February 1998 Issue | Stanislaw Burzynski, M.D., Ph.D.

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Welcome to *Functional Medicine Update*™ for February 1998. The upcoming Fifth International Symposium on Functional Medicine will focus on Functional Medicine Applications to Disorders of Gene Expression. We chose this focus for the Symposium because we at HealthComm International believe the emerging focus of medicine in the new millennium will be gene regulators and modification of gene expression.

Lifestyle, thoughts, attitudes, beliefs, environment, diet, relationships, and energy – all of these are modulators of gene expression. Therefore, the key to improving health, reducing disease, and even treating certain diseases is locked into our understanding of gene messages, uncovering the right messages, and putting to sleep the wrong gene messages. This understanding will enable us to promote a phenotype that exhibits high-level health for eight, nine, ten, or more decades of life. The emphasis at the Symposium will be on homocysteine and inflammation, nutrient modulation of adverse drug side effects through the impact of nutrients on gene expression and detoxification, and nutrient modulation of cancer genes. We will focus on this third topic this month in *Functional Medicine Update*™.

Through the Human Genome Project that is taking place in laboratories around the world, we are learning about the diversity of human genes and the sequencing of the genetic structure. Dr. Lewis Thomas, a chronicler of the evolution of medicine in the 20th Century, stated, "The uniformity of earth's life, more astonishing than its diversity, is accountable by the high probability that we derived, originally, from some single cell, fertilized in a bolt of lightning as the earth cooled." Ever since, diversity has been developing.

In the field of genomic medicine, evaluation, genetic counseling, preventive and prospective medicine, nutrition and lifestyle management, and the pharmacology of today will converge into a single new type of medicine. Doctors, patients, nurses, and skilled health paraprofessionals will be parts of a team collaborating to develop a treatment program to help patients improve the expression of their phenotypes from the polymorphic genotypes that exist.

Genomic medicine is described in an article in the *Journal of the American Medical Association* (1997;278:1212). I urge you to visit the website www.hhml.org/Genetic Trail/. On that website you will find a self-study program on human genetics, the Human Genome Project, and the relationship to gene-specific disease risks. It is an example of how this information is becoming more available, not only to practitioners and professionals, but also to patients.

This month we will focus on the modulation of cancer genes as an example of the theme we will be

discussing at the Fifth International Symposium on Functional Medicine. Some of you may be thinking this will be a theoretical discussion that has little clinical relevance to the way you practice medicine today. I think, however, that you will see there is an immediate payoff from the application of what we know today about modulation of gene expression, and it can open new opportunities for improving patient outcome and decreasing problems related to chronic degenerative disease.

The authors of a review paper in the *Journal of the National Cancer Institute* (1997;89:1489) entitled "Aging and Cancer: Issues of Basic and Clinical Science," discuss the theories of aging and the evidence that people tend to get more cancer as they grow older. According to the authors, it is likely that certain genes in humans relate to aging and life span. We know about the genetic regulation of disease. Clues about this regulation are emerging from the Human Genome Project.

Disorders of aging that are related to gene uniqueness include like progeria, Werner's syndrome, and Down's syndrome. These are outliers on the continuum of gene alteration, gene mutations, or gene uniqueness related to aging represent precocious, accelerated aging. A child with Werner's syndrome may undergo what appears to be the entire aging process in 15 years and die an old-appearing individual in his or her mid-teens. This disorder is connected to certain genes related to oxidative stress and inflammation reactions that encode for increased exposure to oxidants like superoxide hydroxyl radical. The result of this exposure seems to be increased cellular damage, formation of lipofuscin pigment, deposition of seroid pigment, and deposition of amyloid in various organs. The process chokes off the function of the organs and causes them to undergo apoptotic cell death and rapid biological aging.

Various sections called telomeres within genes actually seem to guide and influence how the genes are expressed and how they relate to the aging process. Besides telomere length, there are other factors that nonspecifically influence gene or protein function that accumulate damage over time. These factors include not only the reactive oxygen species, ionizing radiation, and drug and chemical-induced damage, but even stress. Over time, stress can be toxic. It increases cellular damage and the deposition of secondary debris of cellular apoptotic function.

Apoptosis is a process by which cells undergo death, not by necrosis, but by the change of the cytoskeletal structure that holds the cell in its three-dimensional shape. It tends to shrink, like a puppet whose strings are pulled in, until it pinches itself off, almost like micropinocytosis. In this process, the cell ultimately loses its function. It may occur as a consequence of the deposition of amyloid protein, as a consequence of glycation reactions that occur to proteins, or as a consequence of oxidative stress, free radical-induced damage to proteins, nucleic acids, and membrane lipids. All these are tied back to genetic uniqueness and the expression of those genes under the influence of lifestyle.

