Ray Peat's Newsletter

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THE ORIGINAL ARGUMENT:

Cancer is the result of ordinary physiological processes which become autonomous because of regulatory weaknesses in the organism.

Respiration is essential for the maintenance of the higher forms of life, and it is a respiratory defect, on both the cellular and the organismic levels, which allows cancer to persist and develop.

The heme group, because it serves many respiratory functions--hemoglobin, mitochondrial respiratory enzymes, steroid synthesizing enzymes, formation of thyroid hormone, detoxifying enzymes--is regulated in relatively primitive ways within each cell, and in more complex ways at higher organismic levels.

When the cell needs more respiratory energy, some fuel is diverted into the production of porphyrin, which is then turned into heme, which would normally provide for the efficient production of energy and protective factors.

When the efficient energy-producing systems are blocked, by injury, oxygen deficiency, toxins, or by the lack of one or more essential nutritional factors, heme production is activated.

Excess heme is destroyed by the enzyme heme oxygenase, which converts heme into biliverdin and carbon monoxide. Both of these factors have effects on the cell which are characteristic of cancer.

Estrogen, radiation, chemical carcinogens, and other forms of stress, activate the heme oxygenase enzyme.

Estrogen causes both porphyria and jaundice and is associated with increased formation of carbon monoxide. It inhibits many types of liver function, including detoxification.

The production of carbon monoxide by cancer cells can account for cancer's self-sustaining, "hereditary," property, without invoking genetic mutations which are now known to be consequences, rather than causes of cancer.

The production of carbon monoxide and biliverdin can account for many of the structural and biochemical abnormalities of cancer cells, and for their induction of abnormalities in adjacent cells.

"Genetic" theories of cancer have now reached a dead end, and the epigenetic, developmental-physiological approach remains as the only plausible description of cancer.

Carbon monoxide, estrogen, and the medical cancer cult

Previously when I wrote about the role of endogenously formed carbon monoxide in cancer, I probably didn't say enough about the way the idea fits into our cultural context. If an idea is very different from the existing cultural matrix, it's probably useful to consider it in its historical setting, and to contrast its theoretic models and implications with conventional models and practices, besides looking at some of the evidence that could confirm it.

During Otto Warburg's lifetime, many people working on the cancer problem were sufficiently aware of his work (because of his Nobel prize) that they occasionally mentioned it dismissively. Now, very few people even know about his cancer research and his conclusion that the prime cause of cancer is a cellular respiratory defect. For about 30 years, the dunces were in confederacy against him, then they forgot what it was about his work that had bothered them.

Dean Burk, who was head of the cell biochemistry laboratory at the NIH for many years, was the only well known American who defended Warburg's interpretation of cancer, and now that they both have died, cancer researchers just don't feel the need to mention Warburg's work at all.

In practice, science isn't a matter of a rational evaluation of evidence, but rather it's a matter of power, funding, and propaganda. In our culture, the understanding of cancer has been guided since the late 1940s by the propaganda of the American Cancer Society, supported by the corporate cancer industry and, especially since Nixon's War on Cancer began in 1971, by government funding.

Warburg's work showed that anything which causes tissue atrophy contributes to the development of cancer, and that interference with the

cells' ability to use oxygen for energy production was the essential factor in cancer. Warburg was exploring this simple deterministic biochemical, physiological and developmental process in Germany just as quantum mechanics was destroying classical physics and Nazism was enforcing the dogma of genetic determinism and eugenics. The revision of Darwinism taking place at this time turned the doctrines of random mutation of genes and selection of "superior genes" into the essential core of biology and medicine.

The same concepts were used to describe socially undesirable people (people whose genes had "degenerated") and the biologically undesirable cells of cancer.

There were reasons for commerce and government to favor a theory of cancer in which a mysteriously random process turned a normal cell into a deadly alien cell that multiplied wildly and invaded and destroyed surrounding healthy tissues. One reason was that causes of cancer, such as soot, radiation, and estrogen, would become very unpopular if the public recognized the causal pathways between them and cancer, and polluters could be sued or accused of murder, and drug companies would lose the chance to market all of their infinitely profitable estrogens.

