Altitude and Mortality

From the original article in 2006. Author: Ray Peat.

Breathing pure oxygen lowers the oxygen content of tissues; breathing rarefied air, or air with carbon dioxide, oxygenates and energizes the tissues; if this seems upside down, it's because medical physiology has been taught upside down. And respiratory physiology holds the key to the special functions of all the organs, and to many of their basic pathological changes.

Stress, shock, inflammation, aging, and organ failure are, in important ways, respiratory problems.

Definitions:

- **Haldane effect:** Oxygen displaces carbon dioxide from hemoglobin, in proportion to its partial (specific) pressure.
- **Bohr effect:** Carbon dioxide (or acidity) displaces oxygen from hemoglobin.
- **Lactic acidemia:** The presence of lactic acid in the blood.
- **Alkalosis:** A pH of the blood above 7.4.
- **Acidosis:** A blood pH below 7.4.
- **Lactate paradox:** The reduced production of lactic acid at a given work rate at high altitude. Muscle work efficiency may be 50% greater at high altitude. ATP wastage is decreased.

There are some popular medical ideas that obstruct clear thinking about respiration. One is that high altitude deprives you of oxygen, and is likely to be bad for people with heart disease and cancer. Another is that breathing pure oxygen helps sick people to oxygenate their tissues while exerting less effort in breathing. These are both exactly wrong, and the errors have been explored in quite a few publications, but the ideas persist in the culture to such a degree that our ***perceptions and intuitions*** have been misled, making closely related things seem to be unrelated. In this culture, it is hard to see that heart disease, cancer, and cataracts all involve a crucial respiratory defect, with the production of too much lactic acid and too little carbon dioxide, which leads to a "swelling pathology"**:** A pathological retention of water. The swollen heart beats poorly, the swollen lens turns milky, other cells divide rapidly as a result of swelling.

People who live at very high altitudes live significantly longer**;** they have a lower incidence of cancer (Weinberg, et al., 1987) and heart disease (Mortimer, et al., 1977), and other degenerative conditions, than people who live near sea level. As I have written earlier, I think the lower energy transfer from cosmic radiation is likely to be a factor in their longevity, but several kinds of evidence indicate that it is the lower oxygen pressure itself that makes the biggest contribution to their longevity.

"Mountain sickness" is a potentially deadly condition that develops in some people when they ascend too rapidly to a high altitude. Edema of the lungs and brain can develop rapidly, leading to convulsions and death. The standard drug for preventing it is acetazolamide, which inhibits carbonic anhydrase and causes carbon dioxide to be retained, creating a slight tendency toward acidosis. This treatment probably mimics the retention of carbon dioxide that occurs naturally in altitude adapted people. The reasons for mountain sickness, and the reasons for the low incidence of heart disease, cancer, cataracts, etc., at high altitude, offer clues to the prevention of death and deterioration from many other causes.

When the weather in a particular place is cool, sunny and dry (which in itself is very good for the health) the atmospheric pressure usually is higher than average. Although sunny dry weather is healthful, **periods of higher pressure correspond to an increased incidence of death** from heart disease and strokes.

The Haldane-Bohr effect describes the fact that oxygen and carbon dioxide destabilize each other's binding to hemoglobin. When oxygen pressure is high, the blood releases its carbon dioxide more easily. In stormy weather, or at high altitude, the lower oxygen pressure allows the body to retain more carbon dioxide. Carbon dioxide, produced in the cells, releases oxygen into the tissues, relaxes blood vessels, prevents edema, eliminates ammonia, and increases the efficiency of oxidative metabolism.

Hyperventilation, breathing excessively and causing too much carbon dioxide to be lost, is similar to being in the presence of too much oxygen**;** it's similar to being at low altitude with high atmospheric pressure, only worse. Therefore, the physiological events produced by hyperventilation can give us an insight into what happens when the atmospheric pressure is low, by looking at the events in reverse. Likewise, breathing 100% oxygen has known harmful consequences, which are very similar to those produced by hyperventilation.

Hyperventilation is defined as breathing enough to produce respiratory alkalosis from the loss of carbon dioxide. Lactic acid is produced in response to the alkalosis of hyperventilation.

Breathing too much oxygen displaces too much carbon dioxide, provoking an increase in lactic acid**;** too much lactate displaces both oxygen and carbon dioxide. Lactate itself tends to suppress respiration.

Oxygen toxicity and hyperventilation create a systemic deficiency of carbon dioxide. It is this carbon dioxide deficiency that makes breathing more difficult in pure oxygen, that impairs the heart's ability to work, and that increases the resistance of blood vessels, impairing circulation and oxygen delivery to tissues. In conditions that permit greater carbon dioxide retention, circulation is improved and the heart works more effectively. Carbon dioxide inhibits the production of lactic acid, and lactic acid lowers carbon dioxide's concentratrion in a variety of ways..

When carbon dioxide production is low, because of hypothyroidism, there will usually be some lactate entering the blood even

at rest, because adrenalin and noradrenalin are produced in large amounts to compensate for hypothyroidism, and the adrenergic stimulation, besides mobilizing glucose from the glycogen stores, stimulates the production of lactate. The excess production of lactate displaces carbon dioxide from the blood, partly as a compensation for acidity. The increased impulse to breath ("ventilatory drive") produced by adrenalin makes the problem worse, and lactate can promote the adrenergic response, in a vicious circle..

Since the 1920s when A. V. Hill proposed that the prolonged increase in oxygen consumption after a short period of intense work, the "oxygen debt," was equivalent to the amount of lactic acid that had entered the circulation from the muscles' anaerobic work, and that it had to be disposed of by oxidative processes, physiology textbooks have given the impression that lactic acid accumulation was exactly the same as the oxygen debt. In reality, several things are involved, especially the elevation of temperature produced by the intense work. Increased temperature raises oxygen consumption independently of lactic acid, and lower temperature decreases oxygen consump-tion, even when lactic acid is present.

