A R T I C L E

Osteoporosis, harmful calcification, and nerve/muscle malfunctions

During pregnancy, a woman's ability to retain dietary calcium and iron increases, and the baby seems to be susceptible to overloading. A normal baby doesn't need dietary iron for several months, as it uses the iron stored in its tissue, and recently it has been reported that normal fetuses and babies may have calcified pituitary glands. Pituitary cell death is sometimes seen with the concretions. (Groisman, et al.) Presumably, the calcification is resorbed as the baby grows. This is reminiscent of the "age pigment" that can be found in newborns, representing fetal stress from hypoxia, since that too disappears shortly after birth. Iron overload, age pigment, and calcification of soft tissues are so commonly associated with old age, that it is important to recognize that the same cluster occurs at the other extreme of (young) age, and that respiratory limitations characterize both of these periods of life.

Calcium is probably the most popular element in physiological research, since it functions as a regulatory trigger in many cell processes, including cell stimulation and cell death. Its tendency to be deposited with iron in damaged tissue has often been mentioned. In hot weather, chickens pant to cool themselves, and this can lead to the production of thin egg shells. Carbonated water provides enough carbon dioxide to replace that lost in panting, and allows normal calcification of the shells. [Science 82, May, 1982] The deposition of calcium is the last phase of the "tertiary coat" of the egg, to which the oviduct glands successively add albumin, "egg membrane," and the shell, containing matrix proteins (including some albumin; Hincke, 1995) and calcium crystals. Albumin is the best understood of these layers, but it is still complex and mysterious; its unusual affinity for metal ions has invited comparisons with proteins of the immune system. It is known to be able to bind iron strongly, and this is considered to have an "immunological" function, preventing the invasion of organisms that depend on iron. Maria de Sousa ("Iron and the lymphomyeloid system: A growing knowledge," Iron in Immunity, Cancer and Inflammation, ed. by M. de Sousa and J. H. Brock, Wiley & Sons, 1989) has argued that the oxygen delivery system and the immune system evolved together, recycling iron in a tightly controlled system.

The role of macrophages in the massive turnover of hemoglobin, and as osteoclasts, gives us a perspective in which iron and calcium are handled in analogous ways. Mechnikov's view of the immune system, growing from his observations of the "phagocytes," similarly gave it a central role in the organism as a form-giving/ nutrition-related process. In a family with "marble-bone disease," or osteopetrosis, it was found that their red blood cells lacked one form of the carbonic anhydrase enzyme, and that as a result, their body fluids retained abnormally high concentrations of carbon dioxide. Until these people were studied, it had been assumed that an excess of carbon dioxide would have the opposite effect, dissolving bones and causing osteoporosis or osteopenia, instead of osteopetrosis. The thyroid hormone is responsible for the carbon dioxide produced in respiration. Chronic hypothyroidism causes osteopenia, and in this connection, it is significant that women (as a result of estrogen's effects on the thyroid) are much more likely than men to be hypothyroid, and that, relative to men, women in general are "osteopenic," that is, they have more delicate skeletons than men do.

In an experiment, rats were given a standard diet, to which had been added 1% Armour thyroid, that is, they were made extremely hyperthyroid. Since their diet was inadequate (later experiments

showed that this amount of thyroid didn't cause growth retardation when liver was added to the diet) for their high metabolic rate, they died prematurely, in an apparently undernourished state, weighing much less than normal rats. Their bones, however, were larger and heavier than the bones of normal rats. A few incompetent medical "studies" have made people fear that "taking thyroid can cause osteoporosis." Recognizing that hypothyroid women are likely to have small bones and excessive cortisol production, the inadequate treatment of hypothyroidism with thyroxin (the thyroid-suppressive precursor material), is likely to be associated with relative osteoporosis, simply because it doesn't correct hypothyroidism. Similar misinterpretations have led people to see an association between "thyroid use" (generally thyroxin) and breast cancer--hypothyroid women are likely to have cancer, osteoporosis, obesity, etc., and are also likely to have been inadequately treated for hypothyroidism. T3, the active form of thyroid hormone, does contribute to bone formation. (For example, M. Alini, et al.)

Around the same time (early 1940s) that the effects of thyroid on bone development were being demonstrated, progesterone was found to prevent age-related changes in bones, and "excessive" seeming doses of thyroid were found to prevent age-related joint diseases in rats.

