

Ray Peat's Newsletter

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A focused and dramatic movement to shift the course of history is what is needed. N.P. Bekhtereva

Stress, inertia, aging

The "epigenetic" processes of development are always present, and interactions with our environments can either limit or expand our capacity to keep developing. The events of any day can move us toward "learned helplessness" or toward "creative productivity." When recurring discomforts can be seen as meaningful steps toward a goal, our physiology adjusts, increasing skills that make the tasks easier, but adaptation to a poor environment has a biological cost. To the degree that recurring tasks conflict with our sense of meaning, they can cause our functional capacity to shrink.

One of the good things about consciousness is that it can sometimes guide us away from harmful courses of action, or development, by reducing their interest, making other things more interesting. When those hints have been ignored too long, other defensive processes in the body can reduce the availability of energy needed to continue the harmful activity. In the 1950s, the psychologist Abraham Maslow wrote about a young woman's loss of interest in life, which was diagnosed as anhedonia, considered at the time to be a psychiatric or neurological problem. He guessed that the young woman's condition resulted from looking forward to a life of meaningless work. He described her complete recovery, when she found an opportunity to put her abilities to work in a demanding academic situation.

When Maslow wrote, his interpretation of her problem was contrary to the spirit of the time, in which the main currents of psychological theory emphasized the importance of "adaptation," fitting into society. Repression and discipline were said to be necessary for society to function. Maslow rejected both the goals and methods of the

standard psychotherapies of the 1950s, asking "What shall we think of a well-adapted slave?"

The worst features of the ideology of repression that had justified many barbarous practices (including corporal punishment in schools, lobotomy and electroshock in psychiatry) had disappeared by the end of the century, but a basic attitude toward the body and its instinctive urges has survived, and "educational" doctrine has returned to an emphasis on shaping the individual to match the needs of the society.

In this setting, all of the features of stress physiology are tending to be evaluated with reference to the ideal of adapting to the mold, rather than developing toward higher, still undefined, goals. All of the components of "learned helplessness" are being revalued, removing the stigma.

Natalia Bekhtereva, a brain physiologist, observed that prolonged stress can destabilize the brain, producing first an overexcited state, and then an emotionally desensitized state. The brain's long-term memory tends to lock it into either a healthy responsive state, or one of the pathological states. She believed that large numbers of people, especially world leaders, suffered from stable pathological states of the brain.

In animals, learned helplessness and stress-induced analgesia are known to involve the endogenous "opioid" peptides, or endorphins (Riley, et al., 1980; Maier, et al., 1983; Whitehouse, et al., 1983; Hemingway and Reigle, 1987; Barfield, et al., 2010). Like the parasympathetic nervous system, the normally protective adaptive system of endogenous opiates can become harmful when it's too strongly activated.

Around 1980, Yevgeny Chazov did a series of experiments with the endogenous opioid peptides, that had been recently discovered. He found that when the brain was injured in a particular way that caused a particular kind of paralysis, certain

of the opioid peptides were produced, that allowed the brain to compensate, and to resume a normal posture. Specific peptides were produced to compensate (Krivosheev, et al., 1980; Chazov, 1981) for damage to each side of the brain.

When a peptide that was specific for a wound on one side of the brain was given to normal animals, it produced a postural abnormality of an opposite sort. That is, if a peptide could correct an injury that caused the left leg to contract, when it was given to a normal animal it would cause the right leg to contract. In the absence of a specific injury, an excess of these peptides could interfere with normal relaxation and movement (Vankova, et al., 1996; Kryzhanovskii, et al., 1987; Powell-Jones, 1987). At certain doses, morphine can produce catalepsy, immobility that seems to overlap with depression and learned helplessness. Repetitive, stereotyped behavior (Cronin, et al., 1986; Horner, et al., 2012), and asymmetrical, circling behavior (Morelli and Di Chiara, 1985; Geula and Asdourian, 1985; Jenck, et al., 1988) can also be produced by the opioids.

These behavioral effects of the stress-induced endogenous opiates are paralleled by some related effects on the cellular and metabolic levels.

Since muscle contraction is the main source of body heat production, inappropriate and prolonged muscle contraction would account for the odd ability of morphine to increase the body temperature, while inhibiting mitochondrial oxygen consumption. Even when the spinal cord is cut, morphine can increase the body temperature. This could account for fevers that are produced by stress or anxiety, in which the endogenous opiates are increased.

