February 1997 Issue | Serafina Corsello, M.D.

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Welcome to the second issue of *Functional Medicine Update*, February, 1997, which will deal with women's health and age-related disorders. The topic will be highlighted in a Clinician of the Month interview with Dr. Serafina Corsello, a physician in New York who focuses on women's health. We will wrap *FMU* around this topic to provide a clinical focus for this issue.

Back in 1987, a prominent molecular biologist said you can't study aging -- it just happens. This is an interesting, but unrealistic point of view, because it suggests there is a message locked within our genome that encodes for what many years ago was called the death-clock mechanism. This is a pretty Machiavellian view of the life process, as if we are caught up in an inexplicable, incurable disorder called the disease of aging. If that is true, perhaps we had better live with careless abandon in the short time we have left in order to do all the things we want to do. We would become hedonistic, self-consuming individuals by this philosophy, spending little time worried about reserve, working to get the most out of the moment. Yet, as we have seen in the evolution of both laboratory and human clinical research in age-related diseases, many of the disorders that plague people in mid- to late life are, in fact, extraordinarily modifiable by the way we treat those genes over the course of a lifetime. We can build a reserve from which to draw later, when the inevitable times of stress occur within our lives. This month, we will focus on the relationships among genes, environment, lifestyle, and women's health issues. We will address men's age-dependent disorders in a subsequent issue of *Functional Medicine Update*.

What controls a woman's aging process? Within our genes are time-dependent processes that are built within the embryogenic machinery. This temporal aspect of our physiology gives rise to the maturation process and, ultimately, to the aging process. We all know people 65 years old who perform biologically like 30-year-olds, and we know the opposite -- 30-year-olds who perform biologically like 65-year-olds. In the past, it was thought to be just the luck of the draw, little could be done about it because it was determined when the sperm met the egg, and we must live with it. Now, we recognize there are many gene expression modifiers that modulate, modify, promote, suppress, augment, or inhibit the function of various genetic messages. This gives rise to a very plastic phenotype that is modifiable based upon attitudes, beliefs, activities, environment, diet, and the like.

Cell Types and Cell Aging

To apply this information to women's health issues, we can go back and look at the lowly fruit fly, *Drosophila melanogaster*. We can learn something interesting from the fruit fly, because its body wall cells are all the identical chronological age. It is difficult to study cellular aging in humans, because we are composed of cells of differing ages. Some cells, as in our skin, are sloughed off and replaced every

few days. Our oral or gastrointestinal mucosal cells are similar. Other cells, such as certain neurons in the brain, may have lived since our early developmental period. If we were to ask about the state of aging of the body from a biological perspective, we might be led to false conclusions if we took a random tissue or cell type.

In the fruit fly, all cells were formed at the same time, and all have had similar experiences throughout its short lifetime. You can examine senescence at a biochemical level much more easily in the fruit fly. You can also do strange things to fruit flies, like making them exercise more or causing them to become more sedentary. You can give them antioxidants or restrict antioxidants; you can cause or withhold stress; you can crowd them or not crowd them; you can expose them to pollutants, etc.

What do we learn from *Drosophila melanogaster*? We learn that diet plays a role in the aging of the cells. Debris is formed from oxidant stress reactions that occur throughout the aging process. I am referring to Dr. Denham Harman's free radical theory of aging, which he proposed in the early 1950s. Dietary antioxidants play a role in life extension, and the genes of the fruit fly that relate to the expression of antioxidant enzymes (like superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase) also relate to how rapidly the animal ages. Those with extra copies of certain antioxidant-encoding enzymes will, in fact, live considerably longer than those with normal copies or mutant copies of these genes, which are less able to defend against oxidant stress. So oxidant stress has something to do with cell damage that has occurred over the course of life, and we might associate this with biological aging.

The endocrine system in higher animals affects the regulation of reduction/oxidation capabilities, giving rise to different types of oxidative stress reactions. Even in *Saccharomyces cerevisiae* (brewer's yeast) we find that different gene structures give rise to different oxidative stress, mutational frequencies, and life expectancies. Considerable work has been done with unicellular organisms as well as the *Drosophila*, rats, mice, and guinea pigs, looking at this oxidant stress connection.

