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The Immune System in Cancer

Keith I. Block, MD, D. Barry Boyd, MD, Nicholas Gonzalez, MD, and Aristo Vojdani, PhD

Cancer patients face immune system challenges primarily in 2 areas: (1) fighting malignancies through immune mechanisms and (2) confronting the immune-suppressive effects of the disease and treatments. In this Point-Counterpoint, we explore the potential role of the immune system with practitioners and researchers active in the area of integrative and alternative cancer treatment: D. Barry Boyd, MD, a medical oncologist who uses integrative approaches in his practice; Nicholas Gonzalez, MD, a physician in private practice who uses an alternative medicine intervention for cancer patients based on the work of Dr. William Kelley; and Aristo Vojdani, PhD, of Immunosciences Lab Inc., a diagnostic and research facility that specializes in innovative microbiology and immunology laboratory testing. Drs. Gonzalez and Vojdani were interviewed by telephone for this article, whereas Dr. Boyd submitted written responses to our questions.

Mobilizing the body's immune system against cancer has long been an elusive goal in cancer medicine. The idea that the human immune system provides continuous surveillance for cancer cells is appealing to the general public and continues to be presented as gospel in many popular health books, particularly those aligned with alternative medicine. It seems almost axiomatic to the layperson that a system designed to help the body ward off pathogenic influences should also help ferret out cancer cells. When immune surveillance falters, cancers can more readily develop and progress. The allure of this belief is further heightened by the recognition that many factors within our control can influence immune function, and by the fervent hope that enhancing such immune function should, in turn, support one's ability to combat cancer.

Originally proposed by Ehrlich in 1909 and elaborated on by Burnet in the 1960s, the immune surveillance hypothesis states that cell-mediated immunity can recognize and destroy proliferating cancer cells.[1,2] This hypothesis was founded on the premise that cancer cells bear qualitatively or quantitatively unique antigens that are by-products of the process of malignant transformation. During transformation, genetic mutations result in aberrant expression of cancer-related genes and protein products that are potentially immunogenic and thus serve as tumor-specific antigens. The theory assumes that cancer cells should be sufficiently antigenic to elicit their elimination via cytotoxic T lymphocytes, natural killer (NK) cells, and tumoricidal macrophages. In some instances, however, weakly immunogenic cancer cells or cells that fail to express the tumor-specific antigens could elude the surveillance system and develop into overt tumors. Other mechanisms of escape from surveillance include the down-regulation of major histocompatibility (MHC) class I expression and tumor-specific cytotoxic T cells, as well as up-regulation of suppressive T cells, immunosuppressive cytokines, and other factors.[3-6]

An important corollary to the immune surveillance theory is that the immune system's capacity for surveillance can be modified through both medical and lifestyle interventions. A severely depressed or impaired immune system would probably fail to respond even to a highly immunogenic tumor. Initially it was thought that such impairment was due to genetic factors as well as to treatment with radiation or immunosuppressive drugs. We now know that all the conventional modalities of cancer therapy except hormone therapy (i.e., surgery, radiotherapy, and chemotherapy) can suppress immune response.[7] More recently, biobehavioral factors such as high-fat diets,[8-11] insufficient or erratic exercise,[12-14] and stressful situations or events[15-17] have been added to the list of immunodepressive factors that might, in turn, enable cancer to flourish. These additional factors would logically exacerbate or prolong the tumor- and treatment-induced suppression of immunity.

To lend support to the immune surveillance theory, proponents point to the increased cancer rates in conditions of clinical immune deficiency such as those associated with AIDS or with immunosuppressive

KB is at the Block Center for Integrative Cancer Care, Evanston, IL. DBB is with Integrative Oncology, Greenwich, CT. NG is in private practice in New York, NY. AV is at Immunosciences Lab Inc, Beverly Hills, CA.

Correspondence: Keith I. Block, Block Center for Integrative Cancer Care, 1800 Sherman Avenue, Suite 515, Evanston, IL 60201. Tel: 847-492-3040. Fax: 847-492-3045. E-mail: kblock@blockmedical.com.

therapy for organ transplantation. Nevertheless, it is striking to note that common epithelial neoplasms such as breast, colon, and lung cancers rarely if ever occur under these circumstances. This is despite the fact that epithelial cancers maintain a high degree of antigenicity. In all likelihood, the reason for this discrepancy has to do with 2 facets of the host-tumor interrelationship. One is that tumor-cell evasion mechanisms may prevail over the immune surveillance mechanisms against these cancers. As mentioned above, cancer cells can circumvent immune surveillance through a variety of pathways.