The drugs digitalis and ouabain (steroid-glycosides used to stimulate the heart), nicotine, and morphine can be synthesized in small amounts by animal and human cells. The binding and activation of their "receptors" by other, more abundant, substances has distracted attention from them. They are all thermogenic. Cancer cells can produce morphine (Stefano, et al., 2008) as well as endorphins. The effects of the opiates involve the interactions of receptor proteins with the actin cytoskeleton filaments, and it is these actin filaments that are responsible for the peculiar

stiffness of cancer cells. Opioids and nitric oxide are closely associated with mitochondrial function (Fimiani, et al., 1999; Cadet, et al., 2004; Stefano and Kream, 2009; Kream and Stefano, 2009), and the actions of different types of opioid peptides seem to allow for complex adaptive adjustments of energy production under conditions involving limitation of oxygen or fuel.

Under prolonged stress, these subtle adaptive processes become distorted. The "contractile" function, activated by the opioid peptides, and under some conditions by the associated nitric oxide (Eu, et al., 2003), becomes a generalized activating process. One of the long-standing questions of cancer biology is the nature of the excitatory process that keeps the cells in the chronically reduced state of sulphydryl excess that supports cell division, consuming energy constantly, preventing maturation and differentiated useful functioning. Chronic exposure to increased amounts of the endogenous opiates and nitric oxide can stimulate tumor growth (Scopsi, et al., 1989; Weidemann, 2012). Abnormal amounts of the endogenous digitalis-like substances that can result from stress (Köbel and Schreiber, 1996) would be another possible tumor-stimulating condition. In some cases, an opioid peptide appears to act on the same site as ouabain (Dumont and Lemaire, 1996). The opiate/nitric oxide activated actin cytoskeleton helps to organize the "cancer metabolism" by stabilizing the hypoxia inducible factor (Shin, et al., 2010).

Thermography can be used to identify some tumors, because of their increased production of heat. The increased hardness of cancerous tissues, associated with their heat production, suggests that we should focus on the factors that stimulate their unproductive breakdown of ATP. Red blood cells become rigid when their ATP is reduced (this is probably analogous to muscle cramps produced by extreme ATP depletion). Red cells require glucose for maintaining their ATP, which is depleted by the stress of passing through narrow capillaries, so hypoglycemia increases their stiffness. Glucose starvation is a general feature of tumors (Huang, et al., 2015), because of its uncontrolled conversion to lactate, and

starvation increases lactate production, while blocking its oxidation (Wu, et al., 2013). Production of endogenous opioids is increased by a variety of stressors, all of which are related to the availability of energy. Hypoglycemia, lactic acid, hypoxia, and darkness increase their formation.

The behavioral effects of the opiates are appropriate for organisms confronted by limited energy availability, namely, to reduce the behaviors that require energy for their completion. Immobility, learned helplessness, depression, and the repression of urges and needs have been experimentally relieved by a variety of chemicals that are related to energy production, such as thyroid hormone, and by specific opioid antagonists, such as naloxone and naltrexone. The ability to oxidize glucose is impaired by morphine, involving the inactivation of the pyruvate dehydrogenase complex (Chen, et al., 2007), which is also inhibited by glucose deprivation.

More than 100 years ago, George Crile abandoned the use of morphine in surgery, arguing that it increased the risk of shock, by blocking the production or use of energy. In the 1970s, when naloxone and other antiopiates were found to be effective treatments for shock, few doctors were influenced by the research. Around the same time, intravenous glucose was seen to be effective for "septic" shock, but nearly all doctors believed that the problem was "sepsis," not energy.

In the 1970s, morphine was considered to be a "euphoriant," and cancer surgeons in the US usually refused to prescribe doses sufficient of control the pain of terminal cancer patients, with the argument that they mustn't allow their patients to become addicted. A television network broadcast a shocking documentary, showing a doctor assuring a patient that she needn't go to England for pain control in the last stage of sickness, then showed him later, explaining why he wouldn't prescribe it. This public exposure of that conventional horror gradually changed the US standards for pain control. The larger doses of morphine now used for terminal patients haven't produced problems of addiction. Morphine, like the endorphins and nitric oxide, stimulates cancer growth and suppresses immunity.