What derives from all of this is that both the external and internal environments interact with genes to give rise to the expression of various factors that regulate redox capability of cells. Inappropriate regulation can accelerate release of oxidants and increase damage to proteins, unsaturated fatty acids, membranous materials like the endoplasmic reticular membrane, mitochondrial and nuclear DNA, and enzymes. Oxidation of enzyme sulfhydryl residues can change their activity.

Also, under oxidative stress conditions associated with insulin insensitivity or hyperglycemia, we see glycation of proteins, where glucose attaches itself to proteins and forms advanced glycosylated endproducts (AGEs), which decrease metabolic efficiency. Therefore, the molecular action of various processes that give rise to accelerated aging and age-related diseases (such as cardiovascular disease, hypertensive disorder, maturity onset diabetes, various endocrinopathies, and certain forms of cancer) are now better understood from a mechanistic perspective. This relates to various substances that have recently been in the news, including DHEA (dehydroepiandrosterone), melatonin, Coenzyme Q10, vitamin E, N-acetylcysteine, and selenium. Age-associated diseases in both women and men are related to oxidant stress, redox imbalances, and, ultimately, to life decisions -- how we eat, where we live, how we think. "Longevity, Genes, and Aging" is an interesting review article in *Science*(1996; 273:54) by Dr. S. Michal Jazwinski from the Department of Biochemistry and Molecular Biology, Louisiana State University Medical Center, New Orleans.

What happens if we remove some stress from the organism by having it not eat as much? Would that change the flux of electrons through mitochondria, reduce oxidative stress, and have beneficial effects on endocrine balance, proteins, membranous fatty acids or phospholipids, or DNA? That question has been the topic of extensive studies by many researchers, including Dr. Sohal and his colleagues at the Department of Biological Sciences, Southern Methodist University in Dallas. Calorie restriction (30 percent calorie reduction) is the only unequivocally defined dietary approach to significantly increase life expectancy in animals. This is not total dietary restriction. Calories are restricted in these studies, but vitamins, minerals, and other accessory nutrients are given at the same -- or sometimes even greater -- levels than in a normal diet. Restricting calories restricts the fuel for the flame of oxidative phosphorylation,. In these animal studies, there has been reproducible improvement of life expectancy -- sometimes, as much as 50 percent increased life expectancy in animals whose normal calorie consumption is reduced by 30 percent.

Some human inhabitants of Biosphere II were on a calorie-restricted diet. Because they are going to stay on this regimen for a period of time, they may be studied repeatedly to see what impact their diet has on aging parameters. Most Americans, living where restaurants, fast foods, and hedonistic food consumption patterns have become the watchwords, would find it very difficult to consider a 30 percent calorie restriction. Calorie-restricted animal studies, however, have shown that some imbalanced hormone patterns are normalized, oxidative stress parameters are significantly reduced, and some effects on mitochondrial energy production are normalized with calorie restriction, suggesting lowered biological aging can result.

Many published papers in this field have helped us recognize that diet does play a profound role in influencing metabolism and, subsequently, the functional capacity of the endocrine, nervous, immune, cardiovascular, urogenital, and musculoskeletal systems. In addition to supplying fuel to produce energy, diet provides a number of important secondary metabolic principles. Their impact on the functional status of various organ systems can be traced back to biological changes and changes of gene expression in various tissues and cells. An interesting paper, "The Effects of Caloric Restriction on Age-Related Oxidative Modification of Macromolecules and Lymphocyte Proliferation," appeared in *Free Radical Biology & Medicine*(1996; 19:859). Investigators found animals on calorie-restricted diets (30 percent restriction of calories) demonstrated significant improvement in lymphocyte proliferation and improved function of various enzymes because of lowered protein carbonyl formation as a consequence of protein denaturization from oxidative stress and glycosylation reactions. Mechanisms are emerging that would link dietary variables, oxidant stress, environmental factors, and modulation of the endocrine, immune, nervous, gastrointestinal, and hepatic systems. Functional connections are being defined.