The second major facet of the host-tumor interrelationship pertains to the concept of clonal evolution, the microevolutionary nature of tumor growth and progression. Tumor cells are genetically unstable and constantly evolving. The dual properties of genetic instability and clonal expansion allow tumor development to occur through a process of successive adaptations. Among the typical epithelial cancers, this process is characterized by the evasion of apoptosis, loss of sensitivity to growth inhibitory signals, tumor-mediated angiogenesis, and progressive capacity for invasion and metastasis. One tumor- and lymphocyte-derived cytokine, transforming growth factor-beta (TGF-β), seems to embody the multidimensional character of this process. TGF-β may contribute to increased breast tumor growth in the absence of estradiol,[18] induction of angiogenesis,[19] formation of connective tissue and deregulation of pericellular proteolysis,[20,21] and suppression of several aspects of the immune response.[22-24] TGF-β is considered to be the most potent immunosuppressor described to date,[25] yet the cytokine's immune-suppressive action may not even be the most important mechanism by which it increases the invasive potential of tumors.

Escape from immune-mediated killing may be part of a coevolutionary race by which cancers ultimately manage to circumvent the usual immune defense mechanisms. One might broadly speculate that a competent immune system could run the race against cancer for a longer period than an incompetent immune system. Nonetheless, given the diverse array of tumor-evasive mechanisms at its disposal, it is easy to see how the clonal evolutionary process of tumor progression could surpass any attempts by the host to eradicate cancer immunologically. However efficient the immune response might be, if a tumor's mutation rate is relatively high, the immune system will be overwhelmed by the collective plasticity displayed by the mutating population of cancer cells; most research to date suggests that the malignancy will be several steps ahead of the "floundering" immune response. Some malignant cells may be eliminated; nonetheless, those that remain most often prove even more resistant to immune attack.

Point 1.

Can the immune system support cancer recovery? If so, please explain in general terms the importance of the immune system before, during, and after conventional treatment.

Boyd: Over the past 100 years, there has been growing evidence of a tumor-specific immune response. This began in 1898, when William Coley reported to the American Medical Association on 140 advanced sarcoma patients who were treated with a streptococcal extract (Coley's toxin) with some evidence of clinical response. Since Coley's report, there has been continual growth in our knowledge of cellular and humoral immunity and the complex interactions of cytokines, interleukins (ILs), and interferons, as well as the recognition of the nature of antigen processing in concert with MHC proteins on the surface of effector cells. The experimental basis for tumor immunology has been well defined for both specific antitumor cytotoxic T-cell mediated responses in concert with antigen presenting cells and nonspecific NK-cell cytotoxicity.

Over the past 20 years, there has been an effort to define tumor-specific antigens. However, it is now acknowledged that in the majority of cases, recognition of antigens on the surface of the tumors has been limited to that of so-called tumor-associated antigens, which reflect the presence of normal tissue antigen expression in higher amounts on tumor cells rather than specific and selected antigens present only on tumors. Tumor antigens are likely to be tissue specific, reflecting the tissue of origin of the cancer. Unfortunately, such tumor immunity has also been relatively limited despite the hopes of many researchers. One of these proteins was first identified as an antigenic peptide in melanoma, subsequently determined to be the gene MAGE-1. Numerous other tumor-associated antigens have been described. Rather than being unique to tumors (i.e., neoantigens arising from mutations), the majority of these are simply more highly expressed differentiation antigens on normal tissues. Despite the evidence for this antigenic expression and the potential specific and nonspecific cellular mechanisms against cancer, most malignancies are not effectively controlled by the patient's immune system.

Several mechanisms have been proposed to explain this escape from immune control. Many patients will have circulating lymphocytes within the peripheral blood that show tumor responsiveness in vitro, but are inactive in vivo. As tumors evolve, they may lose the expression of tumor antigens or the expression of accompanying MHC gene products, resulting in a failure of T-cell recognition. Many tumors, particularly the common tumors arising from

epithelial cells, are not recognized because of the limited presence of "nonself antigen" expression.

