes (Mitchell et al. 1974, 1981; Peterson and Rumack 1978; Lauterburg et al. 1983; Smilkstein et al. 1988; Ostapowicz et al. 2002). NAC is extremely effective in preventing liver damage due to APAP toxicity. NAC administered promptly and at a sufficient dose is the standard of care for treatment of APAP poisoning (Mitchell et al. 1974; Lyons et al. 1977; Prescott et al. 1977; Peterson and Rumack 1977a, b, 1978; Marquardt 1977; Maurer and Zeisler 1978; Macy 1979; Stewart et al. 1979; Bailey 1980; Black 1980; Sellers and Freedman 1981; Rumack et al. 1981; Prescott and Critchley 1983; Miller and Rumack 1983; Rumack 1984, 1986, 2002; Davis 1986; Larrauri et al. 1987; Slattery et al. 1987, 1989; Smilkstein et al. 1988, 1991; Burgunder et al. 1989; Beckett et al. 1990, 1985; Harrison et al. 1990; Keays et al. 1991; Bray et al. 1991; Winkler and Halkin 1992; Lee 1993, 1995, 1996; Larsen and Fuller 1996; De Roos and Hoffman 1996; Perry and Shannon 1998; Salgia and Kosnik 1999; Ammenti et al. 1999; Buckley et al. 1999; Broughan and Soloway 2000; Kearns et al. 2000; Woo et al. 2000; Amirzadeh and McCotter 2002; Schmidt et al. 2002; Jones 2002; Kearns 2002; Peterson et al. 1998) and can improve survival (Harrison et al. 1990) and cardiovascular function (Harrison et al. 1991) in those already with hepatic failure.

Interestingly, although the acute dose of APAP likely to cause severe liver toxicity is well established for healthy individuals (Peterson and Rumack 1978), under conditions in which GSH levels are compromised, doses of APAP that are within the usual prescribed range can cause hepatic injury (Peterson and Rumack 1978;

Larsen and Fuller 1996). Thus, usage of APAP and other GSH-depleting drugs may be quite important to overall pathology in diseases and conditions where GSH deficiency is known to occur.

This is especially important in patients with chronic alcohol consumption (Bray et al. 1991; Salgia and Kosnik 1999) because they often have lower GSH levels. In such patients, doses of APAP below those usually considered toxic could deplete GSH below the critical threshold for hepatocellular necrosis (Lauterburg and Velez 1988). Thus, it has been suggested that patients with chronic alcoholism and suspected APAP poisoning should be treated with NAC regardless of risk estimation (Johnston and Pelletier 1997; Ozaras et al. 2003; Moss et al. 2000). This has prompted the FDA to a special warning for individuals with chronic alcohol use in regard to APAP use.

#### 20.3.5.2 Gastrointestinal Disease

Several studies have demonstrated GSH depletion in children with the edematous syndromes of protein-energy malnutrition (PEM), kwashiorkor, and marasmic kwashiorkor (Badaloo et al. 2002; Golden and Ramdath 1987; Jackson 1986; Reid et al. 2000). Children with edematous PEM have biomarkers of oxidant damage (Lenhartz et al. 1998; Fechner et al. 2001). The observation that biomarkers of oxidant damage normalize as soon as clinical signs and symptoms resolve (Lenhartz et al. 1998) suggests that oxidant damage plays an important role in the pathogenesis of the disease.

In a study of children with edematous PEM, Jahoor and colleagues showed that RBC GSH depletion is due to a slower rate of GSH synthesis secondary to inadequate cysteine availability (Reid et al. 2000). In another study of children with edematous PEM, Jahoor and colleagues demonstrated that GSH synthesis rate and concentration can be restored during the early phase of nutritional rehabilitation if diets are supplemented with NAC (Badaloo et al. 2002). The observation that edema is lost at a faster rate by the group whose GSH pools were restored early with NAC suggests that early restoration of GSH homeostasis accelerates recovery. This possibility is supported by another study showing that increases in GSH levels in children with kwashiorkor are associated with recovery (Fechner et al. 2001).

These findings also raise the question of whether the modest malnutrition common in elderly people, who also frequently have low GSH levels (Anderson et al. 1993, 2001), puts the elderly at risk for developing clinically significant cysteine/GSH deficiency and hence at increased risk of hepatic and other tissue injuries associated with consumption of GSH-depleting pharmaceuticals such as APAP.

