Todd Guthrie, MD

FREE RADICALS IN PRACTICE

THE GOOD, THE BAD, AND OXIDATIVE STRESS

FIRST PRINCIPLES

- The Bible is its own expositor. Scripture is to be compared with scripture. The student should learn to view the word as a whole, and to see the relation of its parts. He should gain a knowledge of its grand central theme, of God's original purpose for the world, of the rise of the great controversy, and of the work of redemption. He should understand the nature of the two principles that are contending for supremacy, and should learn to trace their working through the records of history and prophecy, to the great consummation. He should see how this controversy enters into every phase of human experience; how in every act of life he himself reveals the one or the other of the two antagonistic motives; and how, whether he will or not, he is even now deciding upon which side of the controversy he will be found. Ed 190.2

FREE

- (adj) not under the control or in the power of another; able to act or be done as one wishes.
- (adj) not physically restrained, obstructed, or fixed; unimpeded.
- (adv) without cost or payment.

FREE

- Therefore if the Son makes you free, you shall be free indeed. John 8:36
- But the free gift is not like the offense. For if by the one man's offense many died, much more the grace of God and the gift by the grace of the one Man, Jesus Christ, abounded to many.
- And the gift is not like that which came through the one who sinned. For the judgment which came from one offense resulted in condemnation, but the free gift which came from many offenses resulted in justification. Therefore, as through one man's offense judgment came to all men, resulting in condemnation, even so through one Man's righteous act the free gift came to all men, resulting in justification of life. Rom. 5:15-18

RADICAL

- (n) a group of atoms behaving as a unit in a number of compounds.
- (adj) late 14c., in a medieval philosophical sense, from Late Latin radicalis "of or having roots," from Latin radix (genitive radicis) "root" (see radish). Meaning "going to the origin, essential" is from 1650s.
- (adj) (especially of change or action) relating to or affecting the fundamental nature of something; far-reaching or thorough.
- (adj) advocating or based on thorough or complete political or social change
- “Even now the ax is laid at the root of the tree.” Luke 3:9

PRACTICE

- (v) c. 1400, "to do, act;" early 15c., "to follow or employ; to carry on a profession," especially medicine, from Old French pratiser, practiser "to practice," alteration of practiquer, from Medieval Latin practicare "to do, perform, practice," from Late Latin practicus "practical," from Greek praktikos "practical" (see practical).
- From early 15c. as "to perform repeatedly to acquire skill, to learn by repeated performance;" mid-15c. as "to perform, to work at, exercise." Related: Practiced; practicing.
- Strong's #4238 - πράσσω: perform repeatedly or habitually

PRACTICE

- For we must all appear before the judgment seat of Christ, that each one may receive the things done in the body, according to what he has done, whether good or bad. 2 Cor. 5:10.
- The things which you learned and received and heard and saw in me, these do, and the God of peace will be with you. Phil. 4:9.
- “For as the Father has life in Himself, so He has granted the Son to have life in Himself, and has given Him authority to execute judgment also, because He is the Son of Man.
- “Do not marvel at this; for the hour is coming in which all who are in the graves will hear His voice and come forth—those who have done good, to the resurrection of life, and those who have done evil, to the resurrection of condemnation.” John 5:26-29.

WHAT DO WE REALLY KNOW?

“In science without the Bible, that by which things are held together is Cohesion. But when it is asked, What is Cohesion? the only answer is "That by which things are held together." In science without the Bible, that by which all things are held up or held in place, is Gravitation. But when it is asked, "What is Gravitation?" the only answer is, "That by which all things are held up or held in place." But such answers as these are not answers at all: they are simply the saying of the same thing in another way.

WHAT DO WE REALLY KNOW?

“Yet it is a fact that such is just the instruction that is given in the books, and such is the teaching that is given to students. But by it the mind of the student is caused to travel in a circle, and is left wandering there, ever inquiring and finding no certain or satisfactory answer. It is proper for a student to ask, "What holds, in their places, the worlds and all things?" And it is proper enough that the answer should be, "Gravitation." It is then proper for him to ask, "What is Gravitation?" But it is not in any sense proper to answer that, "Gravitation is that by which all things are held in their places." It is proper for the student to ask, "What is it that holds things together?" And it is proper enough that the answer should be, "Cohesion." It is then proper that he should ask, "What is Cohesion?" But it is not in any sense proper, nor is it at all sensible, to answer this question by saying that "Cohesion is what holds things together."