An additional problem is the active immunosuppressive effect of tumor-secreted cytokines, such as TGF-β and IL-10, which inhibit the antitumor lymphocyte cytotoxicity. There is evidence also for a direct immune suppression of the antitumor immune mechanism, presumably linked to the need for tolerance to self-antigens and the inhibition of resulting autoimmunity. Hyam I. Levitsky and colleagues at Johns Hopkins University, working with a B-cell lymphoma model, demonstrated that CD4+ T cells specific for B-cell antigens became tolerant in lymphoma development. Unresponsiveness occurred early and was specific only to the B-cell tumor, but not to other antigens. The cytotoxic T-lymphocyte antigen 4 (CTLA-4), expressed by activated T cells, directly inhibited the T-lymphocyte response to tumors. Antibody to this CTLA-4 antigen in vivo in this mouse model was able to reverse this inhibition and induce tumor regression. This model suggests that, paradoxically, the immune system is capable of suppressing the T-cell-mediated antitumor response, particularly in the early development of tumors, allowing for tumor progression.

A limitation recently described in immune surveillance is that tumors may occur peripherally at sites that do not enter organized lymphoid tissue in levels sufficient to induce an effective cellular T-lymphocyte response and, therefore, may be ignored by the immune system. When immunity is induced late in the course of tumor evolution, it is at a time when it is ineffective and likely to have minimal effect on tumor progression.

Thus, multiple barriers exist that explain the limitation of immune surveillance. In addition, evidence from multiple "experiments of nature" serves to demonstrate further the limits of immune surveillance. HIV disease, first seen in the early 1980s, is characterized by profound changes in cellular immunity, concurrent with a high risk of viral, fungal, and protozoan infections and a high incidence of multiple but specific malignancies. These cancers include the B-cell lymphomas, Kaposi's sarcoma, and squamous cancers of the anogenital and cervical mucosa, all of which have been linked to viruses. The increase in these malignancies reveals a failure to recognize virally related cancers, specifically Epstein-Barr virus (lymphoma), herpes virus (Kaposi's sarcoma), and human papilloma virus (squamous cancers), rather than failure of tissue-associated antigen recognition. In contrast, other epithelial cancers, including breast, lung, colorectal, pancreatic, and prostate cancers, have not significantly increased, except when concurrent risk factors such as smoking and intravenous drug use are present.

A similar risk has been noted in the posttransplant patient population treated with prolonged immunosuppressive therapy. There has been a notable increase in lympho-proliferative disease, anogenital cancers, in situ squamous cancers, and Kaposi's sarcoma, again suggesting specific defects in immune surveillance against virally mediated oncogenesis, rather than against typical epithelial cancers.

The NK cell reflects nonantigen-specific lymphocyte-mediated cytotoxicity. In contrast to the widely recognized cellular immune deficiency states noted above, descriptions of NK-cell deficiency are rare. A few reports have described a "low NK cell syndrome," including one study with 23 patients characterized by low NK-cell activity with symptoms of recurring fever and fatigue and the presence of an otherwise normal immune system, with no evidence of HIV or other retroviral infections. In addition, there was no evidence of increased levels of other viral infections or viral antibody response. These patients were free of any evidence of increased malignancy, and none had died during follow-up at the time of publication. An additional patient has been described in the literature with an absence of "classical NK-cell activity." She was noted to have cervical cancer and hyper coagulability. However, her course was not characterized by recurrent multiple tumors or by the presence of disseminated or frequent viral infections.

Thus, in both profound T-cell immune dysfunction typified by HIV and transplantation-related immune suppression, as well as the limited data on NK-cell deficiencies, elevated susceptibility to malignancies appears to be limited to virally mediated cancers (reflecting a failure of viral control by T-cell immunity) rather than to the typical spectrum of epithelial cancers. Research beginning in the early 1980s aimed at using lymphokine-activated NK cells stimulated by IL-2 further supports the limited effect of natural immunity on epithelial cancers. This work, undertaken initially by Steven Rosenberg and others at the surgical division of the National Cancer Institute, used lymphokine-activated NK cells stimulated with IL-2 in vitro and subsequently infused into patients with advanced cancer. This was followed by studies employing specific tumor-infiltrating lymphocytes again activated with IL-2. Numerous centers participated in these studies in an attempt to induce tumor responses. The initial optimism was met with limited success, with significant responses only in a limited number of malignancies, specifically melanoma, renal cell carcinoma, and lymphomas. These malignancies are known to express the most readily identified tumor-associated antigens and have been known to respond to immune-modulating therapy such as interferon, in contrast to limited effects noted with other epithelial cancers. Furthermore, pathologic evidence for immune response, such as lymphocyte infiltration of the primary tumor or lymph nodes at the time of surgery, has been inconsistently associated with prognosis, suggesting further that immune response to common epithelial cancers is a late event and largely ineffective. Thus, significant immune deficiency may not contribute to a significant increase in risk, except for those cancers that are virally mediated

such as the HIV-associated cancers or those that are highly expressive of tumor-associated antigen such as melanoma and renal cell cancer.