How does this relate to cancer and aging? We recognize the cumulative damage that occurs to these cells as a consequence ultimately can influence the regulation of genes that may encode for cellular architecture and cellular state. As individuals age, DNA damage occurs. This damage may be in tumor promoter regions or it may have modified the cell signals that increase the probability of the wrong message being promoted. These events can lead to an oncogenic event. There are many processes that we are now identifying that are related to the genetic event that is associated with the de-differentiation of a cell that becomes a juvenile-like cell or embryonic cell that has the characteristics we associate ultimately with a cancer cell. These events become more probable as we age because we have had more opportunity for damage to occur within our genome that might increase the probability of expression of these altered

messages. However, it doesn't mean that chronological aging, in and of itself, encodes for cancer.

An article in *Molecular Medicine Today* (1997;4:147) focused on the benefits for patients of cancer gene testing. We are learning more about the P53 and P21 oncogenes, the *ras*oncogenes, and the BRCA genes of breast cancer. These genes encode for specific potential of risk to an individual who is exposed to certain lifestyle or environment factors that could trigger the expression of these messages.

Some of these gene messages are inducible and some are not. Constitutive gene messages are those that are less susceptible to modification. Inducible factors, whose presence have been identified in a range of newly identified heredity cancer genes, can be modified by environment, lifestyle, and other reducible risk factors. This molecular basis of cancer prevention is beginning to capture the attention of the scientific community, tying genetic risk factors to their inducibility or suppression factors and seeing how that regulates or normalizes cell differentiation and cell function.

P53 is one protein factor that has been identified as a cancer gene component. Scientists are finding ways to target these specific gene factors to put them to sleep or awaken them in immunotherapy or cancer therapy. (*Molecular Medicine Today. 1997;4:160)* This is the biological basis of cancer therapy, as contrasted to killing all cells that have undergone a specific transformation in the traditional approach of introducing enough cytotoxic agents in the body to kill every cell that has undergone a change of this type. In this cytotoxic therapy, you also kill normal cells that have similar mitotic and physiological function.

This other biological approach to cancer tries to identify specific areas in the body where certain gene regulators associated with cancer have been upregulated or downregulated and directs the attention of the immune system specifically to turn off or turn on those messages and normalize cellular function.

A number of so-called cancer genes have been identified recently. These genes, which encode for risk, include not just the P21, P53, *ras*, and BRCA genes, but also a series of genes that relate both to constitutive and modifiable, inducible detoxification enzymes. Cytochrome P450s, such as cytochrome P450 2D6, and the Phase II detoxifying enzymes are encoded for on specific regions of our genes. A whole range of isoforms of these cytochrome P450 gene products exists. There are probably more than 100 different isoforms in the human that encode for detoxification efficiency of specific classes of substances or chemicals.

You might have gene characteristics that are adequate for one family of detoxification and have inactivity or underactivity for another. There is a very specific genetic link to susceptibility factors for specific endo- and exotoxic substances. Cytochrome P450 2D6 polymorphism is interesting because this is the isoform of cytochrome P450 that is responsible for detoxifying many drugs, including Prozac-like compounds. Therefore, individuals who have altered detoxification, as controlled by their genes – cytochrome P450 2D6, may have differing toxicity reactions associated with these kinds of substances that pass through that principal pathway on their way to being detoxified

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INTERVIEW TRANSCRIPT

Clinician of the Month:
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We have become accustomed to having the top clinicians in the world as guests on the Clinician of the Month corner on *Functional Medicine Update*™, and we won't be disappointed this month. Stanislaw Burzynski, M.D., Ph.D., has developed a treatment approach for cancer that has caught the attention of integrative and complementary medicine practitioners and those in the broader range of science and medicine as well. It seems also to have opened some eyes on the federal level and even at the National Cancer Institute.

Dr. Burzynski received his medical doctorate degree from the Lublin, Poland, Medical Academy in 1967, and his Ph.D. in biochemistry in 1968 from the same institution. He was an assistant professor of medicine at Baylor College of Medicine from 1972 to 1977. Since then he has been president of the Burzynski Research Institute in Houston, Texas. Dr. Burzynski has more than 100 publications in his curriculum vitae. His contributions to the field, the political situations he has faced, and his vigilance in fighting for the continued evolution of information are described in a book entitled *The Burzynski Breakthrough* Thomas Elias, published this year by W. Quay Hays Company in Santa Monica, California.