WHAT DO WE REALLY KNOW?

“Yet that and such as that throughout the curriculum, is what is offered as science. It is science without God, science without the Bible; but it is not genuine science. By it, all that any person can ever know is merely something about things; he cannot know the reality of the things themselves.

WHAT DO WE REALLY KNOW?

“In science with the Bible, it is altogether different. In that, when a child or a student asks, "What holds all things in their places?" he can be told that it is Gravitation. And when he asks, "What is Gravitation?" he can be answered, "God made the worlds by his Son, who, being the brightness of his glory, and the express image of his person, and upholding all things by the word of his power." Heb. 1:1-3. Thus, gravitation is the power of God manifested in his word through Jesus Christ. When it is asked, "What holds all things together?" and it is answered, "Cohesion;" and when it is asked, "What is Cohesion?" the true answer is, "God hath translated us into the kingdom of his dear Son, . . . by whom all things were created, visible and invisible, whether they be thrones or dominions or principalities or powers, all things were made by him and for him; and he is before all things and by him all things consist"—[hold together]. Thus Cohesion is the power of God manifested through Jesus Christ our Lord….

WHAT DO WE REALLY KNOW?

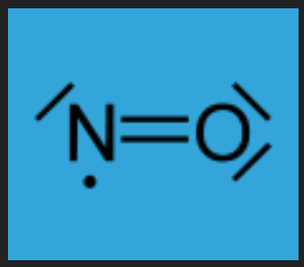
“He who believes the Bible and thus becomes so acquainted with God and the power of his word, that he knows and rests with perfect confidence in the knowledge that God possesses and has revealed in the Bible a philosophy and a science that is as far beyond any that this world ever knew, as heaven is higher than the earth, is counted as fairly beyond the pale of respectability. But all that makes no difference with the truth. And it is the everlasting truth that in the Bible there is more and better science, truer and more profound philosophy, than this world ever knew or ever can know without this book.

“God is. He is the former of all things. He is the only true teacher. He is ever ready and is waiting to be the teacher of all. He will willingly teach all who will be taught by him. And to all such he will teach all knowledge and all wisdom, all science and all philosophy. For in him are hid all the treasures of philosophy and science, and ye are complete in him who is the head of all principality and power.” September 2, 1897 ATJ, AMS 530.

FREE RADICAL

- atom, molecule, or ion that has unpaired valence electrons.
- usually highly reactive - will give or take to gain parity
- can be formed through process that puts enough energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions.

NO – NITRIC OXIDE



- Gaseous signaling molecule which is a free radical
- Signals endothelial smooth muscle cells to relax
- Increases blood flow
- Nitric oxide synthase OR nitrate-rich vegetables, in particular leafy greens, such as spinach and arugula, and beetroot
- Contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium.
- Also generated by phagocytes (monocytes, macrophages, and neutrophils) as part of the human immune response. Toxic to bacteria and parasites.

OH – HYDROXYL RADICAL

- extremely reactive, immediately removes electrons from any molecule in its path, turning that molecule into a free radical and so propagating a chain reaction.
- cannot be eliminated by an enzymatic reaction.
- dangerous: can damage virtually all types of macromolecules: carbohydrates, nucleic acids (mutations), lipids (lipid peroxidation), and amino acids.
- occasionally produced as a byproduct of immune action (which is actually good).
- Mechanisms for scavenging peroxyl radicals for the protection of cellular structures includes endogenous antioxidants such as melatonin and glutathione, and dietary antioxidants such as mannitol and vitamin E.

EXOGENOUS OR ENDOGENOUS DAMAGE TO CELL

ERYTHROCYTE

Cell membrane

Sialic Acids (negative charge)

Antioxidative Enzymes e.g. (SOD,CAT,GSHPX)

- free radicals
- lipid peroxidation
- hypoxia
- anaemia

microbial binding

haemolysis

- ❑ Enzyme Inactivation
- ❑ Damage to DNA
- ❑ Lipid peroxidation
- ❑ Other cytotoxic actions

Na^+, K^+ electrolyts change

pathogens

white Cells

pyogenic

synthesis of mucoproteins

Reactive Oxygen Species (ROS)

INFLAMMATION

PATHOLOGICAL STAGE, e.g. CANCER

pus formation

- tissue protection
- impaired killing of pathogens

Research Article

Activities of Anti-Oxidative Enzymes, Catalase and Glutathione Reductase in Red Blood Cells of Patients with Coronary Artery Disease

