# Ray Peat's Newsletter

*A change of meaning is a change of being. David Bohm*

 **Raymond Peat P.O. Box 5764 Eugene OR 97405** **November 2017**



## From "heroic medicine" to "hormesis": First deny that harm is done

The holistic view of the organism and its adaptive potentials, advocated by Hippocrates and Aristotle, was rejected by the new science of the last few centuries. Recovering that view, and using it creatively, has become urgent, if we want to understand the processes of development, including aging and the degenerative diseases such as cancer, dementia, systemic inflammation, and fibrosis. Systematic efforts are being made to keep organismic thinking on the sidelines.

**The idea that a little bit of something harmful is good for you was adopted by the petroleum, chemical and nuclear industries and treated as a scientific concept, with the name "hormesis."**

When the "heroic medicine" that was taught in the U.S. 200 years ago was replaced by milder, less risky procedures, some of the old attitudes and ideas persisted—for example, the "healing crisis," in which getting worse means that you're getting better. When mercury and arsenic were very commonly used in medicine, a "healing crisis" often involved the same symptoms as poisoning by those chemicals, but patients were convinced that the suffering was caused by the disintegration of the bacteria, not the medicine. When patients are ruined by surgeries, chemotherapy, and radiation, they are convinced that it was all an effect of the cancer.

Looking at the larger culture of western civilization, "mortification of the flesh" for the good of the soul might be a relevant context for these persistent attitudes in medicine and biology. Athletes are told "no pain, no gain," and many people are accepting the idea that suffering toughens you in general ways—fasting, cold showers, jogging, are said to improve immunity and delay aging.

**Recovering the holistic view of the organism has become urgent, if we want to understand the processes of development, including aging and degenerative diseases such as cancer, dementia, systemic inflammation, and fibrosis.**

The idea that a little bit of something harmful is good for you was adopted by the petroleum, chemical and nuclear industries and their agents in government around 1950, and treated as a scientific concept, with the name "hormesis." When the public was starting to worry about the increased radioactivity of the environment because of nuclear bomb explosions, the US government was actively suppressing information on the increasing amount of environmental ionizing radiation, but they were even more active in promoting the idea that "small amounts" of radiation are harmless and even beneficial. People like John Gofman and Ernest Sternglass were ostracized for demonstrating that sickness and death were increased by those "harmless or beneficial" amounts of radiation.

In recent decades, it has been recognized that our bodies produce small amounts of very toxic substances—carbon monoxide (CO), nitric oxide (NO), hydrogen sulfide (H2S), and hydrogen

cyanide (HCN). The drug industry saw this as an opportunity to sell new drugs, and agents of the polluters have discovered that these endogenous toxins can be useful to them. The reasoning is that if every harmful experience of the organism increases these substances, and if the organism survives those experiences, then the substances must have been produced as a protective-defensive reaction, meaning that there is an opportunity to sell drugs to increase them to prevent or treat disease, and an opportunity for polluters to argue that the substances are direct evidence of the beneficial effects of the harm they have inflicted.

**When patients are ruined by surgeries, chemotherapy, and radiation, they are convinced that it was all the effect of the cancer.**

About 15 years ago, the proponents of the hormesis idea gave it a more formal-sounding definition, as "a biphasic dose response," which can be graphed with a "U" or inverted "U' shape rather than the more common ascending or descending line representing the relation of a certain function to increasing doses of a substance. The intention is to make the hormesis phenomenon seem like any general property of nature, such as osmosis, or electrical charge, or gravity, in which a mathematical expression corresponds to a general property of matter, advancing our understanding of nature.

The claim is that hormesis describes a relation between an organism and its environment, but in reality each adaptive situation in which there is a response to a single substance or stimulus involves the whole organism, not simply a single receptor substance. The reason that an organism's response to a particular stimulus increases or decreases depends on the history and condition of the organism, as well as on the nature and intensity of the stimulus. Different aspects of the organism are affected by different substances or forces, and by different quantities of those substances or forces. The "hormetic principle" corresponds to nothing useful in the realm of organisms adapting to their environment.

The hormetic principle in ecology is analogous to Noam Chomsky's approach to linguistics, in which a person's speech function is treated as a black box, that can be adequately understood without studying the brain and its use of language. It makes things very simple, but at best, it's perfectly useless. A collection of grammatical rules, supposedly derived from genes, could "account for" the structures of speech, but something else is needed to account for the selection of the right rules in the right order in each particular circumstance. Chomsky's linguistics had the structure of reductionist science, but what it lacked was the intelligence that characterizes language use. The hormetic principle suffers from the same radical absence of knowledge about the nature of adaptation, which it claims to be explaining.