A logical course of events, building on these and subsequent discoveries, would have been to observe that the glucocorticoids cause a negative calcium balance, leading to osteoporosis, and that thyroid and progesterone oppose those hormones, protecting against osteoporosis. But the drug industry had discovered the profits in estrogen ("the female hormone") and the cortisone-class of drugs. Estrogen was promoted to prevent miscarriages, to stop girls (and boys) from growing too tall, to cure prostate and breast cancer, to remedy baldness, and 200 other absurdities. As all of those frauds gradually became untenable, even in the commercial medical culture, the estrogen industry began to concentrate on osteoporosis and femininity. Heart disease and Alzheimer's disease back those up.

"If estrogen causes arthritis, prescribe prednisone for the inflammation. If prednisone causes osteoporosis, increase the dose of estrogen to retard the bone-loss. People are tough, and physiological therapies aren't very profitable."

Fifteen years ago I noted in a newsletter that hip fractures most often occur in frail, underweight old women, and that heavier, more robust women seem to be able to bear more weight with less risk of fracture. Although I hadn't read it at the time, a 1980 article (Weiss, et al.) compared patients with a broken hip or arm with a control group made up of hospitalized orthopedic patients with problems other than hip or arm fractures. The fracture cases' weight averaged 19 pounds lighter than that of the other patients. They were more than 3.6 times as likely to be alcoholic or epileptic. It would be fair to describe them as a less robust group.

Since the use of estrogen has become so common in the U.S., it is reasonable to ask whether the incidence of hip fractures in women over 70 has declined in recent decades. If estrogen protects against hip fractures, then we should see a large decrease in their incidence in the relevant population.

Hip fractures, like cancer, strokes, and heart disease, are strongly associated with old age. Because of the baby-boom, 1945 to 1960, our population has a bulge, a disproportion in people between the ages of 35 and 50, and those older. Increasingly, we will be exposed to publicity about the declining incidence of disease, fraudulently derived from the actually declining proportion of old people. For example, analyzing claims based on the pretense that the population bulge doesn't exist, I have seen great publicity given to studies that would imply that our life-expectancy is now 100 years, or more.

Comparing the number of hip fractures, per 1000 75 year old women, in 1996, with the rate in 1950, we would have a basis for judging whether estrogen is having the effect claimed for it.

The x-ray data seem to convince many people estrogen is improving

bone health, by comparing measurements in the same person before and after treatment. Does estrogen cause water retention? Yes. Does tissue water content increase measured bone density? Yes. Are patients informed that their "bone scans" don't have a scientific basis? No. The calcification of soft tissues under the influence of estrogen must also be taken into account in interpreting x-ray evidence. (Hoshino, 1996) Granted that woman who are overweight have fewer hip fractures (and more cancer and diabetes), what factors are involved? Insulin is the main factor promoting fat storage, and it is anabolic for bone. (Rude and Singer, "Hormonal modifiers of mineral metabolism.") The greatest decrease in bone mass resulting from insulin deficiency was seen in white females, and after five years of insulin treatment, there was a lower incidence of decreased bone mass (Rosenbloom, et al., 1977). McNair, et al. (1978 and 1979) found that the loss of bone mass coincided with the onset of clinical diabetes. Since excess cortisol can cause both high blood sugar and bone loss, when diabetes is defined on the basis of high blood sugar, it will often involve high blood sugar caused by excess cortisol, and there will be calcium loss. Elsewhere, I have pointed out some of the similarities between menopause and Cushing's syndrome; a deficiency of thyroid and progesterone can account for many of these changes. Nencioni and Polvani have observed the onset of progesterone deficiency coinciding with bone loss, and have emphasized the importance of progesterone's antagonism to cortisol.

Johnston (1979) found that progesterone (but not estrone, estradiol, testosterone, or androstenedione) was significantly lower in those losing bone mass most rapidly.

Around the age of 50, when bone loss is increasing, progesterone and thyroid are likely to be deficient, and cortisol and prolactin are likely to be increased. Prolactin contributes directly to bone loss, and is likely to be one of the factors that contributes to decreased progesterone production.

Estrogen tends to cause increased secretion of prolactin and the glucocorticoids, which cause bone loss, but it also promotes insulin secretion, which tends to prevent bone loss. All of these factors are associated with increased cancer risk.

Thyroid and progesterone, unlike estrogen, stimulate bone-building, and are associated with a decreased risk of cancer. It seems sensible to use thyroid and progesterone for their general anti-degenerative effects, protecting the bones, joints, brain, immune system, heart, blood vessels, breasts, etc.

But the issue of calcification/decalcification is so general, we mustn't lose interest just because the practical problem of osteoporosis is approaching solution.