Rather than being a manifestation of immune suppression, it is likely that tumor progression in the typical epithelial cancer is characterized by progressive clonal evolution with loss of sensitivity to growth inhibitory signals, evasion of programmed cell death (apoptosis), sustained tumor-mediated angiogenesis, and the progressive capacity for invasion and metastasis. Limitations on the occurrence of malignancies may reflect not the importance of immune surveillance but rather the multiple steps required for the acquisition of the malignant phenotype and the need for progressive clonal evolution. Indeed, the most important protections are the mechanisms that maintain genomic integrity through DNA monitoring and repair enzyme mechanisms, ensuring that these multiple steps are indeed rare events. More important in limiting malignant progression than the immune system may be the limitation of exposure to promotional factors leading to sustained high levels of cell replication and, hence, a higher probability of acquisition of genomic changes, which lead to the malignant phenotype. In describing the importance of immune support in cancer recovery, these multiple factors must be considered.

Although immunity may have a limited effect in the progression of established cancers or in the control of recurrent cancer after initial conventional therapy, it still remains an extremely important component in the care of the cancer patient because of the high risk of secondary infections both during treatment and after therapy. Thus, although I do not believe that immune support plays the same role that is presumed by both the public and many physicians, it still is of significant importance in terms of overall care.

Gonzalez: It's currently quite popular in the orthodox medical world and even more so in the unorthodox world to talk about immune manipulation as a means to treat cancer. If you look at the history of cancer immunotherapy over the past 25 years, however, very little success has been demonstrated. The research community has poured hundreds of millions of dollars into studying the immune system. One only need go back to the National Cancer Institute's most lauded immunotherapy proponent, Steven Rosenberg, to see the limited promise of harnessing the immune system for cancer treatment. Rosenberg ended up on the cover of *Time* magazine with IL-2 as if this were the cure for cancer. IL-2 was approved in 1990 by the FDA without any controlled clinical trials, based only on a pilot study and much wishful thinking. Doctors who espoused IL-2 as a "breakthrough" were saying to themselves, "Let it be so, let it be so." Years later, clinical trials showed that IL-2 by itself in kidney cancer worked about as well as placebo.

Robert Good, my original mentor at Memorial Sloan-Kettering, was trained as an immunologist. Sloan-Kettering ostensibly brought him in because they believed immune attack against cancer presented a promising new treatment angle. In the early 1980s, Good was ousted from his position, and today molecular genetics has emerged as the primary research focus at Sloan-Kettering. Since that time, the enthusiasm for cancer immunotherapy has waned considerably, although there have been some revivals over the years. The National Institutes of Health funded a melanoma vaccine trial here in New York, but this was shut down after 8 or 9 years because of poor results.

The interest in cancer immunotherapy goes back to Coley's toxins at the end of the 19th century. This rather primitive form of immunotherapy appeared to produce some dramatic cases of recovery; unfortunately, we have no controlled trials to indicate whether Coley's toxin really had merit. In any case, in my practice we approach cancer very differently. Even though I'm trained as a clinical immunologist, I feel that the optimal treatment for cancer does not involve manipulating the immune system. The primary anticancer system I see is the pancreatic enzyme system.

This idea originated in 1902, when Scottish embryologist John Beard of the University of Edinburgh published the first paper suggesting that pancreatic proteolytic enzymes represent the body's first defense against cancer. He suggested that they be used as a cancer therapy. Even in those days, it was recognized that the main pancreatic enzymes and trypsin were necessary for digestion of protein and other nutrients. Beard suggested that along with digesting protein, they could attack and destroy tumors. Subsequent to that, between about 1904 and 1911, a number of doctors in both the United States and Europe, working under Beard's direction, used proteolytic enzymes with documented success. I have case reports from the orthodox medical literature, such as the *British Medical Journal*, documenting tumor regression, some would say even cure, using proteolytic enzymes. Nonetheless, the therapy never took hold. Beard died in 1923, and the therapy was largely forgotten.