When the endorphins were being discovered in the late 1970s, the association of morphine with euphoria was almost the only thing doctors knew about it; almost none had heard of George Crile. This was apparently responsible for the identification of the endorphins as natural euphoriants, rather than as stress-limiting hormones, possibly with the energy-blocking effects of morphine identified by Crile. Strangely, rather than seeing endorphins as a signal of damage to the organism, they were seen as confirmation that suffering is good, because it produces the "pleasure chemicals."

Surgeons are familiar with the constipation produced by morphine and codeine, especially in old people. Inertia of the intestine and other smooth muscles (bladder, stomach, even esophagus) becomes increasingly common in old age. Both endorphins (Konturek, 1980; Stanghellini, et al., 1984; Narducci, et al., 1986) and nitric oxide are increased in the constipated intestine and in other organs that lack their normal propulsive force.

When learning and memory have been impaired by stress, the opioid peptides are increased (Carey, et al. 2009), and the opiate antagonists can improve learning ability.

If pain produces endorphins, it shouldn't be surprising that pleasure, such as massage, decreases them. A study in a medical school dermatology department (Morhenn, et al., 2012) showed that massage increased oxytocin, but decreased beta-endorphin, nitric oxide and ACTH (adrenocorticotrophic hormone). Ingesting sugar generally lowers the endorphins.

Things that restore oxidative energy production help to restore the endorphins and nitric oxide to their subtle, situational regulatory functions, and this is probably especially effective when it's done at night, when there is a massive increase of all of the anti-oxidative stress-responsive substances. The normal amount of melatonin produced during the night has anti-stress effects, but with aging it can contribute to energy-constrictive processes, including increased endorphins.

In 1885, the French neurologist J.-M. Charcot described cases in which symptoms of paralysis,

contracture, or insensitivity occurred on one side of the body, in a way that couldn't be explained by disease in a particular nerve or part of the brain. Those conditions were classified as "hysteria," but would now probably be explainable in terms of an extreme excess of one of the opioid peptides, probably induced by endocrine problems that were more common in women than men.

After studying briefly with Charcot, Sigmund Freud developed his ideas about the importance of repression in neurosis. Many years later, when Freud's young associate Wilhelm Reich made it clear that society's repressions were the source of psychological problems (as Maslow later said, "Sick people are made by a sick culture"), Freud realized the great danger of that view in authoritarian Europe, and expelled Reich from the psychoanalytic movement. The Vienna massacre of 1927 decisively put Reich and Freud on opposite sides of the "repression" issue, with Reich understanding that the society was deeply irrational. Freud wrote a book to explain why civilization requires repression.

Reich's concept of "character armor" and his interpretation of behavioral rigidity, repetitive, stereotyped and obsessive-compulsive behaviors could at present be interpreted in terms of stress-induced imbalances of the endogenous opiates. He interpreted masochism as an effect of the blockage or distortion of normal biological energies. Self-injurious behavior has been found to be associated with increased production of endorphins in humans and monkeys, and to be alleviated by the anti-opiate drug, naloxone (Crockett, et al., 2007; Richardson and Zaleski, 1983; Sandman, et al., 1990; Barron and Sandman, 1983).

In the 1940s, Reich came to believe that the impairment of biological energy was responsible for cancer, and it was this work that led to the burning of his books and his imprisonment in 1957. During the 1960s, it was somewhat taboo in the US to suggest that the development of cancer might have environmental, socioeconomic, or psychological causes.

In the 1970s I talked to a woman who had a sequence of several symptoms, appearing over a period of several weeks, that were all on the same

side of her body--for example, numbness in her left hand, pain in her left breast, and ringing in her left ear. A few weeks later, her friend told me that she had discovered that she had ovarian cancer. Unexplained symptoms on one side of the body might be explainable in terms of the endogenous opiates.

The occurrence of "degenerative" diseases such as arthritis, cancer, and failure of heart, lungs, and kidneys, is most common between the ages of 60 and 85, but they sometimes occur decades earlier, or never occur even in extreme old age, so it seems reasonable to look for differences in the environment that might be responsible. The absence or deficiency of an intrinsic mechanism to reverse the suppressive effects of the endorphins would account for the fact that the damage done by successive stresses accumulates, with a progressive loss of functions, in the apparently irreversible process of "aging." With the accumulating knowledge of the way the endorphins are regulated, it seems likely that the rate of function loss can be greatly reduced, allowing the regenerative processes to predominate.