For example, healthy high energy metabolism requires the exclusion of most calcium from cells, and when calcium enters the stimulated or deenergized cell, it is likely to trigger a series of reactions that lower energy production, interfering with oxidative metabolism. During aging, both calcium and iron tend to accumulate and they both seem to have an affinity for similar locations, and they both tend to displace copper. (Compare K. Sato, et al., on the calcification of copper-containing paints.) Elastin is a protein, the units of which are probably bound together by copper atoms. In old age, elastin is one of the first substances to calcify, for example in the elastic layers of arteries, causing them to lose elasticity, and to harden into almost bone-like tubes. In the heart and kidneys, the mitochondria (rich in copper-enzymes) are often the location showing the earliest calcification, for example when magnesium is deficient.

Obviously, certain proteins have higher than average affinity for copper, iron, and calcium. For example, egg-white's unusual behavior with copper can be seen if you make a meringue in a copper pan--the froth is unusually firm. My guess is that copper atoms bind the protein molecules into relatively elastic systems. In many systems, calcium forms the link between adhesive proteins.

In brain degeneration, the regions that sometimes accumulate aluminum, will accumulate other metals instead, if they

predominate in the environment; calcium is found in this part of the brain in some of the Pacific regions studied by Gajdusek. Certain cells in the brain used to be called "metalophils," because they could be stained intensely with silver and other metals; I suppose these are part of the immune system, handling iron as described by Maria de Sousa. Macrophages have been proposed as an important factor in producing atherosclerotic plaques (Carpenter, et al.). There is evidence that they (and not smooth muscle cells) are the characteristic foam cells, and their conversion of polyunsaturated oils into age pigment accounts for the depletion of those fats in the plaques. The same evidence could be interpreted as a defensive reaction, binding iron and destroying unsaturated fatty acids, and by this detoxifying action, possibly protecting against calcification and destruction of elastin. (This isn't the first suggestion that atherosclerosis might represent a protective process; see S. M. Plotnikov, et al., 1994.)

Since carbon dioxide and bicarbonate are formed in the mitochondria, it is reasonable to suppose that the steady outward flow of the bicarbonate anion would facilitate the elimination of calcium from the mitochondria. Since damaged mitochondria are known to start the process of pathological calcification in the heart and kidneys, it probably occurs in other tissues that are respiratorily stressed. And if healthy respiration, producing carbon dioxide, is needed to keep calcium outside the cell, an efficient defense system could also facilitate the deposition of calcium in suitable places--depending on specific protein binding. The over-grown bones in the hyperthyroid rats and the women with osteopetrosis suggest that an abundance of carbon dioxide facilitates bone formation. Since no ordinary inorganic process of precipitation/crystallization has been identified that could account for this, we should consider the possibility that the protein matrix is regulated in a way that promotes (or resists) calcification. The affinity of carbon dioxide for the amine groups on proteins (as in the formation of carbamino hemoglobin, which changes the shape of the protein) could change the affinity of collagen or other proteins for calcium. Normally, ATP is considered to be the most important substance governing such changes of protein conformation or binding properties, but ordinarily, ATP and CO2 are closely associated, because both are produced in respiration. Gilbert Ling has suggested that hormones such as progesterone also act as cardinal adsorbants, regulating the affinity of proteins for salts and other molecules.

Cells have many proteins with variable affinity for calcium; for example in muscle, a system called the endoplasmic reticulum, releases and then sequesters calcium to control contraction and relaxation. (This calcium-binding system is backed up by--and is spatially in close association with--that of the mitochondrion.) Ion-exchange resins can be chemically modified to change their affinity for specific ions, and molecules capable of reacting strongly with proteins can change the affinities of the proteins for minerals. What evidence is there that carbon dioxide could influence calcium binding? The earliest deposition of crystals on implanted material is calcium carbonate. (J. Vuola, et al, 1996.) In newly formed bone, the phosphate content is low, and increases with maturity. While mature bone has an apatite-like ratio of calcium and phosphate, newly calcified bone is very deficient in phosphate (according to Dallemagne, the initial calcium to phosphorus ratio is 1.29, and it increases to 2.20.) (G. Bourne, 1972; Dallemagne.)

The carbonate content of bone is often ignored, but in newly formed bone, it is probably the pioneer. Normally, "nucleation" of crystals is thought of as a physical event in a supersaturated solution, but the chemical interaction between carbon dioxide and amino groups (amino acids, protein, or ammonia, for example) removes the carbon dioxide from solution, and the carbamino acid formed becomes a bound anion with which calcium can form a salt. With normal physiological buffering, the divalent calcium (Ca2+) should form a link between the monovalent carbamino acid and another anion. Linking with carbonate (CO32-), one valence would be free to continue the salt-chain. This sort of chemistry is compatible with the known conditions of bone formation.