Beard's work was revived by maverick investigators like the Krebs (Ernst T. Krebs and Ernst Krebs, Jr), who were famous for using laetrile, and my own mentor, Dr William Donald Kelley, a dentist who cured himself of pancreatic cancer using his own therapy in 1964. We believe that the enzymes have a direct anticancer effect that has very little to do with immune function. There are some studies that show that pancreatic enzymes do affect antibody production and other immune parameters, but this isn't the primary effect.

Researchers at the University of Nebraska, funded by Nestlé, are looking into the anticancer effects of pancreatic enzymes. Although it may turn out that the enzymes work in unison with the immune system, I still suspect this will be a secondary issue. The emphasis on immune function has been overstated; the

enzymes seem to work independent of the immune system. The group at the University of Nebraska found that specific proteolytic enzymes could have a powerful anticancer effect against cancer cell lines used in testing chemotherapy. That's in a cell culture, so of course there's no immune system. It's admittedly an artificial system, but according to the researchers this powerful anticancer effect would therefore have to be considered independent of the immune system.

The image of the immune system attacking cancer has become almost a politically correct approach. Many people now treat it as an established conclusion. But I think cancer cells are notoriously capable of bypassing immune system surveillance and attack. I think they can outsmart anything. Much of the failure of cancer vaccines and other forms of immune therapy is due to the fact that cancer cells can change their cell surface proteins and lipids. This enables them to avoid even vaccine-stimulated immune attack. I could be wrong, and next week there may be yet another cover story in *Time* announcing the cure for cancer. But based on historical evidence, this seems unlikely. The published results of controlled clinical trials suggest that the initial enthusiasm has not been particularly justified.

Vojdani: This is a very broad question because there are many different types of cancers and people will be diagnosed at different stages. It seems fairly well established that the immune system will be most effective in early stage cancers, but some tumors are more immunogenic than others, and it is possible to combine immunotherapy with conventional treatment for a more effective outcome with more advanced cancers. Certainly, a strong argument can be made for the immune system's role in cancer *prevention*. This research may in turn shed light on the potential for improving cancer recovery. When cancer develops into a full-fledged clinical disease, it passes through several phases of development. Many of the factors that affect cancer development affect the progressive growth and spread of cancer. We must keep in mind that many cancers are actually diagnosed rather late in their development, so that the so-called risk factors identified in prevention studies are probably also mediating tumor growth and progression to some degree. Many of these risk factors have been shown to affect the growth of established tumors in animal models, thus providing biological plausibility for the connections seen in prevention studies of human populations. So the main point here is that many findings from prevention research may in fact have relevance to individuals already diagnosed with cancer. The immune system can affect cancer both pre- and postdiagnostically speaking, but there are many mitigating factors.

Among my primary research interests has been the role of NK cells in health and disease. First, NK cells appear quite capable of distinguishing "diseased" cells from most normal tissue cells. Also, these natural killers seem to be in a league of their own when it comes to mounting an immune response to cancer because they are capable of spontaneously killing tumor cells. By the term *spontaneous*, I mean that NK cells that have had no previous exposure to tumor antigens will still attempt to kill the tumor cells. This cell-killing activity is not restricted to, or dependent on, the expression of the MHC complex on the target cells. In fact, NK cells are far more sophisticated than we previously thought in this regard. They will kill those target cells that express insufficient amounts of MHC class I, a frequent event in both tumor cells and virus-infected cells. The mechanism is extremely sensitive, as NK cells can sense the loss of even a single MHC class I allele on self cells. A complex array of surface receptors are responsible for triggering the NK cell's cytotoxic response to tumor cells. These receptors essentially switch-on the NK cells, placing them in an active, cytotoxic mode.

The preventive role of NK cells is well established. Back in the early 1980s, I was studying the effects of toxic chemicals on the immune system. In this model, we took groups of mice and injected them with chemical carcinogens such as the nitrosamines found in cooked meats or the benzopyrenes and cyclic aromatic hydrocarbons found in tobacco smoke. To induce tumors in these mice, we first had to destroy their immune systems. Mice that had higher NK-cell activity took much longer to develop cancer than mice that had low or very low NK-cell activity. Of course, other components of the immune system play integral roles. Cytokines, for example, must help orchestrate the activities of NK cells and other cells. The immune system therefore plays a direct role in preventing the onset and development of cancer in our bodies.