M. Firoozrai , H. Mehrabi , A. Ehsani , M. Najafi and M. Ghaffari

ABSTRACT

Free radical scavenging enzymes are an important part of body anti-oxidative system. The aims of this study were to evaluate the enzymatic activities of anti-oxidative enzymes of erythrocytes, catalase (CAT) and Glutathione Reductase (GR), that might be indicators of protective mechanisms involved in atherosclerosis and also to evaluate the serum lipids and lipoproteins which are thought to be correlated with these two anti oxidative enzymes. The study population consisted of 90 patients with angiographically proved coronary stenosis in surgery section of Tehran Rajaee cardiovascular center and 30 subjects without any **coronary heart disease** used as control. Glutathione reductase and catalase activities in erythrocytes were assayed. Patients had not significantly decreased glutathione reductase activity compared to that in control subjects. However the catalase activity was significantly decreased in erythrocytes of the atherosclerotic patient. Atherosclerotic smoking patients had similar catalase activity compared to that in nonsmoking patients. However the glutathione reductase activity was lower in erythrocytes of the atherosclerotic smoking patients. No significant correlations were found between serum lipids and two anti-oxidative enzymes activities in patients and control subjects.

M. Firoozrai , H. Mehrabi , A. Ehsani , M. Najafi and M. Ghaffari , 2007. Activities of Anti-Oxidative Enzymes, Catalase and Glutathione Reductase in Red Blood Cells of Patients with Coronary Artery Disease. *Asian Journal of Biochemistry, 2: 437-440.*

DOI: 10.3923/ajb.2007.437.440

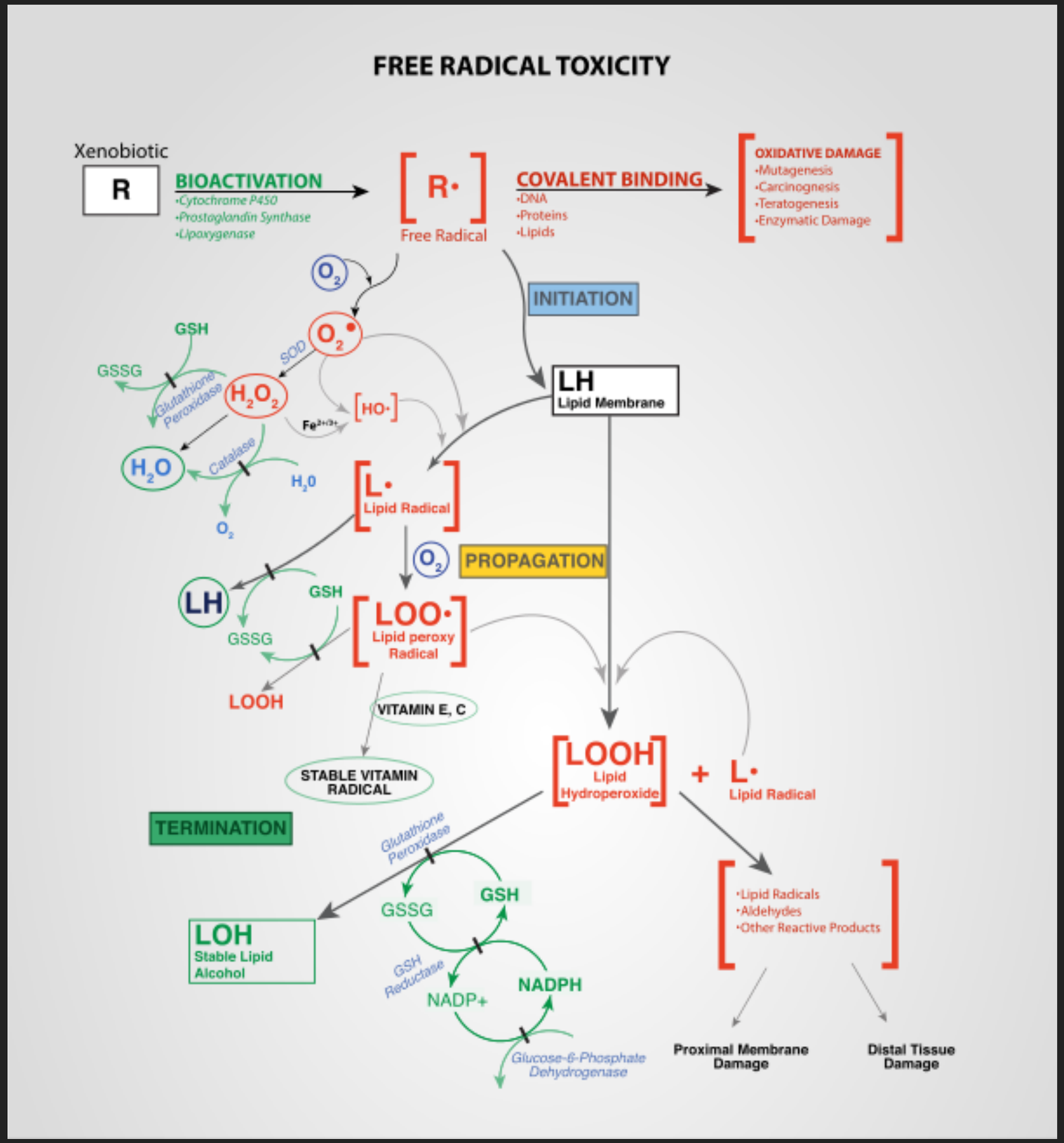
URL: http://scialert.net/abstract/?doi=ajb.2007.437.440