Anti-opiates such as naloxone can be effective in extremely small doses, on the scale of hormones such as thyroid (T3) and estrogen. In doses that are too big, they can produce morphine-like effects, rather than their opposite. The currently popular "low dose naltrexone" therapy is usually done with the intention of increasing the production of endorphins, rather than blocking their effects. I think that ideology can confuse the therapist, who should be thinking in terms of broad-spectrum stress reduction.

In 1957 Norman Mailer, aware of Reich's work, suggested that our collective condition might be to live with ". . . a slow death by conformity with every creative and rebellious instinct stifled (at what damage to the mind and the heart and the liver and the nerves no research foundation for cancer will discover in a hurry) . . ." The need for changing the stifling conditions should be in every therapist's awareness.

REFERENCES

- J Cell Mol Med. 2012 Apr;16(4):920-6. **Role of endothelial nitric oxide synthase (eNOS) in chronic stress-promoted tumour growth.** Barbieri A, Palma G, Rosati A, Giudice A, Falco A, Petrillo A, Petrillo M, Bimonte S, Di Benedetto M, Esposito G, Stiuso P, Abbruzzese A, Caraglia M, Arra C.
- Alcohol Clin Exp Res. 2010 Jun;34(6):1066-72. **Beta-endorphin mediates behavioral despair and the effect of ethanol on the tail suspension test in mice.** Barfield ET, Barry SM, Hodgin HB, Thompson BM, Allen SS, Grisel JE.
- Am J Ment Defic. 1983 Sep;88(2):177-86. **Relationship of sedative-hypnotic response to self-injurious behavior and stereotypy by mentally retarded clients.** Barron J, Sandman CA.
- Front Biosci. 2004 Sep 1;9:3176-86. **Endogenous morphinergic signaling and tumor growth.** Cadet P, Rasmussen M, Zhu W, Tonnesen E, Mantione KJ, Stefano GB.
- J Neurosci. 2009 Apr 1;29(13):4293-300. **Endogenous kappa opioid activation mediates stress-induced deficits in learning and memory.** Carey AN, Lyons AM, Shay CF, Dunton O, McLaughlin JP.
- Experientia 1981;37(8):887-9. **Enkephalins induce asymmetrical effects on posture in the rat.** Chazov EI, Bakalkin GYa, Yarigin KN, Trushina ED, Titov MI, Smirnov VN.
- Neurosci Lett. 2000 Jun 23;287(2):113-6. **Effects of naloxone on lactate, pyruvate metabolism and antioxidant enzyme activity in rat cerebral ischemia/reperfusion.** Chen CJ, Cheng FC, Liao SL, Chen WY, Lin NN, Kuo JS.
- Peptides. 2007 Oct;28(10):1987-97. **Beta-endorphin levels in longtailed and pigtailed macaques vary by abnormal behavior rating and sex.** Crockett CM, Sackett GP, Sandman CA, Chicz-DeMet A, Bentson KL.
- Experientia. 1986 Feb 15;42(2):198-9. **Endorphins implicated in stereotypies of tethered sows.** Cronin GM, Wiepkema PR, van Ree JM.
- Am J Psychiatry. 1992 Sep;149(9):1162-7. **Association of beta-endorphin with specific clinical symptoms of depression.** Darko DF(1), Risch SC, Gillin JC, Golshan S.
- Neuropsychopharmacology. 1989 Sep;2(3):225-8. **Increased cerebrospinal fluid levels of endorphin immunoreactivity in panic disorder.** Eriksson E, Westberg P, Thuresson K, Modigh K, Ekman R, Widerlöv E.
- Proc Natl Acad Sci U S A. 2003 Dec 9;100(25):15229-34. **Concerted regulation of skeletal muscle contractility by oxygen tension and endogenous nitric oxide.** Eu JP, Hare JM, Hess DT, Skaf M, Sun J, Cardenas-Navina I, Sun QA, Dewhurst M, Weissner G, Stamler JS.
- Cancer Lett. 1999 Nov 1;146(1):45-51. **Mu opiate receptor expression in lung and lung carcinoma: ligand binding and coupling to nitric oxide release.** Fimiani C, Arcuri E, Santoni A, Rialas CM, Bilfinger TV, Peter D, Salzet B, Stefano GB.