The idea of the "oxygen debt" produced by exercise or stress as being equivalent to the accumulation of lactic acid is far from accurate, but it's true that activity increases the need for oxygen, and also increases the tendency to accumulate lactic acid, which can then be disposed of over an extended time, with the consumption of oxygen. This relationship between work and lactic acidemia and oxygen deficit led to the term "lactate paradox" to describe the lower production of lactic acid during maximal work at high altitude when people are adapted to the altiude. Carbon dioxide, retained through the Haldane effect, accounts for the lactate paradox, by inhibiting cellular excitation and sustaining oxidative metabolism to consume lactate efficiently.

The loss of carbon dioxide from the lungs in the presence of high oxygen pressure, the shift toward alkalosis, by the Bohr-Haldane effect increases the blood's affinity for oxygen, and restricts its delivery to the tissues, but because of the abundance of oxygen in the lungs, the blood is almost competely saturated with oxygen.

At high altitude, the slight tendency toward carbon dioxide-retention acidosis decreases the blood's affinity for oxygen, making it more available to the tissues. It happens that lactic acid also affects the blood's oxygen affinity, though not as strongly as carbon dioxide. **However, lactic acid doesn't vaporize as the blood passes through the lungs, so its effect on the lungs' ability to oxygenate the blood is the opposite of the easily exchangeable carbon dioxide's.** Besides dissociating oxygen from hemoglobin, lactate also displaces carbon dioxide from its (carbamino) binding sites on hemoglobin. If it does this in hemoglobin, it probably does it in many other places in the body.

According to Meerson, ascending more than 200 feet per day produces measurable stress. People seldom notice the effects of ascending a few thousand feet in a day, but it has been found that a large proportion of people have bleeding into the retina when they ascend to 10,000 feet without adequate adaptation. Presumably, similar symptomless bleeding occurs in other organs, but the retina can be easily inspected.

If hypothyroid people, with increased adrenalin and lactate, are hyperventilating even at rest and at sea level, when they go to a high altitude where less oxygen is available, and their absorption of oxygen is impaired by lactic acidemia, **their "oxygen debt," conceived as circulating lactic acid, is easily increased, intensifying their already excessive "ventilatory drive," and in proportion to the lactic acid oxygen debt, oxygen absorption is further inhibited.**

The lactic acid has to be disposed of, but their ability to extract oxygen is reduced. The poor oxygenation, and the increased lactic acid and free fatty acids cause blood vessels to become leaky, producing edema in the lungs and brain. **This is very similar to the "multiple organ failure" that occurs in inflammatory conditions, bacteremia, congestive heart failure, cancer, and trauma.**

Otto Warburg established that lactic acid production even in the presence of oxygen is a fundamental property of cancer. It is, to a great degree, the lactic acid which triggers the defensive reactions of the organism, leading to tissue wasting from excessive glucocorticoid hormone. The cancer's production of lactic acid creates the same kind of internal imbalance produced by hyperventilation, and if we look at the physiology of hyperventilation in the light of Warburg's description of cancer, hyperventilation imitates cancer metabolism, by producing lactic acid "even in the presence of oxygen." Lactate, a supposedly benign metabolite of the cancer cells, which appears in all the other degenerative conditions, including obesity, diabetes, Alzheimer's disease, multiple sclerosis, is itself a central factor in the degenerative process.

Working out the mechanisms involved in susceptibility to altitude sickness will clarify the issues involved in the things that cause most people to die. At first, all of these changes occur in the regulatory systems, and so can be corrected.

The vitality of the mitochondria, their capacity for oxidative energy production, is influenced by nutrition and hormones. In healthy people, mitochondria work efficiently at almost any altitude, but people with damaged or poorly regulated mitochondria are extremely susceptible to stress and hyperventilation. Progesterone, testosterone, and thyroid (T3 and T2) are protective of normal mitochondrial function, by both local and systemic effects.

The changes that occur in malnutrition and hypothyroidism affect the mitochondria in a multitude of ways, besides the local effects of the thyroid and progesterone deficiency.

Increased estrogen, nitric oxide, excitatory amino acids, cortisol, lactate, free unsaturated fatty acids, prolactin, growth hormone, histamine, serotonin, tumor necrosis factor and other pro-inflammatory cytokines and kinins, and a variety of prostaglandins and eicosanoids, have been identified as anti-mitochondrial, anti-respiratory agents. Edema itself can be counted among these agents. (Carbon dioxide itself directly reduces tissue edema, as can be seen in studies of the cornea.) **Thyroid, progesterone, magnesium, glucose, and saturated fatty acids are among the central protective elements.**

The similarity of the changes occurring under the influence of estrogen excess, oxygen deprivation, aging, and ionizing radiation are remarkable. People who think that radiation's biological effects are mainly on the DNA, and that estrogen acts through "estrogen receptors," aren't interested in the parallels, but the idea of a common respiratory defect, activating common pathways, suggests that there is something useful in the perception that irradiation, hypoxia, and aging have estrogenic effects.

Irradiation by ultraviolet, gamma, or x-rays, and even by blue light, is damaging to mitochondrial respiration. All of the ionizing radiations produce immediate and lingering edema, which continues to damage metabolism in a more or less permanent way, apart from any detectable mutagenic actions. The amount of water taken up following irradiation can be 20% to 30% of the normal weight, which is similar to the amount of swelling that intense work produces in a muscle, and to the weight increase under hormonal imbalances. The energy changes produced by irradiation in, for example, the heart, appear to accelerate the changes produced by aging. Since unsaturated fats accumulate in the respiratory system with aging, and are targets for radiation damage, the involvement of these fats in all sorts of antirespiratory degenerative processes deserves more attention. Darkness, like irradiation, excess lactate, and unsaturated fats, has the diabetes-like effect of greatly reducing the ability of muscle to absorb sugar, while light stimulates respiration..

When the ideas of "stress," "respiratory defect," and "hyperventilation" are considered together, they seem practically interchangeable.

The presence of lactic acid, which indicates stress or defective respiration, interferes with energy metabolism in ways that tend to be self-promoting. Harry Rubin's experiments demonstrated that cells become cancerous before genetic changes appear. **The mere presence of lactic acid can make cells more susceptible to the transformation into cancer cells.** (Mothersill, et al., 1983.) The implications of this for the increased susceptibility to cancer during stress, and for the increased resistance to cancer at high altitude, are obvious.