REACTIVE OXYGEN SPECIES

- Exogenous ROS (free radicals and peroxides) can be produced from pollutants, tobacco, smoke, drugs, xenobiotics, or radiation.
- Endogenous ROS are the natural byproduct of normal oxygen metabolism
- Important roles in cell signaling and homeostasis
- Experimental and epidemiologic research over the past several years has indicated close associations among ROS, chronic inflammation, and cancer.

OXIDATIVE STRESS

Reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g. O2− (superoxide radical), OH (hydroxyl radical) and H2O2 (hydrogen peroxide).

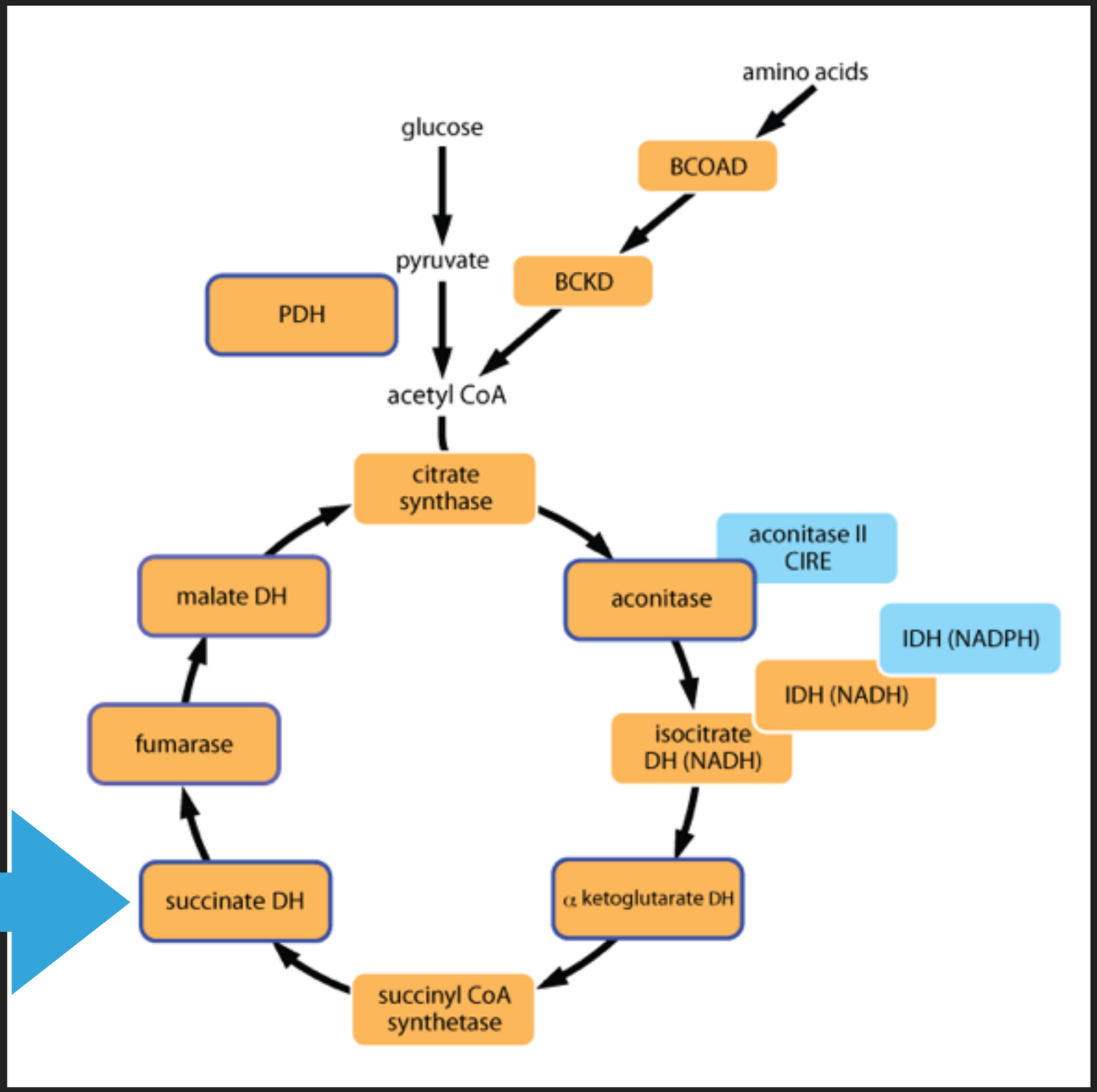


https://en.wikipedia.org/wiki/File:Free_Radical_Toxicity.svg

Metabolic heart disease (MHD) due to consumption of a HFHS “Western” diet causes increased H2O2 production and oxidative stress in cardiac mitochondria associated with decreased ATP synthesis and decreased complex II activity. Impaired complex II activity and ATP production are associated with reversible cysteine oxidative post-translational modifications (OPTM) of complex II…. Mitochondrial ROS may contribute to the pathophysiology of MHD by impairing the function of complex II.

High fat, high sucrose diet causes cardiac mitochondrial dysfunction due in part to oxidative post-translational modification of mitochondrial complex II

Aaron L. Sverdlov et al. J Mol Cell Cardiol. 2015 Jan; 0: 165–173.
Published online 2014 Aug 7. doi: 10.1016/j.yjmcc.2014.07.018 PMCID: PMC4268348/NIHMSID: NIHMS624605



Complex II = succinate dehydrogenase

Complex II is composed of 4 subunits and contains a flavin (FAD), non-heme iron centers and a b-type cytochrome as prosthetic groups. It is both a component of the electron transport chain and an enzyme of the Krebs cycle.

TO SUPPLEMENT OR NOT?

Oxid Med Cell Longev. 2010 Jul-Aug; 3(4): 228–237.
doi: 10.4161/oxim.3.4.12858
PMCID: PMC2952083

Exogenous antioxidants—Double-edged swords in cellular redox state

Health beneficial effects at physiologic doses versus deleterious effects at high doses

Jaouad Bouayed and Torsten Bohn

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Abstract

Go to:

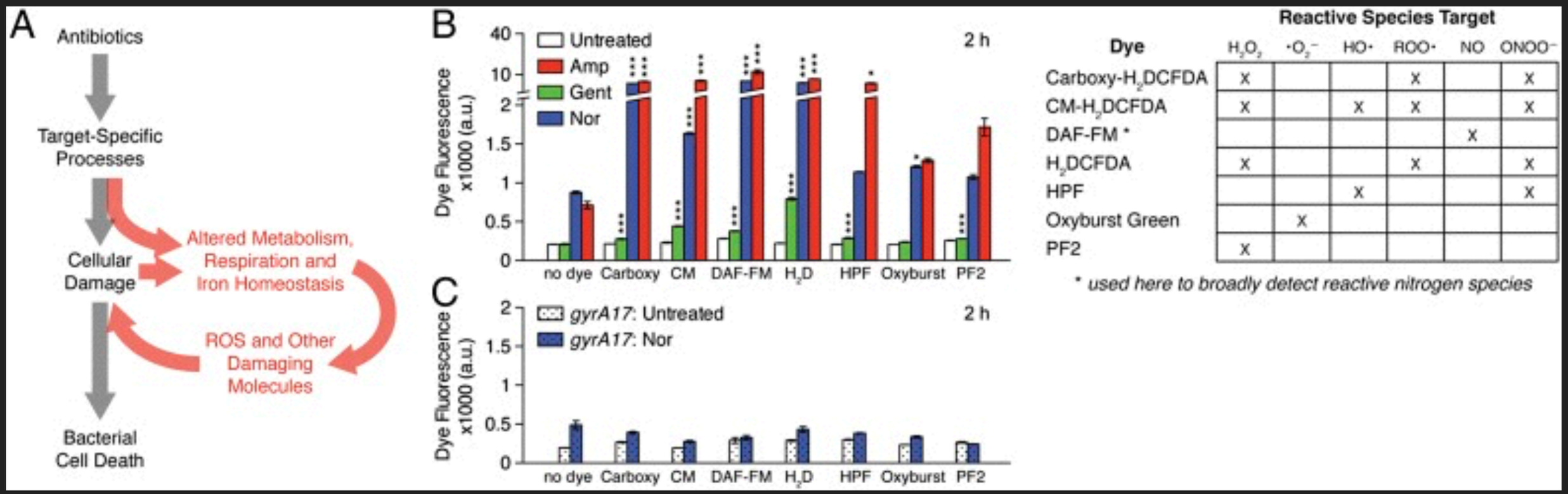
The balance between oxidation and antioxidation is believed to be critical in maintaining healthy biological systems. Under physiological conditions, the human antioxidative defense system including e.g., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH) and others, allows the elimination of excess reactive oxygen species (ROS) including, among others superoxide anions ($O_2^{\cdot-}$), hydroxyl radicals (OH.), alkoxyl radicals (RO.) and peroxyradicals (ROO.). However, our endogenous antioxidant defense systems are incomplete without exogenous originating reducing compounds such as vitamin C, vitamin E, carotenoids and polyphenols, playing an essential role in many antioxidant mechanisms in living organisms. Therefore, there is continuous demand for exogenous antioxidants in order to prevent oxidative stress, representing a disequilibrium redox state in favor of oxidation. However, high doses of isolated compounds may be toxic, owing to prooxidative effects at high concentrations or their potential to react with beneficial concentrations of ROS normally present at physiological conditions that are required for optimal cellular functioning. This review aims to examine the double-edged effects of dietary originating antioxidants with a focus on the most abundant compounds, especially polyphenols, vitamin C, vitamin E and carotenoids. Different approaches to enrich our body with exogenous antioxidants such as via synthetic antioxidants, diets rich in fruits and vegetables and taking supplements will be reviewed and experimental and epidemiological evidences discussed, highlighting that antioxidants at physiological doses are generally safe, exhibiting interesting health beneficial effects.

Key words: antioxidants, reactive oxygen species, oxidative stress, double-edged effects, fruits and vegetables, supplements, physiological doses, high doses

TO SUPPLEMENT OR NOT?

- The balance between oxidation and antioxidation (redox balance) is critical in maintaining a healthy biological system. In cellular redox state, the double-edged effect does not only concern ROS, but also antioxidants. Physiologic doses of exogenous antioxidants are required to maintain or re-establish redox homeostasis. However, high doses of exogenous antioxidants may disrupt redox balance. Considering epidemiological studies and trials on humans taking antioxidant compounds, it is evident that the health benefits of phytochemicals and nutrients were observed predominantly when being consumed within their natural food matrices (fruits, vegetables, grain, etc.). Compounds within plant foods may therefore be considered as being more safe and healthy compared to isolated, high doses, such as present in supplements. Two main factors seem to be predisposing for the beneficial activities of plant foods: (1) the general low concentration of nutrients and non-nutrients in these natural food matrices and (2) the additive or synergistic actions of complex mixture profiles of phytochemicals and nutrients. Supplementation approaches do generally not take into account both aspects, which could explain the controversial results observed in supplementation studies.

"We find that antibiotics dynamically alter cellular respiration and induce lethal levels of intracellular hydrogen peroxide. Antioxidants, including oxidative stress defense proteins, significantly reduce the killing by antibiotics, which is highly sensitive to the presence of molecular oxygen."



Antibiotics induce redox-related physiological alterations as part of their lethality
Daniel J. Dwyer, et al. Proc Natl Acad Sci U S A. 2014 May 20; 111(20): E2100–E2109.
Published online 2014 May 6. doi: 10.1073/pnas.1401876111

J Natl Cancer Inst. 2008 Jun 4;100(11):773-83. doi: 10.1093/jnci/djn148. Epub 2008 May 27.

Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy?

Lawenda BD[1], Kelly KM, Ladas EJ, Sagar SM, Vickers A, Blumberg JB.