- Naunyn Schmiedebergs Arch Pharmacol. 2011 Sep;384(3):221-30. **The role of morphine in regulation of cancer cell growth.** Gach K, Wyre A, Fichna J, Janecka A. Pharmacol Biochem Behav. 1985 Aug;23(2):207-13. **Asymmetric behavior induced by enkephalinergic agents in the basal ganglia.** Geula C, Asdourian D.
- Psychopharmacology (Berl). 1987;93(3):353-7. **The involvement of endogenous opiate systems in learned helplessness and stress-induced analgesia.** Hemingway RB 3rd(1), Reigle TG.
- Fertil Steril. 1982 Mar;37(3):389-91. **Effect of morphine on the hypothalamic-pituitary axis in postmenopausal women.** Hemmings R, Fox G, Tolis G. "It is also of interest that the increase in serum prolactin following morphine injection is of similar magnitude as observed in premenopausal patients."
- J Neurochem. 2012 Mar;120(5):779-94. **Activation of mu opioid receptors in the striatum differentially augments methamphetamine-induced gene expression and enhances stereotypic behavior.** Horner KA, Hebbard JC, Logan AS, Vanchipurakel GA, Gilbert YE.
- Oncol Rep. 2015 Feb;33(2):875-84. **Lactate promotes resistance to glucose starvation via upregulation of Bcl-2 mediated by mTOR activation.** Huang C, Sheng S, Li R, Sun X, Liu J, Huang G.
- Brain Res. 1988 May 31;450(1-2):382-6. **Contraversive circling induced by ventral tegmental microinjections of moderate doses of morphine and [D-Pen₂, D-Pen₅]enkephalin.** Jenck F, Bozarth M, Wise RA.
- Pharmacol Biochem Behav. 2001 Sep;70(1):77-84. **Opioid blockade improves human recognition memory following physiological arousal.** Katzen-Perez KR, Jacobs DW, Lincoln A, Ellis RJ.
- Mol Cell Biochem. 1996 Jul-Aug;160-161:111-5. **The endogenous digitalis-like factor.** Kölbel F, Schreiber V.
- Am J Gastroenterol. 1980 Sep;74(3):285-91. **Opiates and the gastrointestinal tract.** Konturek SJ.
- Dokl Akad Nauk SSSR 1980;253(4):1015-8. **[Development of positional asymmetry during pain, immobilization, and cold stress.]** Krivosheev OG, Stoliarov GK, Bakalkin GI, Chazov EI.
- Med Sci Monit. 2009 Dec;15(12):RA263-8. **Endogenous morphine and nitric oxide coupled regulation of mitochondrial processes.** Kream RM, Stefano GB.
- Bull Eksp Biol Med. 1987 Dec;104(12):657-60. **[Asymmetric distribution of peptide regulators of muscle tonus and substance P in the spinal cord of rats with unilateral hyperactivity of the lumbar enlargement neurons].** Kryzhanovskii GN, Lutsenko VK, Karganov MIu.
- J Exp Psychol Anim Behav Process. 1983 Jan;9(1):80-90. **The opioid/nonopioid nature of stress-induced analgesia and learned helplessness.** Maier SF, Sherman JE, Lewis JW, Terman GW, Liebeskind JC. ("The

nonopioid procedures produce neither a learned helplessness effect nor a reinstatable analgesia. It is argued that these data implicate the learning of uncontrollability in the activation of opioid systems."

Brain Res. 1981 Mar 16;208(2):325-38. Stress-induced release of brain and pituitary beta-endorphin: major role of endorphins in generation of hyperthermia, not analgesia. Millan MJ, Przewlocki R, Jerlicz M, Gramsch C, Hollt V, Herz A.

Brain Res. 1985 Aug 26;341(2):350-9. Non-dopaminergic mechanisms in the turning behavior evoked by intranigral opiates. Morelli M, Di Chiara G.

Altern Ther Health Med. 2012 Nov-Dec;18(6):11-8. Massage increases oxytocin and reduces adrenocorticotropin hormone in humans. Morhenn V, Beavin LE, Zak PJ.