Blocking the production of lactic acid can make cells more resistant (Seymour and Mothersill, 1988); if lactic acid were merely a useful fuel, it's hard to see how poisoning its formation could improve cell survival. But it happens to be an energy-disruptive fuel, interfering with carbon dioxide metabolism, among other things.

Hyperventilation is present in hypothyroidism, and is driven by adrenalin, lactate, and free fatty acids. Free fatty acids and lactate impair glucose use, and promote edema, especially in the lungs. Edema in the lungs limits oxygen absorption. Swelling of the brain, resulting from increased vascular permeability and the entry of free fatty acids, reduces its circulation and oxygenation; lactic acidemia causes swelling of glial cells. Swelling of the endothelium increases vascular resistance by making the channel narrower, eventually affecting all organs. Cells of the immune system release tumor necrosis factor and other inflammatory cytokines, and the bowel becomes more permeable, allowing endotoxin and even bacteria to enter the blood. Endotoxin impairs mitochondria, increases estrogen levels, causes Kupffer cells in the liver to produce more tumor necrosis factor, etc.. Despite its name, tumor necrosis factor stimulates the growth and metastasis of some types of cancer. Dilution of the body fluids, which occurs in hypothyroidsim, hyperestrogenism, etc., stimulates tumor growth.

The inflammatory factors that can promote cell growth can, with just slight variation, deplete cellular energy to the extent that the cells die from the energetic cost of the repair process, or mutate from defective repairs. Niacinamide can have an "antiinflammatory" function, preventing death from multiple organ failure, by interupting the reactions to nitric oxide and peroxynitrile (Cuzzocrea, et al., 1999). The cells' type, environment, and history determine the different outcomes.

Cataracts, cancer, congestive heart failure, seemingly such different degenerative problems, have the same sort of metabolic problem, leading to the abnormal absorption of water by cells, disrupting their normal functions.

The same simple metabolic therapies, such as thyroid, progesterone, magnesium, and carbon dioxide, are appropriate for a great range of seemingly different diseases. Other biochemicals, such as adenosine and niacinamide, have more specific protective effects, farther downstream in the "cascade" effects of stress.

There are many little cliches in the medical culture that prevent serious thought about integral therapy: "Progesterone is the pregnancy hormone," "thyroid makes your heart work too hard," "thyroid uncouples mitochondrial phosphorylation," "magnesium has nothing to do with thyroid or progesterone," "lactate provides energy," etc. But many of these minor cliches are held in place by deep theoretical errors about the nature of cells and organisms. Once those have been corrected, there should be progress toward more powerful integral therapies.

References

Cell Biol Int Rep 1983 Nov;7(11):971-80. **Lactate-mediated changes in growth morphology and transformation frequency of irradiated C3H 10T1/2 cells.** Mothersill C, Seymour CB, Moriarty M. Treatment of mammalian cells with lactate or inhibitors of glycolysis alters their radiation response, particularly in the low dose region of the dose response curve. The occurrence of **both high lactate levels and high glycolytic metabolism in tumours** is well known and therefore the effect of lactate on a cell line sensitive to radiation induced transformation was examined using a single exposure to Cobalt 60 gamma rays as the carcinogen challenge. The results indicate that cells treated with **5mM lactate before irradiation exhibit changes in morphology and growth rate and that the transformation frequency is increased by three to ten fold following 24 hours lactate treatment just prior to irradiation.** Examination of radiation survival curves showed a positive correlation between transformation frequency and size of the shoulder, but increasing transformation frequency was associated with a decrease in Do. A mechanism involving altered Redox potential in lactate treated cells is suggested. The results are discussed in terms of their possible significance for radiotherapy.

Radiat Environ Biophys 1988;27(1):49-57. The effect of glycolysis inhibitors on the radiation response of CHO-K1 cells. Seymour CB, Mothersill C Saint Luke's Hospital, Rathgar, Dublin, Ireland. Exposure of CHO-K1 cells to three different inhibitors of glycolysis, prior to treatment with a single dose of ionising radiation, reduced their survival. The effects were concentration-dependent but occurred under all conditions where cells were exposed to the inhibitors prior to irradiation. The results are similar to those obtained by this group when glycolysis was altered using analogues of D-

glucose or by blocking the pyruvate----lactate reaction using added lactate or oxamate. They support data from other workers suggesting a role for energy metabolism in the final expression of radiation damage.

Crit Care Med 1999 Aug;27(8):1517-23. **Protective effect of poly(ADP-ribose) synthetase inhibition on multiple organ failure after zymosan-induced peritonitis in the rat.** Cuzzocrea S, Zingarelli B, Costantino G, Sottile A, Teti D, Caputi AP

Eur J Cancer 1975 May;11(5):365-371. **Cancer and altitude. Does intracellular pH regulate cell division?** Burton AC.

Monaldi Arch Chest Dis 1999 Aug;54(4):365-72. The pathophysiology of hyperventilation syndrome. Folgering H. Dept Pulmonology Dekkerswald, University of Nijmegen, Groesbeek, The Netherlands.. **Hyperventilation is defined as breathing in excess of the metabolic needs of the body, eliminating more carbon dioxide than is produced, and, consequently, resulting in respiratory alkalosis and an elevated blood pH.** The traditional definition of hyperventilation syndrome describes "a syndrome, characterized by a variety of somatic symptoms induced by physiologically inappropriate hyperventilation and usually reproduced by voluntary hyperventilation". The spectrum of symptoms ascribed to hyperventilation syndrome is extremely broad, aspecific and varying. They stem from virtually every tract, and can be caused by physiological mechanisms such as low Pa,CO_2, or the **increased sympathetic adrenergic tone.** Psychological mechanisms also contribute to the symptomatology, or even generate some of the symptoms. Taking the traditional definition of hyperventilation syndrome as a starting point, there should be three elements to the diagnostic criterion: 1) the patient should hyperventilate and have low Pa,CO_2, 2) somatic diseases causing hyperventilation should have been excluded, and 3) the patient should have a number of complaints which are, or have been, related to the hypocapnia. Recent studies have questioned the tight relationship between hypocapnia and complaints. However, the latter can be maintained and/or elicited when situations in the absence of hypocapnia in which the first hyperventilation and hypocapnia was present recur. Thus, the main approach to diagnosis is the detection of signs of (possible) dysregulation of breathing leading to hypocapnia. The therapeutic approach to hyperventilation syndrome has several stages and/or degrees of intervention: psychological counselling, physiotherapy and relaxation, and finally drug therapy. Depending on the severity of the problem, one or more therapeutic strategies can be chosen.

