Rosacea, inflammation, and aging: The inefficiency of stress

From the original article in 2013. Author: Ray Peat.

> *"Rosacea, or acne rosacea, has been defined as "vascular and follicular dilation involving the nose and contiguous portions of the cheeks . . ." that may involve persistent erythema with hyperplasia of sebaceous glands."*
> Stedman's Medical Dictionary 23rd edition

Light-skinned people, especially women between the ages of 30 and 50, sometimes develop a persistent redness of their cheeks and nose. It may begin as a tendency to flush excessively, but the blood vessels can become chronically dilated. Similar processes occur in dark-skinned people less frequently.

The eyes are sometimes involved, with redness of the exposed areas (conjuctival hyperemia). New blood vessels develop in the area, and the flow of blood through the affected tissue is greatly increased. The tissues become thickened and fibrotic, with the multiplication of fibroblasts and the increased deposition of collagen.

The cornea normally receives its oxygen from the air, and its nutrients from the aqueous humor. As rosacea of the eye develops, the blood vessels surrounding the cornea become increasingly visible, and, especially on the inner (nasal) side of the eye, the vessels tend to enlarge and become tortuous. Rhinophyma, or potato nose, has been described as a late development of rosacea.

Too often, the medical reaction is to give the condition a name, and to distinguish its variants as if they were different problems, and then to use the most direct means to eliminate the problem they have defined.

A typical attitude is that "Rosacea is an enigmatic disease with multiple exacerbations and remissions, and, unfortunately, treatment is directed toward symptomatic control rather than cure" (Randleman).

Lasers or other radiation, caustic chemical abrasion, surgical planing and dermal shaves, and other forms of surgery may be used to destroy the superficial blood vessels, and to reduce the enlarged nose or other irregularities. A few decades ago, when rosacea was believed to be the result of a local infection, antibiotics were used to treat it, and some of them, including tetracycline, helped. It was discovered that some antibiotics have anti-inflammatory actions, apart from their germicidal effects, and now it is very common to prescribe the chronic use of tetracycline to suppress symptoms.

Rosacea, and the fibrotic changes associated with it (pingueculae and pterygia in the eyes, rhinophyma of the nose, etc.), are much more than "cosmetic" issues, involving the skin and eye surface. If the invasive proliferation of blood vessels can be prevented, it's important to do that, because, for example, pannus/neovascularization of the cornea can seriously impair vision.

But possibly the strangest thing about the relationship of the medical profession to rosacea is that its essential features, invasive neovascularization and fibrotic growth, are of great interest when they occur elsewhere, and many physiological processes are known to regulate the growth of blood vessels and fibroblasts, but nearly all the attention given to rosacea and rhinophyma concerns control of symptoms for cosmetic effect. Rosacea is a physiological problem that deserves consideration in the light of all that's known about physiology and developmental biology.

The increased incidence of rosacea after the age of 30, and the fact that it occurs most commonly in the areas that are most exposed to sunlight (bald men sometimes develop it on the top of the head), indicate that aging and irritation are essential causes. Stress, irritation (such as produced by ultraviolet or ionizing radiation or free radicals), and aging are known to cause disorganized growth of fibrous and vascular tissues in various parts of the body. The occurrence of these processes at the surface, where the changes can be observed immediately, and without invasive procedures, should have aroused wide interest among those who study kidney disease, diabetes, and other degenerative diseases in which fibrosis and neovascularization play important roles.

A localized stress or irritation at first produces vasodilation that increases the delivery of blood to the tissues, allowing them to compensate for the stress by producing more energy. Some of the agents that produce vasodilation also reduce oxygen consumption (nitric oxide, for example), helping to restore a normal oxygen tension to the tissue. Hypoxia itself (produced by factors other than irritation) can induce vasodilation, and if prolonged sufficiently, tends to produce neovascularization and fibrosis.

Sensitivity to the harmful effects of light can be increased by some drugs and by excess porphyrins produced in the body (and by the porphyrin precursor, delta-amino levulinic acid), leading to rosacea, so those factors should be considered, but too often alcohol (which can cause porphyrin to increase) is blamed for rosacea and rhinophyma, without justification. There are many ways in which poor health can increase light sensitivity. Some types of excitation produced by metabolites (or by the failure of inhibitory metabolites) can produce vasodilation, involving the release of nitric oxide (Cardenas, et al., 2000), setting off a series of potentially pathological reactions, including fibrosis. The nitric oxide increases glycolysis while lowering energy production. The excitatory metabolite glutamate, and nitric oxide, are both inhibited by aspirin (Moro, et al., 2000).