The organizations that lavishly fund the hormesis doctrine are generally those that have opposed the "precautionary principle" in relation to food and environmental quality (on the grounds that existing human harm must be demonstrated before regulatory action can be taken), and they are now extending the argument to say that the public is being harmed by the regulations that reduce pollution, because they aren't getting an optimal amount of hormetic stimulation.

**. . . lipid peroxidation of PUFA [can increase] heme oxygenase which produces carbon monoxide, which in turn activates aromatase to make estrogen from androgens. The result is that the accumulating PUFA function as amplifier of the cellular stress reactions.**

If toxins such as CO and NO are beneficial, "hormetically," when they occur in city air, then obviously they must be very beneficial when they are produced in the body by enzymes, which evolved through the natural selection of things that supported survival—there is a clear Panglossian aspect to neodarwinism, everything exists because of its fitness. In the neodarwinian worldview, both on the evolutionary time scale of a species and on the time scale of an individual organism, "the world" sets the problem, and the

organism solves it by changing itself so that it fits into the world.

In their view of evolution, changes in the species occur randomly, without meaning for the individual, and meaningful for the species only when its survival is threatened. That view permeated the culture of the 20th century; when Hans Selye described his "General Adaptation Syndrome" he said "I call it adaptive because it stimulates defense." Typical examples of stressors were "starvation, being hit by a car, or suffering through severe weather."

**Existing drugs proposed for increasing heme oxygenase include resveratrol, metformin and the statins. However, many researchers have recognized that the short-term local benefits are associated with very serious long-term harmful effects . . . .**

Another view sees every event in life, starting with fertilization of an ovum, as a process of adaptation—an active, purposeful, formative, constructive process of interacting with the environment and assimilating from it the things that are situationally appropriate. If the environments that the organism encounters are abundant in resources the organism will develop its capacity, tending to maximize its ability to interact constructively.

Experiments over the last 60 years have shown that more or less glucose, carbon dioxide, warmth, and progesterone during embryonic and fetal development can affect the growth of the brain, and the brain's way of guiding future development and adaptive ability.

From a very early stage of development, the nervous system coordinates the interactions of tissues. The rate of growth and function of each tissue is adapted to the availability of the needed materials. Tissues in action consume resources, and idle tissues can dedifferentiate, redifferentiate, or disintegrate, according to the needs of the system. The parts of the developing organism are kept in balance by a hierarchy of mechanisms, intracellular, electronic-redox, mechanical, hormonal, nervous, and perceptual; Buckminster Fuller's architectural concept of tensional integrity, "tensegrity," is a better metaphor for physiology than the mechanistic medical concepts.

"Defense" is only one specialized aspect of stress. In some species, prolonged deprivation leads to hibernation or estivation, decreasing energy needs during the time of dearth. Defensive reactions that simply assure survival often degrade functioning of the individual. In any organism, prolonged deprivation has epigenetic effects that are likely to become transgenerational. Growth of the brain, the organ with the highest requirement for oxidative energy production, is disproportionately affected by gestational stress, with its growth being retarded more than the growth of the rest of the body. For example, exposure to lead early in life (Cragg and Rees, 1984), at levels that aren't directly neurotoxic, inhibits the growth of the brain, while stimulating the growth of the rest of the body, producing adults with a smaller brain/body ratio.

In mediating adaptation, the brain orients the organism toward aspects of the environment that are most likely to satisfy its needs, and this involves making judgments of possible future situations. In the absence of good prospects, the brain concerns itself with defensive changes, increasing the stress hormones, the fight-or-flight mechanisms, and begins to convert some of its own tissues to energy and materials needed for the survival of its essential organs, the brain, lungs, and heart. Cortisol, for example, selectively breaks down proteins in muscles and thymus, and activates their conversion to glucose.

The catabolic turnover of cell materials, including the process of autophagy, is an alternative to the organized disintegration of a cell, "apoptosis," during stress. Autophagy is activated by stresses such as starvation, glucose deprivation, hypoxia, heavy metal poisoning, lipid peroxidation, and irradiation, allowing cells to survive. When the process is a direct response of cells to harmful environmental factors, while the nervous system is in a defensive state, the survival of individual cells will occur without regard to the pattern of the whole organism, and if the process is prolonged, the result will be loss of function of a tissue or organ, fibrosis, or cancerization.