N Engl J Med 1977 Mar 17;296(11):581-585. **Reduction in mortality from coronary heart disease in men residing at high altitude.** Mortimer EA Jr, Monson RR, MacMahon B In New Mexico, where inhabited areas vary from 914 to over 2135 m above sea level, we compared age-adjusted mortality rates for arteriosclerotic heart disease for white men and women for the years 1957-1970 in five sets of counties, grouped by altitude in 305-m (1000-foot) increments. The results show a serial decline in mortality from the lowest to the highest altitude for males but not for females. Mortality rates for males residing in the county groups higher than 1220 m in order of ascending altitude **were 98, 90, 86 and 72 per cent of that for the county group below 1220-m altitude (P less than 0.0001).** The results do not appear to be explained by artifacts in ascertainment, variations in ethnicity or urbanization. A possible explanation of the trend is that adjustment to residence at high altitude is incomplete and daily activities therefore represent greater exercise than when undertaken at lower altitudes.

Br Med J 1980 Jan 5;280(6206):5. Cardiovascular mortality and altitude.

Radiat Res 1987 Nov;112(2):381-390. **Altitude, radiation, and mortality from cancer and heart disease.** Weinberg CR, Brown KG, Hoel DG. The variation in background radiation levels is an important source of information for estimating human risks associated with low-level exposure to ionizing radiation. Several studies conducted in the United States, correlating mortality rates for cancer with estimated background radiation levels, found an unexpected inverse relationship. Such results have been interpreted as suggesting that low levels of ionizing radiation may actually confer some benefit. An environmental factor strongly correlated with background radiation is altitude. Since there are important physiological adaptations associated with breathing thinner air, such changes may themselves influence risk. We therefore fit models that simultaneously incorporated altitude and background radiation as predictors of mortality. The **negative correlations with background radiation** seen for **mortality from arteriosclerotic heart disease and cancers of the lung, the intestine, and the breast** disappeared or became positive once altitude was included in the models. **By contrast, the significant negative correlations with altitude persisted with adjustment for radiation. Interpretation of these results is problematic, but recent evidence implicating reactive forms of oxygen in carcinogenesis and atherosclerosis may be relevant. We conclude that the cancer correlational studies carried out in the United States using vital statistics data do not in themselves demonstrate a lack of carcinogenic effect of low radiation levels, and that reduced oxygen pressure of inspired air may be protective against certain causes of death.**

Biull Eksp Biol Med 1993 Jun;115(6):576-578. **[The effect of high-altitude ecological and experimental stresses on the thrombocyte-vascular wall system].** [Article in Russian]. Bekbolotova AK, Lemeshenko VA, Aliev MA. Experiments in animals (rats) and examinations of the population of high-altitude shepherds were used to study the functional system "Thrombocytes-Vessel Wall" (STVW) for evaluation of the organism ecological adaptation to "pure" high-altitude stress, with and without combination with experimental-adrenergic cardionecrosogenic stress (ACNS, in rats). The adaptive increase of antiaggregation prostacyclin activity of the aorta in rats and PGI2 reaction of vessels in human population of high-altitude in mountains (2000, 3000-3500 m) were found to be a common biologist regularity. The **adaptive increase of coronary reserve of the heart and vasodilatator-antiaggregation status in high-altitude shepherds correlated with an increase of antiaggregation activity of the aorta and decrease of spontaneous aggregation of the thrombocytes in rats under conditions of more prolonged adaptation to high-altitude ecological stress.**

Diabetologia 1982 Jun;22(6):493. **Measurement of glycosylated haemoglobin at high altitudes.** Paisey R, Valles V, Arredondo G, Wong B, Lozano-Castaneda O.

[Change in the ultrastructure of rat myocardium under the influence of 12-months' adaptation to high altitude] Zhaparov B; Mirrakhimov MM. Biull Eksp Biol Med, 1977 Jul, 84:7, 109-12. The right and left ventricle myocardium of rats was studied in the course of a 12-month period of adaptation to high altitude (3200 m above the sea level). A long-term exposure of the animals to the high altitude led the development of ventricular hypertrophy mostly of the right, and partly of the left ventricle. **Hyperplasia and hypertrophy of individual organellae, particularly mitochondria**, were found in most cardiomyocytes of both ventricles. In animals adapted to the high altitude the mitochondrial succinic dehydrogenase activity was more pronounced than in control ones. The results obtained testified to the enhanced intracellular metabolism reflecting myocardial compensatory adaptive responses.

[Morphologic characteristics of the hearts of argali continuously dwelling at high mountain altitudes], Zhaparov B; Kamitov SKh; Mirrakhimov MM, Biull Eksp Biol Med, 1980 Apr, 89:4, 498-501 The hearts of argali [wild sheep] living at 3800-5000 m above the sea level were examined. **Macroscopy showed complete absence of fatty tissue under the epicardium.** Increased number of the capillaries surrounding cardiomyocytes, intercalated discs in many zones of the myocardium, sharp thickening giving pronounced cross lines of myofibrils were revealed on semithin and ultrathin sections. The data obtained demonstrate specificity of the heart structure of argali and are **discussed from the standpoint of increased compensatory-adaptive changes in the test organ, these changes being associated with its enhanced function provoked by high altitude conditions.**