There is an explosion of published literature regarding women's health issues. With its first female director, the National Institutes of Health has begun seriously looking at women's health imperatives and has better funding for related research projects. The diet/women's health issue is gaining in importance as an area of study. We know, for example, about the role of magnesium and calcium in the prevention of pre-eclampsia or eclampsia -- the hypertension and hyperalbuminuria of pregnancy that can be life-threatening to both the fetus and mother. Normal magnesium intake may not be enough. Magnesium supplementation in ranges of 400-600 mg/day, or even the use of IM- or IV-administered magnesium in crisis states, can help lower blood pressure and normalize function in a pre-eclamptic woman. We now know that magnesium plays a role in women's health through an effect on endocrine control of the vasculature, and the vasculature interrelates with factors that are alarm signaling messages pertaining to

hypertension or hypotension. There is evidence that magnesium may play a role in nitric oxide-modulated processes, possibly through nitric oxide synthetase, according to *Medical Hypothesis* (1996; 47:269), which contained an interesting review paper about magnesium and eclampsia and the relationship to nitric oxide and blood pressure control in pregnant women

INTERVIEW TRANSCRIPT

Serafina Corsello, M.D.

JB: Dr. Serafina Corsello is a physician with long-standing experience in women's health issues. Dr. Corsello received her medical education at the University of Rome in Italy. She did an externship at Lutheran Medical Center in New York, residency at King's County Hospital in New York, and has been a key contributor to complementary medicine throughout her many years of private practice in New York City. Tell us, Dr. Corsello, what got you into complementary medicine?

SC: Thank you, Jeff. I want to take this opportunity to thank you for your wonderful *PMU*. I listen to the tapes while I do my jogging in the morning, or in the car, and I could not do without them. I use them to teach my people.

How did I get into this field? Approximately 25 years ago a patient of mine had tardive dyskinesia as a result of a prescription, and I was the last one in a chain of physicians who gave collagen. That got me so upset that it made me search for better ways. From there, I moved into chelation and other things. Then I developed a problem myself; I had a mass in my breast. It was very frightening. I had heard of natural hormone replacement therapy. This forced me overnight to start a search. From there, of necessity, natural hormone replacement therapy became one of my greatest loves, which I practice with pleasure.

JB: One patient who has successfully gone through your program is Gail Sheehy. She was very complimentary about your approach in her book about menopause. It seems we are having increasing numbers of hormone-related problems in women and in men. Where do you think these challenges and problems are coming from?

SC: I feel it starts from the disaster of menarche that we see in Western culture, especially in our culture -- sooner, earlier, and earlier. The reason is that our girls (also boys, for that matter) are fed lots of estrogen through milk, cheese, and ice cream. Estrogen is given to cows, and, of course, it comes straight from the meat, milk, and milk products. And so, this culture has been overfed estrogen. The mere level of estrogen that begins to appear in the blood of these girls triggers the diencephalic response. Ultimately, they have a problem producing the gonadotropin-releasing hormone to cleanse the maturation of ovaries.

Another thing that bothers me is television. I want to alert all parents about television, with its explicit sex and violence. The mixing of the two drives is very dangerous. It, too, triggers the diencephalic response that commences the cascade of events that starts the maturation of the gonads. That is the second one. The first one is bad enough, but the second one is a social disaster. I would like all concerned people to look into this and limit viewing on the part of children and patients. So we have early menarche. We know that the longer we have estrogen in the body, the longer we have the possibility of problems.

Which estrogen? Not the good estrogen, but the bad estrogen. We do have xenoestrogens that are byproducts of petrochemicals present in our environment, and they go straight into our food chain to the vegetables if they are not free or organic. We have everyone consuming a great amount of foreign estrogens or xenoestrogens, which are very toxic. They bind to the receptors in the breast, the gonads, or the fatty parts of the body and stay with the fat forever. When we lose weight, they are released into the system and are very carcinogenic. This is not the good estrogen. As you know, good estrogen actually prevents the ability of the xenoestrogen and the toxic estrogen to bind to the receptor. One has to be aware of the very distinct difference. Genistein flavones in soy products are excellent because they actually protect us from binding with these xenotoxic estrogens and the estrogens in milk products and meats. So, of course this creates possibilities of disturbances, although they are in the system forever.

What happens after menarche commences is that these subliminal levels of estrogen hide the ones we produce, which the girls could use, and those taken exogenously from food. We now have too much estrogen. This excess of estrogen inhibits the maturation of the gonads by inhibiting the luteinizing hormone (LH). I believe this is why we have defects in LH: the endogenous versus the exogenous estrogen is too much. This defect in LH produces a defect in maturation of the corpus luteum. What we now have is the maturation phase of the ovary or the egg. The movement of the ovocyte to the surface for expulsion of the egg commences. But at the time the egg should begin a secretion on day 8, 9, 10 to give a high level of LH, it is not there. So, this egg comes toward the surface but does not transform itself; the corpus luteum does not release the egg. The corpus luteum normally produces progesterone Now, we have osteoprogesterone, and we do have, as everyone knows, anovulatory processes, where the process does not occur at all. We have a defect in ovulation where there is paucity of progesterone. In either case, we have the possibility of this egg becoming a cyst. Ergo, the excess of ovarian cysts that we see in our patients. In today's world more than ever it is much increased.