Author information

Abstract

Despite nearly two decades of research investigating the use of dietary antioxidant supplementation during conventional chemotherapy and radiation therapy, controversy remains about the efficacy and safety of this complementary treatment. Several randomized clinical trials have demonstrated that the concurrent administration of antioxidants with chemotherapy or radiation therapy reduces treatment-related side effects. Some data indicate that antioxidants may protect tumor cells as well as healthy cells from oxidative damage generated by radiation therapy and some chemotherapeutic agents. However, other data suggest that antioxidants can protect normal tissues from chemotherapy- or radiation-induced damage without decreasing tumor control. We review some of the data regarding the putative benefits and potential risks of antioxidant supplementation concurrent with cytotoxic therapy. On the basis of our review of the published randomized clinical trials, we conclude that the use of supplemental antioxidants during chemotherapy and radiation therapy should be discouraged because of the possibility of tumor protection and reduced survival.

"On the basis of our review of the published randomized clinical trials, we conclude that the use of supplemental antioxidants during chemotherapy and radiation therapy should be discouraged because of the possibility of tumor protection and reduced survival."

THE PERFECT SUPPLEMENT?

"Humifulvate is a chemically identifiable source of a standardized peat-derived humic acid, fulvic acid andphenolic acid complex intended for oral consumption. Humifulvate is the base compound used in combination with minerals and trace elements as a dietary supplement. Since 1993, humifulvate has been an approved dietary supplement sold in numerous European countries as an OTC drug in the form of a liquid mineral concentrate called Humet R. A significant body of research has been carried out on the pharmacokinetics, toxicology, and efficacy of this product.

"The uniqueness of Humifulvate is attributed to its specific properties, method of preparation, as well as its source,near Lake Balaton, Hungary. Humifulvate is solely derived from a fern peat deposit discovered over forty years ago near Lake Balaton, Hungary. The discovery was made after veterinary doctors observed that animals grazing on or near this peat deposit were exceptionally healthy, compared to other animals, especially off-spring."

THE PERFECT SUPPLEMENT?

“Studies found that the animals consuming the grass growing on these peat deposits experienced accelerated growth and resisted diseases commonly seen in other regions of Hungary and nearby countries. This suggested that the animals had ingested something that had enhanced their immune function and promoted optimal growth and disease resistance. It was believed that the peat enhanced absorption of minerals found in the plants livestock was eating.

“Extensive scientific research has established that this peat deposit contains significant quantities of two predominant humate compounds, humic acid and fulvic acid. Phenolic acid is a minor constituent.”

THE PERFECT SUPPLEMENT?

"In summary, it appears that fulvic acids may act similarly to humic acids. This may be due to their acidic functional groups, primarily carboxylic acid and phenolic hydroxyl groups, that give them the capacity to react with various species such as free radicals, minerals, and biological enzyme systems.

"However, due to the complexity of the structure and functions of fulvic acid, it is difficult to determine the exact mechanisms responsible for the effects seen in vivo. Further research may help to explain how these substances interact with biological systems."

Scientific Report submitted to FDA

Peat-derived Organic Humifulvate Concentrate (HFC): A New Multimineral Dietary Supplement

Amy Addington, MS, Research Associate

Alexander Schauss, PhD, Director

American Institute for Biosocial and Medical Research

http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0091_02_attachment_01.pdf

THE PERFECT SUPPLEMENT?

- Promotes electrochemical balance as donor or receptor
- Powerful free radical scavenger and antioxidant
- Complexes and dissolves minerals and trace elements
- Enhances bioavailability and transport of nutrients
- Detoxifies pollutants, chelator of metal ions
- Enhances cell membrane permeability
- Increases protein metabolism
- Increases enzyme activity

LIFE AND DEATH SPIRITUAL LESSONS

- Are we givers (and forgivers) , effective messengers of the love of God?
- How do we best neutralize the toxicity around us?
- Do we have a perfect “antioxidant” source in the life and death of Jesus?
- What is our role in the function of “reactive oxygen species?”

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ADAM CLAY MANSFIELD

Surgeon slain, gunman found dead in day of crisis at Brigham

Shooter's mother was recent patient at Boston hospital

DAVID L. RYAN/GLOBE STAFF

Brigham and Women's Hospital lowered its flag on Wednesday, one day after the shooting death of Dr. Michael Davidson.