When blood flow in skin affected by rosacea was measured, circulation was 3 or 4 times higher than normal (Sibenge & Gawkrodger, 1992), and oxygen tension may be increased. An inability to extract oxygen from the blood, or to use it to produce energy, will produce the same hyperemia that would be produced by a lack of oxygen. These measurements suggest that mitochondrial defects would be the best place to look for a general cause of rosacea.

When mitochondria are damaged, active cells produce increased amounts of lactic acid, even in the presence of adequate

oxygen. Otto Warburg identified this kind of metabolism, aerobic glycolysis, as an essential feature of cancer, and showed that it could be produced by stress, ionizing radiation, carcinogenic toxins, and even by a simple oxygen deficiency. Other investigators around the same time showed that lactic acid produces vasodilation (for example, in the cornea), and more recently it has been shown to promote the development of fibrosis, and it has been called a "phlogogen," a promoter of inflammation.

Riboflavin, vitamin B2, is an essential component of the mitochondrial respiratory enzymes, and it is very easily destroyed by light (blue light and especially ultraviolet). When it is excited by high energy light, it can spread the damage to other components of the mitochondria, including the cytochromes and the polyunsaturated fatty acids. The other B vitamins are affected when riboflavin's actions are disturbed.

Vitamin K is also extremely light sensitive, and it interacts closely with coenzyme Q in regulating mitochondrial metabolism. For example, mitochondrial Complex-I, NADH-ubiquinone reductase, is probably the most easily damaged part of the mitochondrion, and it is protected by vitamin K. Vitamin E, coenzyme Q, and the polyunsaturated fatty acids are also light sensitive, and they are more susceptible to free radical damage when vitamin K is deficient.

Niacinamide, one of the B vitamins, provides energy to this mitochondrial system. Under stress and strong excitation, cells waste niacinamide-NADH, but niacinamide itself has a sedative antiexcitatory effect, and some of its actions resemble a hormone. Estrogen tends to interfere with the formation of niacin from tryptophan. Tryptophan, rather than forming the sedative niacin (pyridine carboxylic acid), can be directed toward formation of the excitatory quinolinic acid (pyridine dicarboxylic acid) by polyunsaturated fatty acids. Excitation must be in balance with a cell's energetic resources, and niacinamide can play multiple protective roles, decreasing excitation, increasing energy production, and stabilizing repair systems. The state of excitation and type of energy metabolism are crucial factors in governing cell functions and survival.

The polyunsaturated fatty acids, besides their interactions with estrogen and tryptophan metabolism, promote excitation and decrease energy production in several other ways. For example, they increase the excitatory effects of the glutamate pathways (Yu, et al., 1986; Nishikawa, 1994), and their breakdown products inhibit mitochondrial respiration (Humphries, et al., 1998; Picklo, et al., 1999; Lovell, et al., 2000).

The excess excitation that produces nitric oxide and lactic acid lowers the energy production of vascular cells, possibly enough to lower their contractile ability (Geng, et al., 1992), causing vasodilation. When flushing is caused by a mismatch between energy supply and energy demand, caffeine can decrease the vasodilation (Eikvar & Kirkebøen, 1998), but when vasodilation is caused more physiologically by carbon dioxide, caffeine doesn't have that effect (Meno, et al., 2005). In a study in which drinking hot water or coffee was compared with drinking room-temperature coffee or caffeine, it was found that the hot liquids caused flushing, but cool coffee and caffeine didn't.

Caffeine increases cells' energy efficiency, and by opposing the effects of adenosine (secreted by cells that are stressed and energy-depleted), it can inhibit vasodilation, angioneogenesis (Merighi, et al., 2007; Ryzhov, et al., 2007), and fibrosis (Chan, et al., 2006).

One nearly ubiquitous source of inappropriate excitation and energy depletion is the endotoxin, bacterial lipopolysaccharides absorbed from the intestine (Wang and White, 1999). That this ubiquitous toxin has a role in rosacea is suggested by the observation that intestinal stimulation, to speed transit through the bowel, immediately relieved symptoms (Kendall, 2002). Increased cortisol (Simon, et al., 1998) and sepsis (Levy, 2007) interfere with mitochondrial energy production.