An elegant experiment in this area was published recently.[26] The study focused on the correlation between suppressed NK activity and altered host resistance to cancer in mice. The researchers injected antibodies to the NK cells in mice, and this essentially destroyed the murine NK cells. They then introduced the melanoma cell lines simultaneously with the antibodies to the NK cells. The degree of NK destruction correlated directly with the development of melanoma tumors. With up to 20% destruction with NK cells, NK cells totally prevented the development of tumors in the lungs and other target tissues. With up to 40% or 50% destruction of NK cells, a small amount of tumors began to develop. When 80% of the NK cells had been destroyed, tumor cell development was almost 100%. This clearly shows the importance of NK cells in fighting tumor cells, both in vitro and in vivo.

In terms of long-range management of cancer, NK cells seem to play a vital role in preventing metastasis and, thus, keeping cancer from spreading beyond the primary tumor. In a series of experiments, Elieser Gorelik and Ronald B. Herberman showed that removing NK cells from mice with surgically resected melanoma resulted in uncontrolled metastatic disease and rapid death. Patients with advanced metastatic disease often show abnormalities in NK-cell function or NK-

cell numbers. It has been well established that patients with a variety of solid malignancies and large-tumor burdens have decreased NK activity, and this low NK activity is significantly associated with the development of distant metastases. Thus, when NK activity is very low, the risk of metastases increases and survival tends to be quite poor. Conversely, high levels of NK activity might prevent the spread of tumor cells and lead to improved survival. I believe we can actually evaluate the long-range effectiveness of any cancer therapy based on the level of NK activity before, during, and especially after the treatment.

Recent studies suggest that a special subset of NK cells, the A-NK cells, are critically involved in immune surveillance against cancer and in the elimination of metastases in tissue as well as in the circulation. My personal conviction is that NK cells are probably more effective in fighting advanced cancers *after* the patient has received conventional treatment, a point I will return to shortly.

Point 2.

Immunologic responses to most malignancies are inadequate, since cancer displays many ways of evading the immune system. Despite these challenges, are there clinically effective ways the immune system can be modulated to respond to cancers?

Boyd: As noted in the initial answer, the majority of malignancies are essentially nonrecognized by the patient's immune system for a variety of reasons. Both conventional and nonconventional complementary therapies have attempted to address this often by increasing the level of immune effector cells, either total lymphocyte number or subpopulations such as cytoxic T cells or NK cells. For most malignancies, the evidence that simple modulation of circulating cell numbers plays any therapeutic role is limited. However, in specific cancers such as melanoma and renal cell cancer where there is immune recognition and evidence for immune-mediated cellular cytotoxicity, a significant percentage of patients (between 10% and 15%) will have clinical responses when treated with combinations of lymphokine-activated NK cells and IL-2. Some of these responses are sustained and complete and have led to probable cures. In addition, in melanoma there is evidence that combinations of chemotherapy with interleukin-2 and interferon together (biochemotherapy) produce significant responses in a minority of patients. These effects have been limited in number, although dramatic. In addition, conventional immunomodulation with interferon has been effective in a variety of cancers, particularly those noted above (lymphoma, melanoma, and renal cell cancer). The use of interferon alone appears to be effective in high-risk melanoma patients in an adjuvant setting but not in metastatic disease and has shown a limited response rate in renal cell cancer. It is also active as an adjunct in low-grade lymphomas. Despite these successes, immune-modulating therapies have had a limited effect or no effect in most epithelial cancers.

Gonzalez: Pancreatic enzymes may also have some effect, according to European researchers, on the tumor evasion mechanisms by which cancer escapes the immune attack. The product WobEnzym is thought to knock out the fibrin coat and make the cancer cells more amenable to immune attack. I don't know that this is true. I know that in my experience, the enzymes have a direct anticancer effect that is independent of any immune system function. If anything, it's the opposite: the enzymes kill cancer, and then the immune system steps in and cleans up the mess.

To be completely fair to everybody, however, the molecular biology hasn't been worked out. Assuming that pancreatic enzymes turn out to be a great anticancer therapy, which I believe, and assuming the rest of the world starts believing this, then we still have to do basic science studies. We're starting to do those studies, and we may very well find that the European researchers are correct, and that enzymes do interfere with at least some of those tumor evasion mechanisms that render the immune system impotent. However, there are many mechanisms at work here, possibly too many to block or control.