J Dev Physiol 1990 Sep;14(3):139-46. **Effect of lactate and beta-hydroxybutyrate infusions on brain metabolism in the fetal sheep.** Harding JE, Charlton VE Department of Pediatrics, University of California, San Francisco 94143. Brain uptake of substrates other than

glucose has been demonstrated in neonatal but not fetal animals in vivo. This study was undertaken to investigate the ability of the fetal sheep brain to use potential alternative substrates when they were provided in increased amounts. Brain substrate uptake was measured in chronically catheterised fetal sheep during 2-h infusions of neutralised lactate (n = 12) or beta-hydroxybutyrate (n = 12). **Despite large increases in fetal arterial lactate and beta-hydroxybutyrate during the respective infusions, no significant uptake of either substrate was demonstrated. However during both types of infusion, the brain arterio-venous difference for glucose decreased 30% (P less than 0.05). Since the brain arterio-venous difference for oxygen was unchanged, and blood flow to the cerebral hemispheres (measured in 11 studies) was also unchanged, the infusions appeared to cause a true decrease in brain glucose uptake. This decrease paralleled the rise in lactate concentration during lactate infusions, and the rise in lactate and butyrate** concentrations during the butyrate infusions. Both substrates have metabolic actions that may inhibit brain glucose uptake. **We speculate that the deleterious effects of high lactate and ketone states in the perinatal period may in part be due to inhibition of brain glucose uptake.**

Hypertens 1995 Feb;9(2):119-22. **Pressor effect of hyperventilation in healthy subjects.** Todd GP, Chadwick IG, Yeo WW, Jackson PR, Ramsay LE University Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Sheffield, UK Hyperventilation is an important feature of panic disorder, and an association has been reported between panic disorder and hypertension. We have examined the effect of hyperventilation on the blood pressure (BP) of healthy subjects. Twenty six subjects were randomised in a balanced two-period cross-over study to compare the effects of hyperventilation with that of normal breathing on sitting BP, heart rate and the electrocardiogram. Each study phase lasted 40 min, with 15 min of baseline observation, 5 min of hyperventilation or normal breathing, and 20 min of continued **observation. Hyperventilation significantly increased SBP by 8.9 mm Hg (95% CI 3.8-13.8, P < 0.01), diastolic blood pressure by 8.2 mm Hg (95% CI 1.7-14.7, P < 0.05), mean arterial pressure by 10.0 mm Hg (95% CI 3.3-16.7, P < 0.01) and heart rate by 36 beats/min (95% CI 31-44, P < 0.01). The changes in diastolic and mean arterial pressure correlated significantly with the total** volume of air expired during hyperventilation (r = 0.57, p < 0.01 and r = 0.50 P < 0.01, Arch Biol Med Exp (Santiago) 1989 Dec;22(4):379-85 Pulmonary response to free fatty acid intravenous infusion in the rabbit: role of leukotrienes and the effect of prostacyclin. Arenas G, Del Buono R, Oyarzun MJ, Donoso P, Quijada D Departamento de Ciencias Preclinicas, Facultad de Medicina, Universidad de Chile, Santiago. **Intravenous infusion of free fatty acid (FFA) 20 mg.kg-1.min-1 produces pulmonary edema, hypoxemia, hyperventilation and increase in the alveolar surfactant content in rabbits in less than 15** min.

Respiration 1986;49(3):187-94. **Role of hypocapnia in the alveolar surfactant increase induced by free fatty acid intravenous infusion in the rabbit.** Oyarzun MJ, Donoso P, Quijada D**. Intravenous infusion of free fatty acid (FFA) produces an increase in the alveolar surfactant pool of the rabbit and pulmonary edema, hyperventilation, hypoxemia and hypocapnia. Previous studies suggested that alveolar PCO2 would be a regulator of intracellular storages of surfactant. In order to** study the role of hypocapnia in the increase of lung surfactant in our experiments we administered 20 mg FFA X kg-1 X min-1 i.v. to rabbits breathing room air (n = 10) or 5% CO2, 21% O2, 74% N2 (n = 7). Disaturated phosphatidylcholine (DSPC) was determined in bronchial-alveolar lavage fluid as index of alveolar surfactant content, 5% CO2 in the inspired air prevented the hypocapnia and blocked the increase in DSPC induced by FFA (p less than 0.01). Pulmonary edema post-FFA was not changed by 5% CO2 administration. We conclude that hypocapnia produced by hyperventilation during FFA infusion would be an important factor in the increase of DSPC observed after FFA infusion.

Farmakol Toksikol 1977. Sep-Oct; 40(5):620-3.. **[Effect of combinations of apressin, obsidan, diprazin, adenosine, NAD and nicotinamide on the resistance of rats to hypoxia and on carbohydrate metabolic indices].** [Article in Russian] Abakumov GZ As evidenced from experiments on rats, a combined application of apressin with obsidan and diprazine, and also of adenozine with nicotine-amidadenine-dinucleotide (NAD), as well as of adeozine with nicotine amide potentiates the protective effect of these substances in hypobaric hypoxia, increases the resistance of the animals to cerebral ischemia, **brings down the excess lactate level and raises the redoz potential of the system lactic-acid-pyruvic** acid in the brain of rats exposed to the effects of rarefied atmosphere.

Schweiz Med Wochenschr 1977 Nov 5;107(44):1585-6. **[Protective effect of pyridoxilate on the hypoxic myocardium. Experimental studies].** [Article in French] Moret PR, Lutzen U The protective action of piridoxilate on hypoxic myocardium has been studied on rats in acute hypoxia (isolated heart, perfused with a non-oxygenated solution) and in prolonged hypoxia (3 days at high [3454 m] altitude). Piridoxilate maintained a higher ATP level with a much lower production of lactate. **The mechanisms of action of piridoxilate are probably fairly similar to those of Na dichloracetate**.