Simple nervous blushing or flushing is usually considered harmless, and when a person is overheated, the reddening of the skin has the function of facilitating heat loss, to restore a normal temperature. But even nerve-regulated flushing can involve a distinct interference with mitochondrial respiration, and can stimulate the overgrowth of blood vessels.

Cancer's respiratory defect that Warburg identified, fermentation with lactic acid production even in the presence of adequate oxygen, was the result of some kind of injury to the mitochondria. He showed that one of the injuries that could produce aerobic glycolysis was a deficiency of riboflavin. He observed that tumors generally were anoxic, and that cancers typically appeared in the midst of tissue that was atrophying, and suggested that the cancer cells' survival was favored by their ability to live without oxygen. This may be relevant to the observations of many surgeons of a small cancer embedded in the fibrous tissue of large rhinophymas that have been removed.

The relatively high incidence of rosacea among women (some studies indicate that it may be 3 times as common in women as in men) isn't likely to be the result of greater sun exposure, so it's reasonable to look for hormonal causes.

In old age, it's well recognized that men's estrogen level rises. But the estrogen industry has convinced women that their estrogen declines as they get older. It's common knowledge that aging rodents often go into "persistent estrus," and that their estrogen levels generally increase with age (Parkening, et al., 1978; Anisimov and Okulov, 1981). Several studies in women have shown that serum estrogen levels rise from the teens into the 40s (Musey, et al., 1987; Wilshire, et al., 1995; Santoro, et al., 1996).

Other studies show that serum and tissue estrogen concentrations are not concordant, and that some tissues may contain several times as much estrogen as the serum (Jefcoate, et al., 2001). Local irritation increases tissue estrogen content.

The antiestrogens, especially progesterone, begin declining in the 30s, so that the rising estrogen has more effect on the tissues during those years. These are the years in which the incidence of rosacea rises suddenly. Rosacea develops later on average in men, whose estrogen levels rise significantly at later ages.

Estrogen's most immediate effect on cells is to alter their oxidative metabolism. It promotes the formation of lactic acid. In the long run, it increases the nutritional requirements for the B vitamins, as well as for other vitamins. It also increases the

formation of aminolevulinic acid, a precursor of porphyrin, and increases the risk of excess porphyrin increasing light sensitivity. Both aminolevulinic acid and excess porphyrins are toxic to mitochondria, apart from their photosensitizing actions. Nitric oxide, glutamate, and cortisol all tend to be increased by estrogen.

Veins and capillaries are highly sensitive to estrogen, and women are more likely than men to have varicose veins, spider veins, leaky capillaries, and other vascular problems besides rosacea. Estrogen can promote angioneogenesis by a variety of mechanisms, including nitric oxide (Johnson, et al., 2006). "Estrogens potentiate corticosteroid effects on the skin such as striae, telangiectasiae, and rosacea dermatitis" (Zaun, 1981). Early forms of oral contraceptives, high in estrogen, were found to increase acne rosacea more than three-fold (Prenen & Ledoux-Corbusier, 1971).

Lactic acid, produced under the influence of estrogen, nitric oxide, or other problems of energy formation, besides causing vasodilation, also stimulates the growth of fibroblasts. Oxygen deprivation, or damage to mitochondria, will increase lactic acid formation, and so it will immediately cause vasodilation, and if the problem is prolonged, new blood vessels will grow, and fibrous connective tissue will increase. Estrogen stimulates collagen synthesis, and it has been associated with a variety of inflammatory and fibrotic conditions (for example, Cutolo, et al., 2003. Payne, et al., 2006, suggest the use of the anti-estrogen, tamoxifen, to treat rhinophyma.)

The cornea normally contains more riboflavin even than the retina, which has a much higher rate of metabolism. When the cornea isn't able to get enough oxygen from the air for its needs (and if riboflavin is deficient, its need for oxygen is increased), surrounding blood vessels at first dilate in response to the diffusing lactic acid, to increase the blood supply to the edges of the cornea. If the problem is prolonged, the conjuctiva becomes chronically blood-shot, hyperemic, and larger more visible blood vessels grow, surrounding the cornea, or even invading the cornea. Many people, especially women, experienced problems of this sort from wearing contact lenses, especially when the lenses were made of materials very impermeable to oxygen (Dumbleton, et al., 2006).