Vojdani: There are many immunologic factors that play an important role in fighting cancer, although again I would have to say that the majority of those functions come into play naturally, without manipulation, in the earliest phases of the disease. We need to keep in mind that the immune response is quite complex. In particular, the anticancer activities of T cells, NK cells, and macrophages are all directed by cytokines, chemical messengers produced by immune cells as well as to some extent by cancer cells. The experiments of Rosenberg were focused on the patient's own lymphocytes, which were activated in vitro with IL-2 before being injected back into the patient. This experiment was a failure, but it did teach us about the value of cytokines. I believe the experiment failed, in part, because it did not recognize the entire symphony of immune participants—that is, the multiple cytokines and cell types that govern the immune response to cancer. We must always keep in mind that the immune system attacks cancer with the help of multiple cytokines and cell types. Additionally, cancer cells pump out antigens and heat shock proteins, which then enable the macrophages and NK cells to recognize them as the enemy in our bodies. This is only in the earliest stages of cancer, before it takes root. At this early stage, the NK number and activity increase. In other words, the body increases both the soldiers and the ammunition in order to fight the enemy.

Unfortunately, when NK activity and T-cell functioning are weak, perhaps due to stress or poor nutrition or both, the cancer cells grow and secrete factors that enable them to go undetected by the NK cells. This is usually the case when cancer is well established. Prior to that time, healthy populations of NK and T

cells will maintain the upper hand over cancer. On rare occasions, these soldiers of the immune system will pass by and disregard the deviant cancer cells. It is likely that suppressor cells or suppressive chemical factors are responsible for curbing the assaults of NK and T cells. Only when the tumor cell is identified as hostile will these NK cells bind themselves to the tumor cells and kill them. These killer cells are the immune system's special combat units in the battle against cancer, but they are by no means invincible or entirely reliable. Because of the varying characteristics of cancer cells, and the suppressive factors they secrete, the tumor can often obtain a temporal advantage, growing until it constitutes such a large conglomeration of cells that the immune system, once it gets started, finds it difficult to destroy.

In this situation, I believe that treatments aimed at reducing the tumor mass can enable the immune forces to gain the upper hand and restore the patient back to health. This complementary strategy can be summarized as follows. First, you attempt to reduce the patient's tumor burden with surgery and other conventional treatments. Once you have removed the tumor, the bulk of the disease, the immune-suppressive impact of the cancer, is much lower. At this point, the clinical goal is to enhance the activity of NK cells, since these cells play such a critical role in eliminating micrometastases. One can also use vaccines at this point to generate specific cytotoxic T cells that will help destroy whatever is left of the cancer in the body. I believe this kind of integrated approach holds much promise for the future of cancer medicine.

Point 3.

Malignant melanoma is widely regarded as being fairly responsive to immunologic intervention. Are there other cancers that respond well to specific immunologic interventions, perhaps used as adjuncts to primary treatment? Please elaborate.

Boyd: The answer to this question is essentially the same as the answer to the previous question. In addition to melanoma, renal cell cancer and lymphomas are sensitive to specific immune interventions.

Gonzalez: Again, the options for cancer immunotherapy as classifically defined seem very limited. Vaccines have not done much beyond melanoma. Much of the interest in interferon, ILs, and other cytokines has not translated into clinical benefits for most cancers, with the exception of a few areas such as monoclonal antibodies for certain lymphomas. As we all know, IL-2 therapy so far has been a wash, and today very few doctors use IL-2 except as an experimental last-treatment option. Of course, the immune system is far more complicated than the 18 or 20 or so ILs that have been isolated, or the various interferons and lymphocytes. But I think cancer is far more complicated than a bacterial infection. To succeed against cancer, you'd have to do so much aggressive manipulation of the immune system that you'd place the cancer patient at risk. You're basically doing what chemotherapy is doing. You're creating substantial changes in the normal physiology of the patient. Even evoking major changes may not be desirable. Even IL-2, given intravenously in high doses, can kill people. People did die in the original studies of IL-2. It's a very powerful agent. When you're administering toxic and costly immune-modulating agents with minimal return, then you know it's time for something different.