And the idea of a mysteriously mutated cancer cell ruled out the idea of any therapy that would cause the cancer to regress or disappear in a physiological manner that didn't harm any other part of the body. The already established treatments of surgical removal, destruction by radiation, or destruction by cytotoxic chemicals were justified by the doctrine that the tumor, the clone of cells produced from the mutant cell, was irreversibly committed to its condition.

The scientific foundation for that view of cancer has really been destroyed over the last fifty years, but it is rare to encounter a physician or professor of medicine who is aware of that. Even the majority of biology professors haven't realized the decisive nature of the evidence against it, because most of them don't read outside their own specialty.

Oncology (which should mean the study of tumors) is really a medical religion, filled with rituals and incantation-like use of language. Despite the abundant evidence that access to medical diagnosis and treatment doesn't improve health, most people are mysteriously bound to the "health care system." Hotels don't have 13th floors, many people don't like it when a black cat crosses their path, or they knock on wood at odd moments in a conversation, even though they aren't superstitious. The culture influences behavior, just by being there. When your friends recite their version of the medical incantations, and your doctor repeats them while wearing a white jacket and expensive shoes, it seems only decent to go along with the system. Even if patients would like to question their doctors' assumptions, they can't do it successfully within the medical culture, and few people are willing to take a hostile stance toward a system that monopolizes many useful drugs.

The mutant cell/clonal theory of cancer reduces the issue to a matter of choosing the best way to kill the patient's tumor without killing the patient. Very slowly, the practice of using a single modality against each type of tumor is being replaced by trials using several substances at the same time, or sequentially, and oncologists now sometimes magnanimously allow their patients to take vitamins as well as psychotherapy, though many have feared that the vitamins might interfere with their work.

Outside the medical world of oncogenes and mutations, the understanding of cancer as a disorganization of metabolism and regulatory processes is advancing.

Johanes Muller argued in 1840 that cancer might originate at the level of tissues, rather than in the nature of the individual cells making up the tissue. More recently, David Smithers described cancer as a problem of organization, analogous to a traffic jam, which can disrupt the system even while no particular vehicle is defective. Generally, this view speaks of a "cancer field," in which whole regions of an organ show different degrees of a precancerous or cancerous state.

The "precancerous" condition of some of the cells within the cancer field can be shown to be induced by something emitted by seriously injured cells nearby. In radiation research, these effects are now described as the "bystander effect," in which unirradiated cells that are exposed to

radiation-damaged cells will develop some of the physiological features of the irradiated cells. Some kind of "toxic signal" has been released from an injured cell, inducing a similar injury in the healthy cells.

Irradiated tissues respond with most of the features that are involved in general systemic stress--lipid peroxidation, free radicals, increased glycolysis, and a shift of metabolism toward production of the "emergency" factors that increase resistance in the short term. Other kinds of injury--overstimulation or energy deprivation, for example--cause cells to produce the same sorts of signals that affect surrounding cells. The extracellular matrix in which cells are embedded transmits these signals, partly by undergoing its own transformation into a differently structured matrix.

Systemic metabolic problems make local problems worse, and if a local injury is serious, it can cause the liver to produce stress-related proteins called "acute phase proteins," including fibrinogen and serum amyloids A and P, C-reactive protein, and other inflammation-related proteins. These proteins are a primitive sort of immune system, that can directly bind to some harmful substances. Endotoxin absorbed from bowel bacteria is probably the commonest reason for increased production of these proteins. The acute phase proteins contribute to the development of tumors in various ways. For example fibrinogen degradation products are pro-inflammatory. Although these are called acute phase proteins, they sometimes might better be called chronic inflammation proteins, since they are associated with diabetes, cancer, and heart disease.

The systemic principle of cancer involves the same inflammatory mechanisms that are involved in circulatory diseases, strokes, multiple sclerosis, multiple organ failure, etc. An inflammatory process that isn't controlled causes blood vessels to leak, and the process of disposing of the leaked materials, if the leakage is extensive, leads to reactions of the whole organism; usually, the signals reaching the higher levels of organization evoke a stress-limiting response, and stability is restored, but if conditions aren't just right, the stress-induced damage accumulates. With repeated injury, and with chronic accumulation of polyunsaturated fats, fibrosis, atrophy and inflammation increase, and the energetic intensity of corrective responses decreases.