Sunlight, and mechanical obstruction of the cornea, produce very localized effects, but those local effects are more likely to be harmful when there is a systemic nutritional deficiency or excess of estrogen. When the systemic problem is very severe, the cheeks, nose, and eyes might not be the first tissues to experience a functional disturbance.

The mitochondrial inhibition produced by the action of the parasympathetic nervous system (occurring in simple blushing) can occur wherever those nerves act, and blood vessels in all parts of the body are responsive to the acetylcholine secreted by those nerves. Sleep typically involves a shift of dominance in the autonomic nervous system toward the parasympathetic nerves, with vasodilation. Nosebleeds, especially in children, commonly occur during sleep (Jarjour & Jarjour, 2005: high incidence in sleep, and association with migraine).

A 3 year-old child who had been having an average of 3 nosebleeds every day, during a nap and at night, for several months, also had an extreme behavior problem. He became angry and sometimes violent when he went a little longer than normal between meals. After an oral dose of about ten milligrams of riboflavin, he was able to sleep without having another recurrence of the nosebleeds, and his tantrums became rare. Apparently, the nerve-regulated vasodilation produced by sleep, combined with a riboflavin deficiency, had been enough to produce nosebleeds. The energy deficit resulting from a systemic riboflavin deficiency had probably been causing him to be abnormally sensitive to glycogen depletion, producing sudden anger. In another individual, the energy problem might have taken the form of a memory problem, or of a hemorrhage in the brain or other essential organ.

A 37 year old slightly alcoholic man with a bright red nose and cheeks was an amateur fiction writer, but he was having trouble with his memory for words, and for everyday events. Even conversationally, he had to struggle for relatively familiar words. On the suggestion that riboflavin might help his memory, by allowing his brain cells to use oxygen more efficiently, he had his doctor give him an intravenous injection of B vitamins. When I saw him the next day, his conversation was perfectly fluent, and he obviously had easy access to a good vocabulary. Just as noticeable was the normal color of his nose and cheeks. For a week, he had a daily injection of the B vitamins, and his nose color and vocabulary stayed normal. But on the weekend, after not having the shots for two days, his nose and cheeks were again maraschino cherry red, and his speech was halting, as he struggled for words. He forgot the whole episode, and neglected to return to the doctor for more of the vitamin injections. Ten years later, he had developed a medium-sized potato nose, and had his heart valves replaced.

His vitamin requirements were apparently abnormally high. At first, the problems resulting from damaged mitochondria seem mostly functional (flushing, mood, memory problems, etc.) and variable, but chronically disturbed functions lead to structural, anatomical changes, as prolonged stimulation alters tissue maintenance and growth.

Abram Hoffer, who had been treating schizophrenia and senile dementia with niacin, accidentally discovered that it cured his bleeding gums. That led to its use to treat heart disease.

The "orthomolecular" ideas of Hoffer and Linus Pauling were developed in a context of biochemistry governed by genetics, molecular biology, in which the goal was to provide a chemical that was lacking because of a genetic defect in metabolism. Their idea of using nutrients as drugs has led to many unphysiological practices, in which an isolated nutrient is supposed to have a drug-like action, and if in isolation it doesn't act like a drug, then it should be used only according to the normal genetically determined nutritional requirement.

But in reality, nutritional requirements are strongly influenced by history and present circumstances. For example, when corneal mitochondria have been damaged by riboflavin deficiency, they have been found to subsequently require more than the normal amount of the vitamin to function properly. And the presence of a certain amount of one nutrient often increases or decreases the amount of other nutrients needed.

When the interactions among energy expenditure and energy production, and cellular activation and cellular inhibition, are taken into account, then it's clear that any particular problem is likely to have many causes and many factors that could

contribute to a cure.

Lactate, glutamate, ammonium, nitric oxide, quinolinate, estrogen, histamine, aminolevulinate, porphyrin, ultraviolet light, polyunsaturated fatty acids and endotoxin contribute to excitatory and excitotoxic processes, vasodilation, angioneogenesis, and fibrosis.