J. Appl Physiol 1991 Apr;70(4):1720-30. .**Metabolic and work efficiencies during exercise in Andean natives.** Hochachka PW, Stanley C, Matheson GO, McKenzie DC, Allen PS, Parkhouse WS Department of Zoology, University of British Columbia, Vancouver, Canada. **Maximum O2 and CO2 fluxes during exercise were less perturbed by hypoxia in Quechua natives** from the Andes than in lowlanders. In exploring how this was achieved, we found that, **for a given work rate, Quechua highlanders at 4,200 m accumulated substantially less lactate** than lowlanders at sea level normoxia (approximately 5-7 vs. 10-14 mM) despite hypobaric hypoxia. This phenomenon, known as the lactate paradox, was entirely refractory to normoxia-hypoxia transitions. In lowlanders, the lactate paradox is an acclimation; however, in Quechuas, the lactate paradox is an expression of metabolic organization that did not deacclimate, at least over the 6-wk period of our study. Thus it was concluded that this metabolic organization is a developmentally or genetically fixed characteristic selected because of the **efficiency advantage of aerobic metabolism (high ATP yield per mol of substrate metabolized) compared with anaerobic glycolysis.** Measurements of respiratory quotient indicated preferential use of carbohydrate as fuel for muscle work, which is also advantageous in hypoxia because it maximizes the yield of ATP per mol of O2 consumed. Finally, minimizing the cost of muscle work was also reflected in energetic efficiency as classically defined (power output per metabolic power input); **this was evident at all work rates but was most pronounced at submaximal work rates (efficiency approximately 1.5 times higher than in lowlander athletes).** Because plots of power output vs. metabolic power input did not extrapolate to the origin, it was concluded 1) that exercise in both groups sustained a significant ATP expenditure not convertible to mechanical work but 2) that this expenditure was downregulated in Andean natives by thus far unexplained mechanisms.

Br J Anaesth 1975 Jun;47(6):669-78. **Effect of CO2 on myocardial contractility and aortic input impedance during anaesthesia.** Foex P, Prys-Roberts C. The haemodynamic responses to hypocapnia and hypercapnia have been studied in the dog during intermittent positive pressure ventilation under halothane anaesthesia (1% halothane in oxygen) and under nitrous oxide anaesthesia (30% oxygen in nitrous oxide). In the absence of significant **variations of either myocardial contractility or left ventricular end-diastolic pressure, the changes of stroke volume and cardiac output (diminution because of hypocapnia, augmentation because of hypercapnia) were determined by alterations of systemic vascular resistance (augmentation because of hypocapnia, diminution because of hypercapnia).**

J Appl Physiol 1991 May;70(5):1963-76. **Skeletal muscle metabolism and work capacity: a 31P-NMR study of Andean natives and lowlanders.** Matheson GO, Allen PS, Ellinger DC, Hanstock CC, Gheorghiu D, McKenzie DC, Stanley C, Parkhouse WS, Hochachka PW Sports Medicine Division, University of British Columbia, Vancouver, Canada. Two metabolic features of altitude-adapted humans are the **maximal O2 consumption (VO2max) paradox (higher work rates following acclimatization without increases in VO2max)** and the lactate paradox (progressive reductions in muscle and blood lactate with exercise at increasing altitude). To

J Hum Hypertens 1995 Feb;9(2):119-22. **Pressor effect of hyperventilation in healthy subjects.**Todd GP, Chadwick IG, Yeo WW, Jackson PR, Ramsay LE.

J Infect Dis 1998 May;177(5):1418-21.**The effect of lactic acid on mononuclear cell secretion of proinflammatory cytokines in response to group B streptococci.** Steele PM, Augustine NH, Hill HR Department of Pathology, University of Utah School of Medicine, Salt Lake City 84132, USA.**This study found that lactate alone had a stimulatory effect (207.1 +/- 16.3%; P = .001) on tumor necrosis factor (TNF)-alpha production by human mononuclear cells with the most profound secretion being at pathologic concentrations of 4-8 mM lactate. Furthermore, exposure of these mononuclear cells to group B streptococci (GBS, 10(5) cfu) resulted in TNF-alpha production of up to 621.1 +/- 42% of control; the combination of lactic acid and GBS increased TNF-alpha production up to 1019.3 +/- 16.1% (P = .001). The combination of GBS and lactate also enhanced the secretion of interleukin (IL)-1beta and IL-6. Lactate in pathologic concentrations, therefore, likely enhances the secretion of these inflammatory mediators and contributes to septic shock and meningitis caused by GBS.**

J Appl Physiol 1994 Apr;76(4):1462-7**.** Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. Stringer W, Wasserman K, Casaburi R, Porszasz J, Maehara K, French W.

Involvement of nitric oxide and N-methyl- D-aspartate in acute hypoxic altitude convulsion in mice. Chen CH; Chen AC; Liu HJ. Aviat Space Environ Med, 1997 Apr, 68:4, 296-9. "Altitude convulsion is a rather specific form of experimental convulsion which is induced by acute exposure to a hypobaric hypoxic condition. Several neurotransmitters have been shown to be involved in the mechanisms of altitude convulsions." "The novel neurotransmitter nitric oxide (NO) may be involved in the mechanisms of altitude convulsion through its neuronal signalling roles in relation to the NMDA receptor." **"NO synthesis precursor, L-arginine (20, 40, 200, 800 mg/kg), resulted in a dose-dependent decrease in the ACT in mice, while the NO synthase (NOS) inhibitor, NG-nitro-L-arginine-methyl ester (L-NAME, 1.25, 2.50, 5.00 mg/kg, i.p.) increased the ACT."** "CONCLUSIONS: These findings suggest an important signalling role for nitric oxide and NMDA in the development of altitude convulsion and further support the hypothesized relationship between NMDA-receptor mediated neurotoxicity and nitric oxide."