The first reaction to serious injury, challenge or deprivation is to prepare for growth and cell division. The simple production of lactic acid when oxygen supply isn't adequate causes blood vessels to dilate. Energy production becomes inefficient; the fatty acid synthesizing enzyme system is activated, even when large amounts of fat are being made available by lipolysis under the influence of stress. In proportion to the challenge, capillaries become more permeable, and cells may begin to enter the tissues from the bloodstream, along with water and nutrients. A surge of cell division allows renewal of damaged cells. If the inflammation persists, new capillaries grow, and larger vessels develop. Some of the immigrant cells may eat themselves to death removing debris, but others remain as colonists. Every inflammation is an incipient neoplasm. An organ such as the intestine, the liver, ovary, or thymus gland, is always in flux, renewing its cells, but when that renewal is disordered, the functions of the organ change, such that we speak of a neoplasm, a new growth, which in a sense is a new organ. It has been suggested (Zajicek) that the neoplastic organ has an adaptive, survival value, producing one or more substances that the body lacks.

Zajicek supports his idea with careful analysis of cancer statistics, and points out that it's very common for the removal of a large tumor to be followed quickly by the appearance of myriad small tumors. He thinks it would be better to leave the original tumor in place. His orientation is in the tradition of "chalone" research, in which every tissue stops growing at the proper time because it emits a substance which specifically inhibits its own growth. Over the last 50 years the idea has been confirmed by many experiments, but it hasn't made any impression on the cancer industry. Stating the idea in very broad terms, we might say that aging or stress causes atrophic processes including "sarcopenia" and "osteopenia," the reduction of the mass of various tissues below the proper level, and that tumors are the result of an uneven attempt to restore the proper mass of tissue.

I think Zajicek's idea would be more acceptable if it were stated in more general terms, without denying the possible role of chalones, or something like chalones that tends to protect the body or suppress tumors. Using Le Chatelier's principle,* that a system adjusts to disturbance in a way that reduces the disturbance, we could say that one function of a tumor might be to dispose of something that has disturbed homeostasis.

For example, insulin resistance produces an inability to oxidize glucose, and is associated with chronic hyperglycemia, or "type 2 diabetes." Diabetes of that type is associated with a high risk of cancer (e.g., Yam, et al., 1996). V.S. Shapot's decades of research led him to describe a tumor as a glucose scavenger (1979). When the system is disturbed by chronic hyperglycemia and an inability to use glucose, a sort of equilibrium will be restored by the production of a tumor that pumps glucose out of the system. Although tumors consume sugar and release lactic acid, they aren't really living on the sugar, they are doing something very odd: They convert a large amount of glucose into fat, and then oxidize the fat. The enzyme system, fatty acid synthase (FAS), is an effective way to dispose of glucose, because of its energetic inefficiency.

Another way to look at Zajicek's idea is to recognize that the main cause of insulin resistance is the dietary consumption of (both omega -6 and omega -3) polyunsaturated fatty acid, and that the fats produced by the FAS in tumor cells are mainly saturated fatty acids, with some of the antiinflammatory omega -9 series. In this case, Zajicek's suggestion that the tumor is producing something the body needs would be literally correct.

The same "epigenetic" processes that create our organs, under new conditions can create tumors. The doctrine of genetic determinism has almost reversed the basic meaning of "epigenetic," since developmental biologists talk as if developing organs were all programmed in the genome, and that they were created as if from a blueprint contained in the genes. During ordinary development, we think of epigenesis as a process that creates an organism in a certain environment, and we recognize that even the protected intrauterine environment allows great individuality of development, influenced by slight differences in conditions of nutrition, hormones, temperature, etc., during an individual's development. Epigenesis accounts for a lot of normal variation in traits--size of brain and other organs, rate of maturation, degree of pigmentation, etc.--and for many developmental defects. Epigenesis is an even more important concept for understanding tumors, despite the fact that so much money has been invested in explaining tumors according to oncogenes and other ideological inventions of the genetic determinists. Even oncogenes' expression is environmentally determined.