JB: Could you tell us what antineoplaston are, Dr. Burzynski?

SB: Antineoplastons are components of the body's defense system against cancer. According to our theory, there are two defense systems in the body. One is the immune system; the other is what we call the biochemical defense system, or BDS. The immune system protects against invasion of microorganisms, and the biochemical defense system protects us from occurrence of abnormal cells such as cancerous cells. The immune system works mainly by recognition and elimination of the invaders. The biochemical defense system works by reprogramming the cells that develop in an improper way. It begins by using molecular switches. The chemicals we call antineoplastons are small peptides, amino acid derivatives, and certain organic acids. They can regulate the genes involved in the cancer process or the process of manufacturing some other abnormal cells. They turn off the genes that stimulate cancerous growth, and they stimulate the genes that inhibit cancer growth. That is the basic difference between antineoplastons and components of the immune system.

JB: Dr. Burzynski's antineoplaston work and his theory may seem esoteric to some of you, but he has earned the respect of many members of the traditional medical community. Dr. Robert Burdick, a respected medical oncologist in Seattle, Washington, and faculty member at the University of Washington Medical School, made the following comment about the clinical benefit of antineoplaston therapy in brain cancer:

> It is very rare currently to ever get a complete remission or cure in a patient who has a malignant brain tumor, using our standard modalities of surgery, radiation, and chemotherapy. As a rough estimate, neurosurgeons do well to cure one in every 1,000 brain cancer patients they operate on. Radiation therapy slows the growth of an adult tumor, gaining perhaps one month of life and again may result in a cure in only one in 500

to l,000 patients, those cures being in the pediatric age group.

Similarly, despite 30 years of clinical trials, chemotherapy research has not resulted in the development of a single drug or drug combination that elicits more than an occasional transient response in primary brain tumors. I am impressed by the number of complete and partial responses I have seen here with the Burzynski method, compared with the number of responses that I have seen in my personal experience. The responses here are far in excess of any prior series of experience published in the medical literature. The response rate is an astounding 81 percent, with an equally astounding 35 percent complete remission rate. Such remission rates are far in excess of anything anyone else has seen since research work on brain tumors began. It is very clear that the responses here are due to antineoplaston therapy and are not due to surgery, radiation, or standard chemotherapy.

Dr. Burzynski, how did you develop the antineoplaston concept and therapy?

SB: It was coincidental. As a student, I was working on amino acids in human blood in various disorders, trying to see if changes in amino acid concentration could provide us with diagnostic clues. In patients who have cancer, I found there were great decrease of certain amino acid derivatives in their blood. Some of these cancer patients simply have an absence of some amino acid derivatives. I isolated these unknown amino acid derivatives and found they were peptides.

Later on, when I characterized them and found they could inhibit cancer growth, I called them antineoplastons. What is interesting about these compounds is that on the one hand, they were producing substantial inhibition of cancer cell growth in the tissue culture. On the other hand, they were not affecting normal cells. They have high specificity toward cancerous cells, and this was very unusual. That’s why I decided to determine the chemical structure of antineoplastons and do whatever is required to bring them to FDA approval, starting with preclinical trials to clinical status, and phase II clinical trials.

JB: In the 1960s, Dr. Linus Pauling and his colleague Dr. Arthur Robinson were doing amino acid analysis by HPLC of plasma and urine from cancer and normal patients. They also observed an interesting difference in the peptide range of the chromatograms. It seems to me you picked up on this and moved it to a new level against the dominant theory of the time. This theory (which perhaps still exists today) is that small molecules cannot have the kind of regulatory effect that big protein molecules with a lot more structure/function relationship can have. People have overlooked these small molecules as important regulators.

SB: That’s correct. When I was a medical student everyone was excited by large molecules; small molecules were neglected as so-called waste products. Now, the pendulum is swinging in the other direction; now, people are excited about small molecules. We know that even molecules like nitric oxide can produce a tremendous effect in the body. What we found are relatively simple chemicals that may

contain a few amino acids or one amino acid and not a prosthetic group. Such structure allows them to regulate much bigger molecules. They can regulate genes, for example. That is what they do in the body. To control cancer effectively, it is not absolutely necessary to know the complete structure of the genes involved in cancer or the proteins involved in the formation of cancer. It may be sufficient to identify the molecules that control these large molecules, and we may then come to the control of cancer.

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