Part of the basic cellular defense reaction involves enzymes that process toxins in ways that improve the immediate situation, but that can create new problems for the organism if they become chronic. For example, stressed tissues produce carbon monoxide and estrogen, which prevent apoptosis and promote autophagy, with short-term survival value. Surviving in the stressed condition under the influence of CO and estrogen, the cells produce cytokines that affect the sensitivity of surrounding cells to stress and inflammation, and progressively undergo "epigenetic" changes, tending to become cells of a different type, with different types of metabolism, producing collagen to make the tissue more resistant to mechanical stresses, or becoming mobile cells, able to replace cells that have been destroyed, healing wounds.

This is very convenient when there are distinct wounds, and necessary for survival; but when the harmful factors are continuously present in small amounts, the continuing activation of these enzymes has a cumulative effect, creating systemic inflammation and systemic fibrosis, even in the brain, weakening the organized functioning of the organism.

With aging, the accumulation of polyunsaturated fats intensifies those changes. Reacting with oxygen, the peroxidation of PUFA produces many toxins, including carbon monoxide (Wolff, 1976), and one of the basic enzymes induced by stress is cyclooxygenase, producing prostaglandins. One of those, PGE2, activates heme oxygenase (Park, et al, 2009), the enzyme that produces carbon monoxide from the breakdown of heme, and it also activates aromatase, the enzyme that produces estrogen from androgens. The result is that the accumulating PUFA function as amplifiers of the cellular stress reactions. In experimental situations, the epigenetic changes produced by stress are reversible, but when the organism stays in the same sort of environment that started the process, reversals become less likely with increasing age.

Emotional stress is organized by the nervous system, changing hormones and cell functions that improve immediate survival. Glucose deprivation seems to be a feature of stress that activates the cell survival enzymes, including heme oxygenase and aromatase, and the autonomic nervous system controls the organism's reactions to stress, with the cholinergic parasympathetic system tending to reduce glucose oxidation. Exaggerated activation of this system produces shock, with extreme inhibition of respiratory metabolism, but in normal circumstances, this system's activity increases during the night and decreases during the day. Even under the normal cyclic activity of the nervous system, increased activity of heme oxygenase occurs during the night. Cholinergic chemicals activate heme oxygenase (Espada, et al., 2009; Hui, et al., 2012).

**Safe things that lower carbon monoxide or protect against its effects include methylene blue, caffeine, aspirin, progesterone and red light.**

In the state of learned helplessness or chronic despair, the relative dominance of the cholinergic system keeps the body in the inflamed, hypometabolic condition, in which rheumatoid arthritis, fibromyalgia, and sleep apnea are likely to occur. When carbon monoxide is produced in stress, the breakdown of the heme molecule also releases iron, and biliverdin, which is quickly turned into bilibrubin. Increases of bilirubin and carbon monoxide in the body fluids or breath can be seen in many chronic conditions, along with changes in tissue iron content.

Most publications have been concentrating on the increase of heme oxygenase and carbon monoxide during injury, sickness, and stress, with suggestions that treatments (chemicals or radiation) to increase its production could be beneficial. (Existing drugs that have been proposed for increasing heme oxygenase include resveratrol, metformin, and the statins.) However, many researchers have recognized that the short-term, local benefits are associated with very serious long-term harmful effects, including cancer, dementia, Parkinson's disease (Song, et al., 2017) and other neurodegenerative diseases (Schipper, 2000; Song, et al., 2006; Schipper and Song, 2015), arthritis (Devesa, et al., 2005), liver disease, and heart failure. Treatments to lower carbon monoxide production have been tried in

some of these. **Safe things that lower carbon monoxide or protect against its effects include methylene blue, caffeine, aspirin, progesterone, and red light.**

During stress and aging, hemoglobin can be released from red blood cells, and in that free form it's very toxic, and so is the heme fragment (called hemin when the iron is oxidized) that separates from the protein. The main function of heme oxygenase seems to be the removal of that toxic threat, but in the process, free iron and bilirubin are released, creating new toxic threats. Some experimenters (Regan, et al., 2004; Qu, et al., 2005, 2007) found that knocking-out HO-2 *reduced* the oxidative damage produced by hemoglobin and hemin in the brain.