Excitotoxicity in the lung: N-methyl-D-aspartate- induced, nitric oxide-dependent, pulmonary edema is attenuated by vasoactive intestinal peptide and by inhibitors of poly(ADP-ribose) polymerase. Said SI; Berisha HI; Pakbaz H. Proc Natl Acad Sci U S A, 1996 May 14, 93:10, 4688-92. **"Excitatory amino acid toxicity, resulting from overactivation of N-methyl-D-aspartate (NMDA) glutamate receptors, is a major mechanism of neuronal cell death in acute and chronic neurological diseases. We have investigated whether excitotoxicity may occur in peripheral organs, causing tissue injury, and report that NMDA receptor activation in perfused, ventilated rat lungs triggered acute injury, marked by increased pressures needed to ventilate and perfuse the lung, and by high-permeability edema."** The injury was prevented by competitive NMDA receptor antagonists or by channel-blocker MK-801, and **was reduced in the presence of Mg2+.** As with NMDA toxicity to central neurons, the lung injury was nitric oxide (NO) dependent: it **required L-arginine, was associated with increased production of NO,** and was attenuated by either of two NO synthase inhibitors. The neuropeptide vasoactive intestinal peptide and **inhibitors of poly(ADP-ribose) polymerase also prevented this injury, but without inhibiting NO synthesis, both acting by inhibiting a toxic action of NO that is critical to tissue injury.** The findings indicate that: (i) NMDA receptors exist in the lung (and probably elsewhere outside the central nervous system), (ii) excessive activation of these receptors may provoke acute edematous lung injury as seen in the "adult respiratory distress syndrome," and (iii) this injury can be modulated by blockade of one of three critical steps: NMDA receptor binding, inhibition of NO synthesis, or activation of poly(ADP-ribose) polymerase.

Adenosine modulates N-methyl-D- aspartate- stimulated hippocampal nitric oxide production in vivo. Bhardwaj A; Northington FJ; Koehler RC; Stiefel T; Hanley DF; Traystman RJ. Stroke, 1995 Sep, 26:9, 1627-33. "Adenosine acts presynaptically to inhibit release of excitatory amino acids (EAAs) and is thus considered to be neuroprotective. Because EAA-stimulated synthesis of nitric oxide (NO) may play an important role in long-term potentiation and excitotoxic-mediated injury, we tested the hypotheses that adenosine agonists attenuate basal and EAA-induced NO production in the hippocampus in vivo and that adenosine A1 receptors mediate this response." "...these data are consistent with in vitro results showing that NMDA receptor stimulation enhances NO production. Furthermore, we conclude that stimulation of A1 receptors can attenuate the basal as well as NMDA-induced production of NO. Because NMDA receptor stimulation amplifies glutamate release, our data are consistent with presynaptic A1 receptor-mediated inhibition of EAA release and consequent downregulation of NO production."

Anesthesiology 1993 Jan;78(1):91-9. **Hypocapnia worsens arterial blood oxygenation and increases VA/Q heterogeneity in canine pulmonary edema.** Domino KB, Lu Y, Eisenstein BL, Hlastala MP. University of Washington Medical School, Seattle. "Hyperventilation frequently is employed to reduce carbon dioxide partial pressure in patients in the operating room and intensive care unit. However the effect of hypocapnia on oxygenation is complex and may result in worsening in patients with preexisting intrapulmonary shunt." "Both hypocapnia and hypercapnia were associated with an increased VA/Q inequality. However, PaO2 decreased and P[A-a]O2 increased with only hypocapnia. These results suggest that hyperventilation to reduce PaCO2 may be detrimental to arterial PO2 in some patients with lung disease."

Acta Anaesthesiol Scand 1996 Jan;40(1):133-4 Hyperlactatemia associated with hypocarbic hyperventilation. Cheung PY

Am J Physiol 1999 May;276(5 Pt 1):E922-9 Hyperlactatemia reduces muscle glucose uptake and GLUT-4 mRNA while increasing (E1alpha)PDH gene expression in rat. Lombardi AM, Fabris R, Bassetto F, Serra R, Leturque A, Federspil G, Girard J, Vettor R Endocrine Metabolic Laboratory, Department of Medical and Surgical Sciences, University of Padova, 35100 Padova, Italy. **An increased basal plasma lactate concentration is present in many physiological and pathological conditions, including obesity and diabetes. We previously demonstrated that acute lactate infusion in rats produced a decrease in overall glucose uptake.** The present study was carried out to further investigate the effect of lactate on glucose transport and utilization in skeletal muscle. In chronically catheterized rats, a 24-h sodium lactate or bicarbonate infusion was performed. To study glucose uptake in muscle, a bolus of 2-deoxy-[3H]glucose was injected in basal condition and during euglycemic-hyperinsulinemic clamp. Our results show that hyperlactatemia decreased glucose uptake in muscles (i.e., red quadriceps; $P < 0.05$). Moreover in red muscles, both GLUT-4 mRNA (-30% in red quadriceps and -60% in soleus; $P < 0.025$) and protein (-40% in red quadriceps; $P < 0.05$) were decreased, whereas the (E1alpha)pyruvate dehydrogenase (PDH) mRNA was increased (+40% in red quadriceps; $P < 0.001$) in lactate-infused animals. PDH protein was also increased (4-fold in red gastrocnemius and 2-fold in red quadriceps). These results indicate that **chronic hyperlactatemia** reduces glucose uptake by affecting the expression of genes involved in glucose metabolism in muscle, suggesting a role for lactate in t**he development of insulin resistance.**

Radiat Res 1993 Apr;134(1):79-85 **Effects of in vivo heart irradiation on myocardial energy metabolism in rats.** Franken NA, Hollaar L, Bosker FJ, van Ravels FJ, van der Laarse A, Wondergem J Department of Clinical Oncology, University Hospital, Leiden, The Netherlands. To investigate the effect of in vivo heart irradiation on myocardial energy metabolism, we measured myocardial adenosine nucleotide concentrations and mitochondrial oxygen consumption in left ventricular tissue of rats 0-16 months after local heart irradiation (20 Gy). At 24 h and 2 months no difference in myocardial adenosine nucleotide concentration was apparent between irradiated and control hearts. The total myocardial adenosine nucleotide concentrations in irradiated hearts compared to those of nonirradiated controls tended to be lower from 4 months onward. The rate of **oxidative energy production (state 3 respiration) in irradiated hearts was significantly reduced ompared with that of age-matched controls from 2 months onward. Moreover, as a result of aging, time-dependent decrease in the rate of oxidative energy production was observed in both rradiated and control hearts** ($P < 0.001$). The respiratory control index (RCI = oxygen consumption n state 3/oxygen consumption in state 4) in irradiated hearts was not

different from the RCI easured in age-matched control animals. During the period of study the RCI diminished significantly wth age in both groups (P < 0.005). The number of oxygen atoms used per molecule of ADP phosphorylated (P/O ratio) was not influenced by the irradiation. The P/O ratio for the AD(+)-linked substrates remained unchanged at a value of about 3 during the period studied. At 6 months after irradiation activities of myocardial enzymes such as lactate dehydrogenase, creatine kinase, citrate synthase, and cytochrome c oxidase were reduced. The reduction in myocardial energy production and the **changes in energy supplies provide a mechanism to explain impaired contractility after local heart irradiation.**