The normal cyclic function of the ovaries is a model for the potentially creative role of an inflammation-like stress. Every month (in a rhythm influenced by many cues), a productive crisis comes to a focus in the ovary, with the formation of estrogen, prostaglandins, carbon monoxide, and other signal substances, causing rapid changes both locally and systemically, with water, hormones, and nutrients gathering around the ovum (as well as in other parts of the body, such as the feet). Then as the follicle ruptures with the release of an ovum, the excitatory, inflammation-like state is resolved, with a massive increase in the production of the antiinflammatory, antistress substance, progesterone, leading to the suppression of the excitatory substances. **These monthly processes are developmental, they are part of the epigenetic development of the organ.**

Most, if not all, of the substances involved in ovarian physiology are involved in the diseases of stress and degeneration, which progress in proportion to the inability to produce the resolution of inflammation and restoration of the stable condition. The ovary is a major source of estrogen, which can produce the excited, activated, inflammatory and proliferative state in any tissue of the body, though it acts mainly on the uterus, breasts, and pituitary. But the ovary is also, in response, able to produce massive amounts of the protective progesterone, which interrupts the inflammatory effects of estrogen on the various tissues and organs, largely by suppressing the proteins that hold estrogen within cells (especially the "estrogen receptor"), but also by changing the activities of many enzymes away from the

estrogen-controlled, inefficient pattern. **The developmental actions of the ovary cause continuing epigenetic processes in other organs, causing noticeable changes in their structure every month.**

The ovary plays a specialized coordinating role in preparing the whole body for pregnancy, but most of its regulatory features can be seen in a diminished form in other organs, and in any tissue that is unable to completely resolve a crisis of inflammation. Considering ovarian processes and structures in detail will offer some insights into the processes that occur elsewhere during inflammation and tumefaction.

One of the rules of classical mechanistic endocrinology was that a hormone doesn't act on the organ that produces it, and acts only on its "target organ," one with the special "receptors" that allow it to recognize and respond to the hormone. But now, all organs are known to contain "estrogen receptors," and many of those same organs can produce very significant amounts of estrogen. The ovary, according to the classical doctrine, wouldn't be able to respond to estrogen. Oral contraceptive manufacturers used that idea to argue that excessive estrogen couldn't cause ovarian cancer, and in fact prevented it, by preventing ovulation. But the cells of the ovary do respond to estrogen, multiplying, and during *in vitro* exposure, developing a pre-cancerous appearance. For more than 20 years, there has been clear evidence that use of supplemental estrogen increases the incidence of ovarian cancer.

Related claims were made about estrogen and the prostate gland for more than 50 years: "Estrogen can't do anything to a male organ except to decrease its maleness," that is, it couldn't stimulate cell division or cause prostate cancer, but it would cause the prostate to shrink, and prevent prostate cancer. Many of those claims are still being made, and estrogen is still being prescribed to treat it by a large portion of the medical profession, though experiments are demonstrating estrogen's clear contribution to the prostate gland's degeneration into cancer.

The ovary has been a focus of several types of ideology in biology, and as a result real investigation of ovarian physiology has been retarded for 100 years. Weismann's genetic doctrine of the "isolation of the germ line" led to a false theory of ovarian aging, the egg-depletion theory. Despite the absence of evidence for the finite-egg-supply theory, and the increasing accumulation of evidence that eggs are continually produced in adult ovaries, many people still cling to the unfounded theory. The real nature of ovarian aging is very similar to the aging of any organ, and the extreme specialization of the ovary makes some of the issues clearer when we look at analogous processes in other organs, such as the prostate, or breast, or uterus, or the "adventitious organs" of inflammation and tumefaction.

In the normal ovary, under the influence of the pituitary follicle stimulating hormone, several pockets of fluid (primary follicles) begin forming in the ovary, and the largest of these follicles suppresses the development of the others, so that only one usually reaches full development. Under the influence of the pituitary luteinizing hormone, progesterone, and other substances, the ovum completes its meiosis, the follicle ruptures and the ovum along with the fluid containing a high concentration of estrogen is released. The cells that had surrounded and supported the ovum (granulosa cells) multiply to fill the space, forming the corpus luteum, the yellow body that produces mainly progesterone. The corpeus luteum is a thoroughly new organ that's produced periodically, under the influence of chains of interacting stimuli.