#### 20.3.5.3 Kidney Transplantation

Delayed graft function (DGF) after kidney transplantation is probably in large part caused by production of ROS following reperfusion of the transplant organ after a period of warm and cold ischemia. In general, these reactive molecules are detoxified by GSH-dependent mechanisms, including conjugation to GSH by a family of GSH-S-transferase (GST) enzymes, some of which are expressed in large quantity in the proximal tubule of the kidney (Davies et al. 1995). In an observational study

of 229 kidney transplant recipients, donor (but not recipient) GST M1B polymorphism was associated with significantly lower rates of DGF after transplantation (Akgul et al. 2012).

#### 20.3.5.4 Diabetes Mellitus

Three RPCTs demonstrate beneficial effects of NAC treatment in insulin-related disease (Online Table 20.2d). One study demonstrates that oral administration of NAC to patients with non-insulin-dependent diabetes mellitus reverses the elevation of soluble vascular cell adhesion molecule-1 (De Mattia et al. 1998b), a substance that promotes accumulation of macrophages and T lymphocytes at sites of inflammation and increases progression of vascular damage (Marui et al. 1993; Schmidt et al. 1995). A second placebo-controlled study by the same group shows that intravenous GSH infusion significantly increases both RBC GSH/GSSG redox ratio and total glucose uptake in these patients and suggests that abnormal intracellular GSH redox status plays an important role in reducing insulin sensitivity (De Mattia et al. 1998a). Consistent with these findings, in an ongoing study in type 2 diabetics, Jahoor and colleagues have demonstrated that 2 weeks of dietary supplementation with NAC elicited significant increases in both RBC GSH concentration and synthesis, suggesting that positive clinical effects of NAC are mediated through improved GSH availability (McKay et al. 2000).

#### 20.3.5.5 Metabolic and Genetic Disease

Genetic defects that impair GSH synthesis or homeostasis are well known (Ristoff and Larsson 2002). The most common defect affects GSH synthetase (GS) and has a wide range of disease manifestations, including hemolytic anemia, progressive neurological symptoms, metabolic acidosis, and, in the most severe form, death during the neonatal period. Data from a small observational study suggests that early supplementation with Vitamins C and E may improve long-term outcome in these patients (Ristoff et al. 2001).

#### 20.3.5.6 Systemic Inflammatory Response Syndrome

Five of seven RPCTs showed a beneficial effect of NAC as an adjunct therapy for acute lung injury and end-organ failure. These studies indicate that oxidative stress and cysteine/GSH depletion play a major role in inflammation leading to capillary leak syndromes and end-organ failure (De Flora et al. 1997; Suter et al. 1994; Rank et al. 2000). These study show that NAC: (a) decreases the cytotoxic effects of TNF-α and other inflammatory cytokines (Zimmerman et al. 1989), (b) decreases neutrophil elastase production in acute lung injury (Borregaard et al. 1987; De Backer et al. 1996; Laurent et al. 1996; Eklund et al. 1988; Moriuchi et al. 1998), and (c) increases neutrophil protection and decreases mortality in septic shock (Villa et al. 2002).

#### 20.3.5.7 HIV Disease

A broad series of studies clearly demonstrates GSH levels in RBCs, lymphocytes, and other peripheral blood mononuclear cells progressively decrease as HIV disease advances (De Rosa et al. 2000; Herzenberg et al. 1997; Akerlund et al. 1996; Droge

and Breitkreutz 1999; Clotet et al. 1995; Spada et al. 2002; Verhagen et al. 2001). In addition, careful pharmacokinetic studies demonstrate that the low GSH in HIV-infected individuals is due to limited availability of sufficient cysteine to maintain cellular GSH homeostasis (Droge et al. 1991; Roederer et al. 1990). In fact, a massive peripheral tissue catabolism of sulfur-containing peptides and amino acids has been observed in HIV patients (Hortin et al. 1994; Breitkreutz et al. 2000a).

Five of six RPCTs show beneficial effects of NAC treatment in HIV infection. Several trials collectively demonstrated that NAC administration to HIV-infected subjects with low GSH levels replenishes lymphocyte and erythrocyte GSH (Online Table 20.2g) (De Rosa et al. 2000; Breitkreutz et al. 2000b). Importantly, one of these studies demonstrates that NAC treatment significantly improves T-cell function (Breitkreutz et al. 2000b). This finding supports the idea that cysteine/GSH deficiency contributes to the immunodeficiency in HIV-infected individuals and plays an important and reversible role in the functional impairment of those T cells that are still present at later stages of HIV disease.