The accumulation of iron in the tissues during stress and aging makes them progressively more likely to experience serious damage during moments of oxygen deprivation, as the iron atoms catalyze reactions such as lipid peroxidation (in which carbon monoxide is a product). Bilirubin, despite its ability to function as an antioxidant, is very toxic to nerve cells, blocking the respiratory enzyme (Day, 1954; Solá, et al., 2002; Vaz, et al., 2010), and promoting excitotoxic processes (Li, et al., 2012; Barateiro, et al., 2014; Yin, et al., 2016; Watchko, 2016). Bilirubin destabilizes red blood cells, tending to increase the spilling of hemoglobin and heme, contributing to a vicious circle, hemolysis increasing bilirubin increasing hemolysis.

**It's important to minimize "low level" stressors and injuries, and to optimize the protective factors, such as light, carbohydrate, thyroid hormone, carbon dioxide, and a sense of a meaningful future.** A positively beneficial environment supports constructive, and reconstructive, processes in the body that can correct much of the damage done by bad aspects of the environment, at any previous stage of development (Katz, et al., 1982; Yang, et al., 2015; Griñan-Ferré, et al., 2016; Kentner, et al., 2016;). All of the body's tissues, including the brain, are subject to revision and reconstruction. The weight of the brain, and the thickness of the cortex can be increased by environmental enrichment (Díaz, 1988; Rosenzweig and Bennett, 1996; Schrott, 1997; Lehohla, et al., 2004).

Since these major changes are now known to involve epigenetic "transitions" in cell type, of the sort that can be induced by carbon monoxide, it's possible to imagine that the proper function of heme oxygenase is to support progressive improvement in the organism's "phenotype," rather than the aging, inflammation, fibrosis, and cancer, that are now the eventual result of its activity. Heme oxygenase, and enzymes that make NO, HCN, and H2S, might simply need the guidance of an organism's response to an enriched environment.

When the organism is working meaningfully, useless structures tend to atrophy, as new structures are developed. This is a normal part of our design, in which the passive part of a functional system is remodeled to support the integral purpose. Unlike the specialization of a machine, the specialization in consciousness is always increasing the organism's flexibility, diversity, and generality.

Some people studying autism have found that animals exposed to carbon monoxide have some of the behaviors of autistic children. Various toxins that have been associated with the increased incidence of autism, for example acetaminophen, activate the body's production of carbon monoxide. Autistic people are often said to "think concretely," to be "cognitively rigid." Mechanistic reductionists "think concretely," by definition, and are often cognitively rigid.

The quality that's lacking in autism (Boucher, et al., 2007) and in mechanistic reductionism is temporal thinking, the ability to think across time, as well as through space. Reductionists are ideologically opposed to the idea that the future participates in all processes, which they call "teleology."

**Temporal thinking is the faculty that's engaged by an enriched environment, but it's wrong to call it "thinking," because it's simply the way organisms exist, when their development hasn't been blocked, physically or culturally.**

## REFERENCES

Clin Chim Acta. 2006 Dec;374(1-2):46-56. **Bilirubin toxicity to human erythrocytes: a review.** Alexandra Brito M, Silva RF, Brites D.

Ageing Res Rev. 2004 Jul;3(3):303-18. **Heme, iron, and the mitochondrial decay of ageing.** Atamna H.

Mol Neurobiol. 2014 Feb;49(1):424-39. **Rat cerebellar slice cultures exposed to bilirubin evidence reactive gliosis, excitotoxicity and impaired myelinogenesis that is prevented by AMPA and TNF-α inhibitors.** Barateiro A, Domingues HS, Fernandes A, Relvas JB, Brites D.

J Autism Dev Disord. 2007 Sep;37(8):1413-29. **Temporal cognition in children with autistic spectrum disorders: tests of diachronic thinking.** Boucher J1, Pons F, Lind S, Williams D.

Sleep. 2001 Mar 15;24(2):218-23. **Increase in bilirubin levels of patients with obstructive sleep apnea in the morning--a possible explanation of induced heme oxygenase-1.** Chin K, Ohi M, Shimizu K, Nakamura T, Miyaoka F, Mishima M, Nakamura T.

Exp Neurol. 1984 Oct;86(1):113-21. **Increased body:brain weight ratio in developing rats after low exposure to organic lead.** Cragg B, Rees S.

Proc Soc Exp Biol Med. 1954 Feb;85(2):261-4. **Inhibition of brain respiration in vitro by bilirubin; reversal of inhibition by various means.** Day RL.