J Radiat Res (Tokyo) 1993 Sep;34(3):195-203. **Radiosensitization of human lung fibroblasts by chemical that decrease ATP levels.** Kumar A, Kimura H, Aoyama T. **"Radiosensitization by lactate, pyruvate, nalidixic acid and novobiocin was studied in exponentially growing SH-18L human lung fibroblasts. All the chemicals had a slight radiosensitizing effect at a low concentration and a definite effect at a higher one." "Fibroblasts incubated with the low concentration of each chemical for 24 hrs after X irradiation showed no reduction in intracellular ATP content, whereas, the higher concentration produced a significant decrease.** These observations suggest that the decrease in the ATP content may be involved in the radiosensitization of human fibroblasts at high concentrations of these chemicals. **In contrast, radiosensitization at a low concentration is not explained by a relationship to ATP content. Different mechanisms may be involved in radiosensitization at low and high concentrations of these chemicals."**

J Exp Med 1993 May 1;177(5):1391-8. **Enhancement of experimental metastasis by tumor necrosis factor.** Orosz P, Echtenacher B, Falk W, Ruschoff J, Weber D, Mannel D.N. Institute for Immunology and Genetics, German Cancer Research Center, Heidelberg. "The influence of endogenous and exogenous tumor necrosis factor (TNF) on metastasis was investigated in an experimental fibrosarcoma metastasis model." "This effect was time dependent, as administration of rmTNF 5 h before or 1 h but not 24 h after tumor cell inoculation caused an increase of tumor cell colony formation on the lung surface, suggesting an influence of TNF on the vascular adhesion and diapedesis of tumor cells. Since tumor-bearing mice showed an enhanced ability to produce TNF after endotoxin injection compared to control mice, tumor-bearing mice were treated with anti-mTNF antibodies. Neutralization of endogenous tumor-induced TNF led to a significant decrease of the number of pulmonary metastases. Histological analysis of micrometastases in the lung on day 5 by silver staining of proteins associated with nucleolar organizer regions revealed **more metastatic foci and augmented proliferative activity of the tumor cells after rmTNF pretreatment of mice.** However, no direct effect of rmTNF on the proliferation rate of tumor cells was seen in vitro."

Nippon Geka Gakkai Zasshi 1996 Sep;97(9):726-32. **[Energy substrate metabolism during stress].** Sugimoto H. Department of Traumatology and Critical Care Medicine, Osaka University School of Medicine, Suita, Japan. **"Energy substrate metabolism during stress is characterized by increased REE (resting energy expenditure), hyperglycemia, hyperlactatemia and protein catabolism. This stress-induced hypermetabolic responses are closely related to increased secretion of neurohormonal and cytokine mediators. The insulin resistance hyperglycemia has been called "stress diabetes" or 'surgical diabetes.' Glucose disposal has been thought to be impaired in this condition." "This hyperglycemia in stress diabetes results from a postreceptor mechanism. Stress hyperlactatemia is thought to be caused by decreased pyruvate dehydrogenase activity rather than tissue hypoperfusion."**

Clin Physiol 1995 Nov;15(6):581-95. ***Effects of lactate infusion on hepatic gluconeogenesis and glycogenolysis.*** *Haesler E, Schneiter P, Temler E, Jequier E, Tappy L.*

Cancer Res 1993 Apr. 15;53(8):1939-44.. ***Tumor necrosis factor alpha as an autocrine and paracrine growth factor for ovarian cancer: monokine induction of tumor cell proliferation and tumor necrosis factor alpha expression.*** *Wu S, Boyer CM, Whitaker RS, Berchuck A, Wiener JR, Weinberg JB, Bast RC Jr.*

Klin Med (Mosk) 1989 May;67(5):38-41**. ["Dry" carbon dioxide baths in treating patients with myocardial infarction at the sanatorium stage of rehabilitation].** [Article in Russian] Barashkova NL, Kartamysheva NL, Krasnova VP, Kriuchkova LN, Miasoedova E.S. A group of 75 patients with a history of myocardial infarction and repeated myocardial infarction were subjected to treatment involving dry carbon dioxide baths. Its results demonstrated normalization of IHD manifestations, such as coronary and heart failure, functional state of the cardiovascular system, its reserve potentialities and adaptation to physical effort. Under the influence of a course treatment with dry carbon dioxide baths hemodynamic parameters of cardiac output (cardiac and stroke volume) underwent favourable changes, rhythm slowed down, diastole became longer and systolic and diastolic arterial pressure decreased. The data obtained substantiate application of dry carbon dioxide baths in the recovery period to I-III functional classes patients with a history of myocardial infarction.

J Dev Physiol 1989 Nov;12(5):283-6. **Haemodynamic effects of respiratory alkalosis independent of changes in airway pressure in anaesthetized newborn dogs.** Reuter JH, Donovan EF, Kotagal U.R. **"We have recently reported a decrease in cardiac output in newborn dogs during respiratory alkalosis which is independent of changes in airway pressure."**

Undersea Hyperb Med 1994 Jun;21(2):169-83. **Influence of hyperbaric oxygen on left ventricular contractility, total coronary blood flow, and myocardial oxygen consumption in the conscious dog.** Savitt MA, Rankin JS, Elberry JR, Owen CH, Camporesi E.M. **"It is known that hyperbaric oxygenation (HBO) decreases total coronary blood flow (TCBF) and cardiac output (CO)."**

Heart rhythm disturbances in the inhabitants of mountainous regions. *Mirrakhimov MM; Meimanaliev TS Cor Vasa, 1981, 23:5, 359-65.* ***"During exercise heart arrhythmias appeared conspicuously less frequently in the high mountain than in the low altitude inhabitants."***