This could also produce a disturbance on the breast level. Estrogen, which we have now in abundance, stimulates formation and maturation of the breast and potential production of milk if fertilization of the egg occurs. But it is the progesterone that actually produces this increase in suppleness and secretion, and there is incomplete mechanism of action. We have cysts rather than mature eggs ready to bring the process to fruition. Ergo, fibrocystic mastitis. That, too, is a cause of the horrible phenomenon that Dr. John D. Lee pointed out many years ago. Dr. Lee really opened the door for all of us to look into these facts and understand them. He explains all this in his beautiful book, *Natural Progesterone*. Now we have seen the genesis of alpha persisting mastitis and cysts in the ovaries.

To go further, the maturation of the endometrium commences with the estrogen, but again, if we do not have enough progesterone, the citratory phase, which prepares the uterus for implantation of the egg, doesn't occur. Ergo, many failed implantation of eggs and increased infertility. Just one of the causes. The anovulatory processes and inappropriate or incomplete ovulation also plays a big role in infertility.

JB: This is an extraordinary concept. To summarize, as I have understood it, you are talking about estrogen/progesterone imbalances and their effect on signaling specific cellular activity related to reproductive and other functions. So one might look at the problem as being too much estrogen or not enough progesterone, or you could also look at it as incomplete detoxification of estrogen, which, I would presume, implicates liver detoxification function as well.

SC: Absolutely. In fact, there comes the process of intervention. The very first thing, which comes from

European culture, is to clean the bowels of my patients, because toxic estrogen is absorbed like toxic cholesterol from the gut. You must literally scrub the gut out. I use fibers and vitamin C to do this.

But another factor we need to talk about is the systemic effect of this cycle of not having enough progesterone. It is progesterone that allows the uptake in nontoxic tissues of the T3. So, another phenomenon related to cleaning, to fiber conversion and natural inability of the T3 to bind, even if it converts, is the paucity of progesterone. Look at the repercussions. And, of course, progesterone and low thyroid function also lead, among many other things, to infertility. So you see how everything circles around, interrupts, and feeds back with each other. The simple process that starts with our little girls watching lousy television and eating lousy food has repercussions throughout life, not to mention cancer related to this toxic estrogen.

You know about the bra? Women who have very tight bras have more chance of breast cancer than women who wear loose bras. The reason is it forces lymphatic drainage to diminish and therefore, the cleansing and excretion of these toxic estrogens and excessive estrogens of the breast are diminished by the tightness, a mechanical factor. So biochemical factors, nutritional factors, detoxification factors, and mechanical factors all play together to create the problem that we are all aware of, the increase in breast cancer in women. Intervention must be multilevel, very harmonious, and very judicious.

JB: You have eloquently described a model for all of complementary and functional medicine. It is the holographic pattern versus looking at single treatments for single symptoms. What an eloquent way of describing it. One thing that emerges from this discussion is the current debate about soy foods. I have heard a number of people speak on both sides of this issue. Some say women's hormones are balanced and their function is improved by increasing soy products in the diet. Another, more discordant theme is that soy actually increases hormonal imbalances, and may increase risk to various hormone-related cancers. Do you have an opinion on this?

SC: Yes, I have a view. As always, I look at the epidemiology to get some answers, because I feel the debate is so hot. There are many reasons for this debate, and some are not so noble. Some special interest groups do not want to see simple interventions to cure big problems like cancer. I look at epidemiology of Japanese women and Chinese women, before we introduced our Western food. Those who use their traditional diet have significantly less breast cancer. Also, a culture that has lived on this food for millennia might really be doing something else. I am not sure what else they may have been doing. They are also eating fish, which also plays a role. The essential fatty acids play a big role in protecting against cancer in a multitude of ways. But I believe when we look at eating and epidemiology it becomes clear that it was soy that actually protected them. So why, all of a sudden, do we have a debate? What do you think, Jeff?

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