Arthritis Rheum. 2005 Oct;52(10):3230-8. **Influence of heme oxygenase 1 modulation on the progression of murine collagen-induced arthritis.** Devesa I, Ferrándiz ML, Terencio MC, Joosten LA, van den Berg WB, Alcaraz MJ. ". . . *treatment with SnPP,* ***which inhibits HO-1, exerts prophylactic and therapeutic effects.***"

Behav Neural Biol. 1988 Sep;50(2):164-83. **Brain weights correlate with behavioral parameters in individual inbred mice housed in a common and enriched environment.** Díaz JL.

J Neurochem. 2009 Aug;110(3):1107-19. **The muscarinic M1 receptor activates Nrf2 through a signaling cascade that involves protein kinase C and inhibition of GSK-3beta: connecting neurotransmission with neuroprotection.** Espada S, Rojo AI, Salinas M, Cuadrado A. "***carbachol increased the levels of a prototypical phase II antioxidant enzyme, heme oxygenase-1."***

Front Aging Neurosci. 2016 Oct 18;8:241. eCollection 2016. **Environmental Enrichment Modified Epigenetic Mechanisms in SAMP8 Mouse Hippocampus by Reducing Oxidative Stress and Inflammaging and Achieving Neuroprotection.** Griñan-Ferré C, Puigoriol-Illamola D, Palomera-Ávalos V, Pérez-Cáceres D, Companys-Alemany J, Camins A, Ortuño-Sahagún D, Rodrigo MT, Pallàs M.

J Cardiovasc Pharmacol. 2012 Nov;60(5):474-82. **M3-mAChR stimulation exerts anti-apoptotic effect via activating the HIF-1α/HO-1/VEGF signaling pathway in H9c2 rat ventricular cells.** Hui Y, Zhao Y, Ma N, Peng Y, Pan Z, Zou C, Zhang P, Du Z.

J Nutr. 1982 Jul;112(7):1362-8. **Effects of undernutrition at different ages early in life and later environmental complexity on parameters of the cerebrum and hippocampus in rats.** Katz HB, Davies CA, Dobbing J.

Brain Behav Immun. 2016 Oct;57:151-160. **Environmental enrichment rescues the effects of early life inflammation on markers of synaptic transmission and plasticity.** Kentner AC, Khoury A, Lima Queiroz E, MacRae M.

Metab Brain Dis. 2004 Jun;19(1-2):25-33. **Effect of enriched environment on Ca2+ uptake via NMDA receptors into barrel cortex slices of spontaneously hypertensive rats.** Lehohla M, Russell VA, Kellaway L.

Exp Neurol. 2012 Sep; 237 (1) : 96-102. **Minocycline cannot protect neurons against bilirubin-induced hyperexcitation in the ventral cochlear nucleus.** Li CY, Shi HB, Ye HB, Song NY, Yin SK.

Biochem Biophys Res Commun. 2009 Feb 20;379(4):1043-7. **EP2 receptor activation by prostaglandin E2 leads to induction of HO-1 via PKA and PI3K pathways in C6 cells.** Park MK, Kang YJ, Ha YM, Jeong JJ, Kim HJ, Seo HG, Lee JH, Chang KC.

Cardiol Rev. 2009 May-Jun;17(3):99-111. **Targeting heme oxygenase: therapeutic implications for diseases of the cardiovascular system.** Peterson SJ, Frishman WH, Abraham NG.

J Cereb Blood Flow Metab. 2005 Nov;25(11):1466-75. **Effect of targeted deletion of the heme oxygenase-2 gene on hemoglobin toxicity in the striatum.** Qu Y, Chen J, Benvenisti-Zarom L, Ma X, Regan RF.

J Neurosurg. 2007 Mar;106(3):428-35. **Attenuation of oxidative injury after induction of experimental intracerebral hemorrhage in heme oxygenase-2 knockout mice.** Qu Y, Chen-Roetling J, Benvenisti-Zarom L, Regan RF.

BMC Neurosci. 2004 Sep 17;5:34. **Heme oxygenase-2 gene deletion attenuates oxidative stress in neurons exposed to extracellular hemin.** Regan RF, Chen J, Benvenisti-Zarom L.

Early Hum Dev. 1995 Oct 2;43(2):133-44. **Mapping of the consequences of bilirubin exposure in the immature rat: local cerebral metabolic rates for glucose during moderate and severe hyperbilirubinemia.** Roger C, Koziel V, Vert P, Nehlig A.