Carbon dioxide, glycine, GABA, saturated fatty acids (for example, Nanji, et al., 1997), vitamin K, coenzyme Q10, niacinamide, magnesium, red light, thyroid hormone, progesterone, testosterone, and pregnenolone are factors that can be increased to protect against inappropriate cellular excitation.

All of the nutritional factors that participate in mitochondrial respiration contribute to maintaining a balance between excessive excitation and protective inhibition. Riboflavin, coenzyme Q10, vitamin K, niacinamide, thiamine, and selenium are the nutrients that most directly relate to mitochondrial energy production.

Coffee is often avoided by people with rosacea, but it is a very good source of niacin and magnesium, and caffeine has some of the same cell-protective functions as niacinamide.

People suffering from rosacea have been found to be more likely than average to have suffered from styes in childhood, to have varicose veins and spider veins, and to suffer from migraines and depression.

Hypothyroidism has been identified as a factor in all of those. Good thyroid function is necessary for resistance to bacterial infection, for regulation of blood sugar, neurotransmitters, and hormones related to mood, and for the formation of progesterone. Progesterone regulates smooth muscle tone, including the walls of veins, so that a deficiency allows veins to enlarge. It also prevents overgrowth of fibrotic tissue, and in some contexts may inhibit angioneogenesis.

GABA itself tends to raise body temperature (Ishiwata, et al., 2005), by controlling vasodilation, and the factors such as progesterone which protect mitochondrial energy production are also thermogenic, supporting the GABA system. Flushing, both by directly causing heat loss and by reducing mitochondrial energy production, tends to lower body temperature.

The sun-damaged areas in rosacea can be directly provided with some of the protective factors by applying them topically. In the same way that topical lactate can cause vasodilation and disturbed energy metabolism (Rendl, et al., 2001), topical niacinamide, progesterone, vitamin K, and coenzyme Q10 can improve the metabolism and function of the local tissues. Riboflavin can probably be useful when applied topically, but because of its extreme sensitivity to light, it should usually be used only internally, unless the treated skin is covered to prevent exposure to light. Topically applied caffeine, even after sun exposure, can reduce local tissue damage (Koo, et al., 2007). Aspirin and saturated fats can also be protective when applied topically.

Some of the benefit from antibiotics probably results from the reduced endotoxin stress when intestinal bacteria are suppressed. However, antibiotics can kill the intestinal bacteria that produce vitamin K, so it's important to include that in the diet when antibiotics are used.

Some fibers, such as raw carrots, that are effective for lowering endotoxin absorption also contain natural antibiotics, so regular use of carrots should be balanced by occasional supplementation with vitamin K, or by occasionally eating liver or broccoli.

Abram Hoffer's research was instrumental in getting niacin recognized as a heart protective drug, but nearly everyone who prescribes it does so to lower blood lipids. That wasn't Hoffer's understanding of its function. He thought it acted directly on blood vessels to protect their integrity. During his studies of its effects on heart disease, he saw that it also lowered cancer mortality, and so began treating cancer patients with it, with considerable success, but there was no medical cliché that could allow the profession to follow in that direction.

The arguments I have outlined for considering rosacea to be essentially a problem of metabolic energy, and the mechanisms that I mention for restoring mitochondrial functions, might seem more complex than Hoffer's orthomolecular views. However, this approach is actually much simpler conceptually than any of the ideologies of drug treatment. It simply points out that certain excitatory factors can interfere with energy production, and that there are opposing "inhibitory" factors that can restore energy efficiency. Sometimes, using just one or two of the factors can be curative.

Because mitochondrial respiration is very similar in every kind of tissue, a physiological view of rosacea could incline us toward considering the effects of these metabolic factors in other organs during stress and aging--what would the analogous condition of rosacea and rhinophyma be in the brain, heart, liver, or kidney?

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lens cortex, and lens nucleus. A trend toward increasing concentrations of riboflavin occurred in the retina and blood in response to excess dietary riboflavin, but the concentration changes were not statistically significant. The highest concentration of FAD and FMN occurred in the retina followed by the cornea and the lens cortex and nucleus. The relative contribution of riboflavin, FMN, and FAD to the total flavin pool was markedly different in the various tissues of the eye. The proportion of tissue flavins present as riboflavin decreased from anterior to posterior. It was highest in the cornea followed by lens and retina. The pattern of distribution for FMN was: cornea greater than retina greater than lens cortex and nucleus.

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