Klein, et al. (1996), think of uncoupled oxidative phosphorylation in

terms of "subtle thermogenesis," which isn't demonstrated in their experiment, but their experiment actually suggests that stimulated production of carbon dioxide is the factor that stimulates calcification. Their experiment seems to be the in vitro equivalent of the various observations mentioned above. DHEA, which powerfully stimulates bone formation, is (like thyroid and progesterone) thermogenic, but in these cases, the relevant event is probably the stimulation of respiration, not the heat production. In pigs (Landrace strain) susceptible to malignant hyperthermia, there is slow removal of calcium from the contractile apparatus of their muscles. Recent evidence shows that an extramitochondrial NADH-oxidase is functioning. This indicates that carbon dioxide production is limited. I think this is responsible for the cells' sluggishness in expelling calcium.

Stress-susceptible pigs show abnormalities of muscle metabolism (e.g., high lactate formation) that are consistent with hypothyroidism. (T. E. Nelson, et al., "Porcine malignant hyperthermia: Observations on the occurrence of pale, soft, exudative musculature among susceptible pigs," Am. J. Vet. Res. 35, 347-350, 1974; M. D. Judge, et al., "Adrenal and thyroid function in stress-susceptible pigs (Sus domesticus)," Am. J. Physiol. 214(1), 146-151, 1968.)

Malignant hyperthermia during surgery is usually blamed on genetic susceptibility and sensitivity to anesthetics. (R. D. Wilson, et al., "Malignant hyperpyrexia with anesthesia," JAMA 202, 183-186, 1967; B.A Britt and W. Kalow, "Malignant hyperthermia: aetiology unknown," Canad. Anaesth. Soc. J. 17, 316-330, 1970.) Hypertonicity of muscles, various degrees of myopathy and rigidity, and uncoupling of oxidative phosphorylation occur in these people, as in pigs. Lactic acidosis suggests that mitochondrial respiration is defective in the people, as in the pigs. Besides the sensitivity to anesthetics, the muscles of these people are abnormally sensitive to caffeine and elevated extracellular potassium. During surgery, artificial ventilation, combined with stress, toxic anesthetics, and any extramitochondrial oxidation that might be occurring (such as NADH-oxidase, which produces no CO_2), make relative hyperventilation a plausible explanation for the development of hyperthermia. Hyperventilation can cause muscle contraction. Panting causes a tendency for fingers and toes to cramp. Free intracellular calcium is the trigger for muscle contraction (and magnesium is an important factor in relaxation.) Capillary tone, similarly, is increased by hyperventilation, and relaxed by carbon dioxide. The muscle-relaxing effect of carbon dioxide shows that the binding of intracellular calcium is promoted by carbon dioxide, as well as by ATP. The binding of calcium in a way that makes it unable to interfere with cellular metabolism is, in a sense, a variant of simple extrusion of calcium, and the binding of calcium to extracellular materials. A relaxed muscle and a strong bone are characterized by bound calcium.

Activation of the sympathetic nervous system promotes hyperventilation. This means that hypothyroidism, with high adrenalin (resulting from a tendency toward hypoglycemia because of inefficient use of glucose and oxygen), predisposes to hyperventilation.

Muscle stiffness, muscle soreness and weakness, and osteoporosis all seem to be consequences of inadequate respiration, allowing lactic acid to be produced instead of carbon dioxide. Insomnia, hyperactivity, anxiety, and many chronic brain conditions also show evidence of defective respiration, for example, either slow consumption of glucose or the formation of lactic acid, both of which are common consequences of low thyroid function. Several studies (e.g., Jacono and Robertson, 1987) suggest that abnormal calcium regulation is involved in epilepsy. The combination of supplements of thyroid (emphasizing T3), magnesium, progesterone and pregnenolone can usually restore normal respiration, and it seems clear that this should normalize calcium metabolism, decreasing the calcification of soft tissues, increasing the calcification of bones, and improving the efficiency of muscles and nerves. (Magnesium, like carbonate, is a component of newly formed bone.) The avoidance of polyunsaturated vegetable oils is important for protecting respiration; some of the prostaglandins

they produce have been implicated in osteoporosis, but more generally, they antagonize thyroid function and they can interfere with calcium control. The presence of the "Mead acid" (the omega-9 unsaturated fat our enzymes synthesize) in cartilage suggests a new line of investigation regarding the bone-toxicity of the polyunsaturated dietary oils.

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