Behav Brain Res. 1996 Jun;78(1):57-65. **Psychobiology of plasticity: effects of training and**

**experience on brain and behavior.** Rosenzweig MR, Bennett EL.

Exp Gerontol. 2000 Sep;35(6-7):821-30. **Heme oxygenase-1: role in brain aging and neurodegeneration.** Schipper HM.

Int J Mol Sci. 2015 Mar 9;16(3):5400-19**. A heme oxygenase-1 transducer model of degenerative and developmental brain disorders.** Schipper HM, Song W. "*The glial HO-1 response may represent a pivotal transducer of noxious environmental and endogenous stressors into patterns of neural damage and repair characteristic of many human degenerative and developmental CNS disorders.*"

Int J Mol Sci. 2015 Mar 9;16(3):5400-19. **A heme oxygenase-1 transducer model of degenerative and developmental brain disorders.** Schipper HM1,2, Song W3.

Neurobiol Aging. 2017 Oct;58: 163-179. **Parkinsonian features in aging GFAP.HMOX1 transgenic mice overexpressing human HO-1 in the astroglial compartment.** Song W, Cressatti M, Zukor H, Liberman A, Galindez C, Schipper HM.

Acta Paediatr Suppl. 1997 Jul;422:45-7. **Effect of training and environment on brain morphology and behavior.** Schrott LM.

Acta Neurochir Suppl. 2003;86:389-94. **Depletion of endogenous serotonin synthesis with p-CPA attenuates upregulation of constitutive isoform of heme oxygenase-2 expression, edema formation and cell injury following a focal trauma to the rat spinal cord.** Sharma HS, Westman J.

Acta Med Port. 2002 Jul-Aug;15(4):269-75. **[Release of cytochrome C with the interaction of bilirubin, amyloid beta-peptide and glycochenodeoxycholate from isolated mitochondria].** Solá S, Diógenes MJ, Brites D, Rodrigues CM.

J Cell Physiol. 2006 Mar;206(3):655-63. **Overexpression of heme oxygenase-1 promotes oxidative mitochondrial damage in rat astroglia.** Song W, Su H, Song S, Paudel HK, Schipper HM. *"Glial HO-1 hyperactivity may contribute to cellular oxidative stress, pathological iron deposition, and bioenergetic failure characteristic of degenerating and inflamed neural tissues and may constitute a rational target for therapeutic intervention in these conditions."*

J Biol Chem. 2000 Feb 25;275(8):5395-9. **Overexpression of heme oxygenase in neuronal cells, the possible interaction with Tau.** Takeda A, Perry G, Abraham NG, Dwyer BE, Kutty RK, Laitinen JT, Petersen RB, Smith MA.

J Mol Cell Cardiol. 2004 Jun;36(6):821-30. **Transient glucose deprivation causes upregulation of heme oxygenase-1 and cyclooxygenase-2 expression in cardiac fibroblasts.** Takeda K, Lin J, Okubo S, Akazawa-Kudoh S, Kajinami K, Kanemitsu S, Tsugawa H, Kanda T, Matsui S, Takekoshi N.

J Neurochem. 2010 Jan;112(1):56-65. **Bilirubin selectively inhibits cytochrome c oxidase activity and induces apoptosis in immature cortical neurons: assessment of the protective effects of glycoursodeoxycholic acid.** Vaz AR, Delgado-Esteban M, Brito MA, Bolaños JP, Brites D, Almeida A.

Clin Perinatol. 2016 Jun;43(2):297-311. **Bilirubin-Induced Neurotoxicity in the Preterm Neonate.** Watchko JF.

Biochem Biophys Res Commun. 1976 Dec 20;73(4):850-7. **The formation of carbon monoxide during peroxidation of microsomal lipids.** Wolff DG.

J Mol Neurosci. 2015 Jun;56(2): 278-89. **Cognitive Improvement Induced by Environment Enrichment in Chronic Cerebral Hypoperfusion Rats: a Result of Upregulated Endogenous Neuroprotection?** Yang Y, Zhang J, Xiong L, Deng M, Wang J, Xin J, Liu H.

Toxicol Lett. 2016 Jan 5;240(1):1-9. T**he role of gamma-aminobutyric acid/glycinergic synaptic transmission in mediating bilirubin-induced hyperexcitation in developing auditory neurons.** Yin XL, Liang M, Shi HB, Wang LY, Li CY, Yin SK.

**********