Warburg's main point about cancer was that it always has a "respiratory defect," causing it to produce lactic acid even in the presence of oxygen (a process called aerobic glycolysis), while oxygen causes normal cells to suppress lactic acid formation (this is called the Pasteur effect). Warburg believed that this defect in the cells' energy production system meant that it lacked the ability to perform many of its normal functions, but that it remained able to divide. He also believed that oxygen deprivation was one of many stressors that could damage the cells' respiratory system, and he showed that even very small tumors are usually very hypoxic. Other experimenters (including Hans Selye) found that mechanical barriers such as a glass tube or a bent piece of plastic film implanted into an animals

tissues would cause cancer to develop among the enclosed cells (following a period of atrophy).

There are a few normal situations in which aerobic glycolysis occurs--the retina, the ovarian follicle during its preparation for ovulation, the Sertoli cells of the testicle, which are involved in the maturation of sperm cells, and sometimes in the placenta. Except for the retina, these tissues are subject to strong stimulation by estrogen, which stimulates lactic acid formation while interfering with oxygen use. Aerobic glycolysis is associated with the formation of fatty acids (R.A. Walli, 1978), by the enzyme fatty acid synthase, which is increased by estrogen, and the activity of which corresponds to the malignancy of many types of cancer.

Estrogen and other stimuli can cause the formation of lactic acid even in the presence of oxygen (i.e., aerobic glycolysis). Lactic acid has some hormone-like actions, causing, for example, vasodilation and increased permeability of capillaries. It has been suggested that it has some involvement in the process of meiosis, in the formation of mature germ cells.

There are some compartments in the body that have very little oxygen, and that are damaged by increased oxygen. The thymus maintains a very low oxygen tension, but it has a strong Pasteur effect, so normally doesn't produce excess lactic acid. The testicle stops producing testosterone if the oxygen is increased too much. The vitreous body of the eye normally has low oxygen tension.

A special feature of the ovary is that the cells around the ovum are not only isolated from the blood supply, causing localized hypoxia, but they are also (unlike the hypoxic thymus) stimulated by estrogen.

In the expanded ovarian follicle, the ovum is a considerable distance from the closest blood vessels, and so it and its adjoining cells receive very little oxygen. Glucose diffuses into the follicle, and the granulosa cells around the ovum metabolize it into lactic acid. The concentration of lactate in the follicular fluid increases, along with estrogen, as the follicle matures, approaching ovulation. Immediately following ovulation, the granulosa cells multiply, filling the space that was formerly the follicle, and the blood vessels that had surrounded the follicle now infiltrate the developing corpus luteum, so that it receives an abundant oxygen supply as it begins forming progesterone.

The permutations of these variations in oxygen tension, glucose supply, and excitatory stimulation can account for a variety of developmental processes, and the resulting concentrations of lactic acid, carbon dioxide, fatty acids, and pH increase the range of formative possibilities. Carbon monoxide has the ability to mimic hypoxia even in the presence of oxygen.

Estrogen, in many different organs, increases the production of the enzyme heme oxygenase, which produces carbon monoxide, which inhibits respiration and also inhibits a variety of enzymes that use the heme group. (Tian, et al., 2003, 2004; Tschugguel, et al., 2001).

In the ovary, carbon monoxide increases the production of estrogen, but decreases the production of progesterone. An excess of estrogen, acting partly through the increased carbon monoxide, blocks the formation of progesterone, and prevents a successful ovulation.

These are just some of the interactions within the ovary that are similar to processes in the cancerization process wherever it occurs. Any inflamed tissue becomes subject to estrogenic stimulation, by the activation of enzymes, especially beta-glucuronidase, which cause estrogen to be deposited in the cells. Any hypoxic tissue, including inflammations of any sort, will express the heme oxygenase enzyme, producing carbon monoxide. Presumably, in the short term, these increases of estrogen and carbon monoxide have their adaptive functions, such as stimulating cell division for healing, and blocking some kinds of free radicals and excessive calcium uptake. But, as in the ovary, when the system isn't able to suppress them, they become self-sustaining, and begin to spread their influence to neighboring cells. Cancer cells are very resistant to injury from free radicals, which in normal cells accelerate the spontaneous dissolution called apoptosis, and carbon monoxide is one of their defense mechanisms, that makes them relatively immortal (Ghattas, et al., 2002).