Cysteine/GSH deficiency may also contribute to the failure of the innate immune system and the development of opportunistic infections in the final stages of HIV disease. Observational studies have shown that HIV-infected individuals with low CD4 T-cell counts and low cellular and systemic GSH levels frequently have elevated blood levels of Trx, which is an effective chemokine (Bertini et al. 1999). In mice, circulating Trx (like other chemokines) blocks neutrophil migration to infection sites and hence interferes with innate defense against invading pathogens (Villa et al. 2002). Similar interference may occur in HIV infection, since the survival of infected individuals with Trx levels above the normal range is significantly decreased compared to survival of subjects with Trx levels in the normal range (Ghezzi et al. 2002). Since NAC treatment lowers Trx levels (Nakamura et al. 2001, 2002), this may contribute to the observed association between NAC ingestion and prolonged survival in HIV disease (Roederer et al. 1992; De Rosa et al. 2000; Akerlund et al. 1996; Spada et al. 2002).

The improvement in T-cell function observed in HIV-infected subjects treated with NAC (Breitkreutz et al. 2000b) suggests that NAC treatment may be a useful adjunct in HIV vaccination. In addition, this improvement provides a rationale for the strong associations observed between low GSH levels and decreased survival in HIV infection (Herzenberg et al. 1997) and between NAC administration and improved survival in an open-label NAC study (Huengsberg et al. 1998).

#### 20.3.5.8 Otic Disease

Preclinical studies point to the importance of oxidative stress and GSH depletion in the genesis of noise and toxin-induced hearing loss (Kopke et al. 1999, 2001). Medications with inner ear toxicity such as aminoglycoside antibiotics and the chemotherapy agent cisplatin damage the cochlea through the generation of oxygen free radicals. Hearing loss and cochlear damage associated with administration of these compounds have been shown, in animal models, to be greatly reduced by administration of both NAC and methionine (Hoffer et al. 2001; Kopke et al. 2000; Sha and Schacht 2000). Similarly, studies with animal models show that permanent

cochlear damage due to acute acoustic overexposure, which induces ischemia reperfusion, glutamate excitotoxicity, free radical generation, and GSH depletion (Kopke et al. 1999, 2000, 2001, 2002), can be almost completely prevented by systemic administration of NAC or methionine (Kopke et al. 2000, 2002).

## 20.4 Summary

The evidence reviewed here reveals cysteine/GSH deficiency as an emerging clinical entity. The manifestations of this deficiency may vary in different disease settings, as may the biochemical mechanisms that mediate its effects. However, they are united by a common positive response to NAC therapy in RPCTs (Online Table 20.2). The studies we have reviewed collectively argue for consideration of cysteine/GSH deficiency as a significant and treatable clinical entity.

Surprisingly, given the diverse roles that GSH plays in cellular physiology and regulation of enzyme activity and protein function, the consequences of low GSH levels have mainly been discussed from a clinical perspective in terms of the loss of protection against intracellular oxidative stress. However, while antioxidants such as vitamins E and C can spare GSH under conditions of oxidative stress, GSH loss can only be offset by GSH resynthesis, indicating a central role for this molecule over and above its ability to counteract the effects of intracellular oxidants.

Similarly, although NAC is a well-known source of cysteine for GSH replenishment in APAP toxicity, it is principally cast as an antioxidant in other settings. By and large, physicians and the lay public tend to equate NAC with vitamins C and E and other antioxidants. Like GSH, NAC can serve as an antioxidant. However, while other antioxidants can replace NAC and GSH in this role, only NAC or another cysteine source can provide the raw material necessary to replenish GSH and enable GSH-dependent biochemical reactions.

We have pointed out that physicians may find NAC administration useful as adjunct therapy for diseases and conditions in which cysteine/GSH deficiency is likely to play a role. The positive findings in the RPCTs we have discussed support this argument. However, the absence of large multicenter trials testing NAC in various settings leaves this as an open question. The recognition that cysteine/GSH deficiency is an important clinical entity will encourage support for such trials.

In the meantime, the findings we have discussed suggests that patients with diseases or conditions in which cysteine/GSH deficiency has been demonstrated may be well advised to avoid unnecessary exposures to medications that may exacerbate GSH depletion. In fact, when advising such patients, it seems reasonable for physicians to emphasize that alcohol usage be kept at modest levels and that APAP usage should be kept strictly within the recommended dosing.

The availability of OTC NAC, and the low toxicity of this cysteine prodrug in situations where it has been tested, opens the possibility of patient- or physician-initiated therapy. However, if such therapy is elected, we suggest that the NAC preparation(s) used be prepared under Good Manufacturing Practice conditions and packaged to prevent oxidation of the product.

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