Arch Intern Med. 1986 Apr;146(4):716-20. Functional dyspepsia and chronic idiopathic gastric stasis. Role of endogenous opiates. Narducci F, Bassotti G, Granata MT, Gaburri M, Farroni F, Palumbo R, Morelli A.

Stress. 2008 Jan;11(1):42-51. Epub 2007 Jul 25. Neuronal nitric oxide synthase gene inactivation reduces the expression of vasopressin in the hypothalamic paraventricular nucleus and of catecholamine biosynthetic enzymes in the adrenal gland of the mouse. Orlando GF, Langnaese K, Schulz C, Wolf G, Engelmann M.

J Pharmacol Exp Ther. 1987 Oct;243(1):322-32. Skeletal muscle thermogenesis: its role in the hyperthermia of conscious rats given morphine or beta-endorphin. Powell-Jones K(1), Saunders WS, St Onge RD, Thornill JA.

Biochim Biophys Acta. 1992 Feb 3;1133(3):293-300. Red cell filterability determined using the cell transit time analyzer (CTTA): effects of ATP depletion and changes in calcium concentration. Rendell M, Luu T, Quinlan E, Knox S, Fox M, Kelly S, Kahler K.

NIDA Res Monogr. 1986;75:121-4. Opioids and rat erythrocyte deformability. Rhoads DL, Wei LX, Lin ET, Rezvani A, Way EL.

Biol Psychiatry. 1983 Jan;18(1):99-101. Naloxone and self-mutilation. Richardson JS, Zaleski WA.

Neurosci Biobehav Rev. 1980 Spring;4(1):69-76. The role of endorphins in animal learning and behavior. Riley AL, Zellner DA, Duncan HJ.

Am J Ment Retard. 1990 Jul;95(1):84-92. Plasma B-endorphin levels in patients with self-injurious behavior and stereotypy. Sandman CA, Barron JL, Chicz-DeMet A, DeMet EM. "Results indicated that compared to a matched control group, patients with SIB plus stereotypy have elevated b-endorphin plasma."

Mol Med Rep. 2010 Sep-Oct;3(5):815-9. Actin disruption inhibits hypoxia inducible factor-1a expression via inactivity of Mdm2-mediated p70S6K. Shin JJ, Park BK, Ahn YT, Kim Y, An WG.

J Neurochem. 2004 Sep;90(5):1258-68. Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects. Shirayama Y, Ishida H, Iwata

M, Hazama GI, Kawahara R, Duman RS. "Rats exposed to learned helplessness (LH), an animal model of depression, showed a recovery following an intracerebroventricular injection of nor-binaltorphimine dihydrochloride (norBNI; a kappa-opioid antagonist)."

Gastroenterology. 1984 Nov;87(5):1104-13. Effect of opiate and adrenergic blockers on the gut motor response to centrally acting stimuli. Stanghellini V, Malagelada JR, Zinsmeister AR, Go VL, Kao PC.

Semin Cancer Biol. 2008 Jun;18(3):190-8. Endogenous opiates, opioids, and immune function: evolutionary brokerage of defensive behaviors. Stefano GB, Kream R.

Neurochem Res. 2008 Oct;33(10):1933-9. The presence of endogenous morphine signaling in animals. Stefano GB, Cadet P, Kream RM, Zhu W.

Anesthesiology. 1996 Sep;85(3):574-83. Role of central mu, delta-1, and kappa-1 opioid receptors in opioid-induced muscle rigidity in the rat.

Vankova ME, Weinger MB, Chen DY, Bronson JB, Motis V, Koob GF.

J Carcinog. 2012;11:2. "The Lower Threshold" phenomenon in tumor cells toward endogenous digitalis-like compounds: Responsible for tumorigenesis? Weidemann H.

Physiol Behav. 1983 May;30(5):731-4. Opiate antagonists overcome the learned helplessness effect but impair competent escape performance. Whitehouse WG, Walker J, Margules DL, Bersh PJ.

Biochim Biophys Acta. 2013 May;1833(5):1147-56. Nutrient deprivation induces the Warburg effect through ROS/AMPK-dependent activation of pyruvate dehydrogenase kinase. Wu CA, Chao Y, Shiah SG, Lin WW.