When an organism is functioning normally and adapting to stresses, the operation of a functional system, including the part of the

nervous system that coordinates the function, causes that system to be stabilized, and to become more efficient, and even to grow. Work causes muscles and bones to enlarge and become stronger, learning causes the brain to grow. Chronic inflammations have some of the properties of a functional system, with participation of the nervous system, adjustments of the immune system, and changes in the circulatory system, except that the normal and desirable functions are progressively lost, rather than improved. The operation of the short term protective measures contribute, if they persist too long, to atrophy and fibrosis, and potentially, to disordered growth.

In some cases, we know that an excess of stimulation, in reaction to the organ's reduced functioning, promotes the growth and spread of a tumor, for example, prolactin contributes to breast cancer, thyrotropic hormone to thyroid cancer, and gonadotropin to ovarian cancer. Ovarian teratomas are now believed to be parthenogenic, deriving from an unfertilized ovum, and I have suspected that the direction of their development reflects the endocrine situation, for example when a teratoma consisting of thyroid tissue appears in a woman who has taken extremely big doses of iodine for a long time.

In the chronic inflammatory state that develops with stress and aging, besides the extrinsic stimuli that were the subject matter of classical endocrinology--pituitary hormones driving the ovaries, ovarian hormones driving the uterus, etc.--the inflamed tissues begin to stimulate themselves: The breast and uterus begin to synthesize estrogen, for example.

Some of the things produced by tumors, such as estrogen and carbon monoxide, appear to be the result of a short-term adaptive factor that becomes maladaptive when the system can't turn it off. It's generally assumed that when a tumor produces a hormone, its effects will necessarily be harmful, but sometimes it isn't clear whether they are harmful or beneficial, and in a few cases, they clearly seem to be beneficial.

Many cancers cause a great increase in the concentration of calcium in the blood, and this is often the result of the production of parathyroid hormone-related protein (PTH-rP) by the tumor. In some cases, PTH-rP can induce apoptosis by causing cells to take up calcium, but in other cases it is a survival factor, for example for nerve cells in the brain. Some experiments show that increased calcium in a tissue suppresses heme oxygenase and carbon monoxide (Zhang, et al., 2003, 2004). PTH-rP and the parathyroid hormone itself have some functions that overlap with those of vitamin D, which is now known to help to suppress many cancers.

Inhibitors of fatty acid synthase cause many types of cancer cells to die. Vitamin D, which stops the growth of breast, prostate, and bowel cancer cells, inhibits FAS (Qiao, et al., 2003). This could be another example of Zajicek's principle, since it has been discovered that prostate and other **cancer cells are able to create the active form of vitamin D.** Vitamin D also acts as an antiestrogen, and estrogen is a factor in the development prostate cancer, breast cancer, and many other types of cancer (Swami, et al., 2000; Demirpence, et al., 2001).

In some cancers, vitamin D operates through ceramide (Pirianov and Colston, 2001), Palmitic acid, is a product of FAS and a component of ceramide, which inhibits cancer cell growth.

Understanding the causes of tissue atrophy as a failure of energy that allows inflammation to become chronic, leading to a disorganized attempt to regenerate tissue and stabilize the system, our response to both atrophy and cancer should be to restore metabolic processes of the highest type, based on the oxidation of glucose with the production of carbon dioxide, rather than lactic acid and fatty acids, and to eliminate inflammation and its products that have disrupted the normal balance between cell renewal and cell elimination. Aspirin, by inhibiting the production of estrogen, of carbon monoxide, and of several cytokines and toxic lipid products, and by supporting normal respiration, helping to correct hyperglycemia, and suppressing lactate production, is an especially valuable therapy. Sacca et al., have recently (October, 2004) demonstrated that aspirin's anticancer effect appears to involve the inhibition of heme oxygenase.

Caffeine, by inhibiting FAS and sparing glucose, and inhibiting many of the toxic lipid

products and other inflammatory mediators, should have at least additive effects when combined with aspirin.

Vitamin D, by its antiestrogenic and antiinflammatory actions, and by suppressing FAS, parallels the effects of aspirin and caffeine in several ways.

Gelatin, by lowering serotonin, should help to prevent excessive activation of heme oxygenase and formation of carbon monoxide during injury or stress (on the role of serotonin: Sharma and Westman, 2003; Sharma, et al., 2003).

The lower incidence of, and mortality from, cancer at high altitudes might partly be explained by experiments that show that reduced atmospheric oxygen tension down-regulates heme oxygenase in human cells (Kitamuro, 2003).

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