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New MIT innovation hub takes on world's biggest challenges

Celtics waive R.J. Hunter to meet roster deadline

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Vote no on Question 4 -- it's an industry-driven mess of a proposal

Watch Ben Affleck's 'Funny or Die' get-out-the-vote video

Are you good enough for Boston's newest dating app?

Man allegedly caught beating husky at North Station

That Kelly-Gingrich showdown was one for the ages

Apparently, Blake Lively and Ryan Reynolds fell in love at a Boston restaurant

Reno shooter gunned down two doctors, patient at urology clinic

December 18, 2013 | By Matt Pearce

Email | Share | G+1 0 | Tweet | Recommend 0

The man who went on a shooting rampage with a 12-gauge shotgun at a Reno medical clinic Tuesday killed one doctor and injured another physician and a patient before killing himself, officials said Wednesday morning.

Officers escort witnesses to a bus at the Renown Regional Medical Center... (Scott Sady / Associated...)

Dr. Charles G. Gholdoian, who worked at the Urology Nevada office on the Renown Regional Medical Center, was killed, authorities said.

A female doctor at the clinic, who was not identified, and a patient identified as Shawntae Spears were wounded and remained in critical condition Wednesday morning, officials said.

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- “He who loves his life will lose it, and he who hates his life in this world will keep it for eternal life. If anyone serves Me, let him follow Me; and where I am, there My servant will be also.” Jn 12:25,26

- “No temptation has overtaken you except such as is common to man; but God is faithful, who will not allow you to be tempted beyond what you are able, but with the temptation will also make the way of escape, that you may be able to bear it.” 1 Cor 10:13

ADAM CLAY MANSFIELD

- “For the love of Christ compels us, because we judge thus: that if One died for all, then all died; and He died for all, that those who live should live no longer for themselves, but for Him who died for them and rose again. Therefore, from now on, we regard no one according to the flesh.” 2 Cor 5:14-16

- “For we do not have a High Priest who cannot sympathize with our weaknesses, but was in all points tempted as we are, yet without sin. Let us therefore come boldly to the throne of grace, that we may obtain mercy and find grace to help in time of need.” He 4:15,16

ADAM CLAY MANSFIELD

"This is the covenant that I will make with them after those days, says the LORD: I will put My laws into their hearts, and in their minds I will write them," then He adds, "Their sins and their lawless deeds I will remember no more."

Now where there is remission of these, there is no longer an offering for sin.

Therefore, brethren, having boldness to enter the Holiest by the blood of Jesus,

by a new and living way which He consecrated for us, through the veil, that is, His flesh, and having a High Priest over the house of God,

ADAM CLAY MANSFIELD

let us draw near with a true heart in full assurance of faith, having our hearts sprinkled from an evil conscience and our bodies washed with pure water.

Let us hold fast the confession of our hope without wavering, for He who promised is faithful.

And let us consider one another in order to stir up love and good works. Heb. 10:16-24.

"'When the enemy shall come in like a flood, the Spirit of the Lord shall lift up a standard against him.'" Isaiah 59:19. Jesus gives the Holy Spirit in large measure for great emergencies, to help our infirmities, to give us strong consolation." ML 48. "Repentance represents the process by which the soul seeks to reflect the image of Christ to the world." ML 49.

ISAIAH 58:9

When you call out to me, I will be your answer;

Your cry for help will reveal that I have always been closer than you thought.

I will reveal Myself to you and in you.

Because I have been bearing the sin of all humanity and given them My life in exchange,

You can choose to quit burdening others with the guilt of humanity you yourself share,

Pointing out their flaws and faults, telling them how bad they are.

ISAIAH 58:10

If you receive my heart-yearning for those who are hungering for something better,

Who are attacked by the enemy on every side,

The light of My love will conquer your fear,

And dispel the gloom enshrouding those around you.

ISAIAH 58:11

I will cause My Word to guide you in every situation,

My love will satisfy what your soul thirsts for,

You will have the most solid framework of truth;

My never failing love, my selflessness,

Will grow on you, and freely flow out of you.

Your children, those new-born in Christ who see this love in action,

Will join you in placing My righteousness as the cornerstone of the church,

Where it has always belonged.

Then you will truly be called My Commandment-keeping people,

Who have restored the path of righteousness by faith,

Revealing My faith and love as I dwell in you.

MAKE IT A PRACTICE TO BE A FREE RADICAL

Therefore if the Son makes you free,

you shall be free indeed.

John 8:36