Vojdani: The critical problem is the fact that tumor cells evolve to evade the immune system. The key to the success of vaccinations is to somehow recover the antigenicity of tumor cells. Tumor cells do present antigens, to which the patient generates cytotoxic T cells. Those T cells would go after those antigens, locate the tumor cells, and kill them. They do this in the earliest phases of cancer development, but not later, when the cancer has developed a range of evasion mechanisms. I think it's entirely possible that NK cells, with sufficient activation, may be able to bypass some of the tumor evasion mechanisms. But this area still represents a great challenge for immunotherapy after cancer has already developed. There are no clear solutions to this problem at this time, although we have seen some promising results in the treatment of kidney cancer and certain lymphomas, in addition to malignant melanoma.

Point 4.

What is your evaluation of the effectiveness of conventional immunotherapy strategies such as cancer vaccines and monoclonal antibodies?

Boyd: In contrast to innate immunity, because of the lack of effective recognition of tumor antigens, there is a growing interest in the development of therapeutic strategies such as the development of tumor vaccines and monoclonal antibodies. The use of monoclonal antibody therapy has been pioneered in lymphoma and breast cancer by specific antibodies directed against cell surface receptors. These include rituximab (Rituxan®), a chimeric anti-CD20 monoclonal antibody in lymphoma; and trastuzumab (Herceptin®), which targets the HER-2/neu transmembrane receptor expressed in some breast carcinoma patients. Both have been shown to be effective either alone or in combination with concurrent chemotherapy. Indeed, they may enhance the chemotherapy effect in a synergistic manner. Additional monoclonal antibodies are in development, including those that target specific cell surface receptors such as the EGF (epidermal growth factor) receptor in common epithelial cancers. Initial trials suggest a significant additive effect with chemotherapy for head and neck cancer, lung cancer, and colorectal cancer. In a fashion similar to breast cancer, studies are in progress to define the role of concurrent monoclonal

antibody treatments with chemotherapy in a frontline treatment approach for newly diagnosed cancers of the lung, colorectal, and head and neck regions.

There are, in addition, significant new models for generating tumor vaccines, including the use of whole tumor cells rendered safe by radiation and mixed with an adjuvant to enhance the immunologic effect. This model avoids the necessity of obtaining specific tumor antigens because of the incorporation of the whole tumor cell within the vaccine. Several studies are in progress using whole tumor vaccines in colorectal cancer concurrently with BCG (Bacillus Calmette-Guerin) vaccine. Some studies have documented improvement in disease-free survival with this approach. Several trials are also in progress in both melanoma and renal cell cancer. In addition, more specific genetically modified vaccines are in trial, including the use of tumor vaccines that enhance autologous GM-CSF (granulocyte-macrophage colony-stimulating factor) in renal cell cancer, as well as the development of specific tumor antigens creating autologous tumor vaccines. Another approach is the use of dendritic cell vaccines in which dendritic cells are isolated from the patient's peripheral monocytes or CD-34 stem cells and used concurrently with tumor antigens in the form of peptide fragments or tumor cell lysates. Dendritic vaccine trials are currently in progress in metastatic melanoma, renal cell cancer, prostate carcinoma, and breast cancer. The hope is that the concurrent use of dendritic cells will enhance the immune response because of the presence of active antigen-presenting cell populations that will increase immune responsiveness.

Allogeneic lymphocyte therapy has been used particularly in hematopoetic malignancies. The initial recognition of the graft versus host response as a detrimental side effect of allogeneic transplant has led to the recognition that the immune graft versus host response also includes a significant graft versus tumor effect. A higher remission rate has been observed in nonidentical allogeneic transplant recipients with leukemias versus identical twin recipients. There is increasing use of allogeneic lymphocytes in an attempt to take advantage of the graft versus host response as a graft versus tumor effect. The specifically selected allogeneic donor cytotoxic T lymphocytes offer the potential of producing an antileukemia effect with the hope of eliminating a graft versus host effect. Additional trials are examining limited allogeneic transplants in an attempt to maximize this graft versus tumor effect in non-Hodgkin's lymphoma as well as in acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML). However, there are limits to the use of cellular immune therapy because of the presence of tumor-associated antigens on normal tissue and thus the risk of engendering a tumor and autoimmune reaction. This has been typified by the presence of vitiligo in up to 20% of melanoma patients treated with IL-2. Thus, the downside of stimulating an active immune response is the potential for cross-reacting autoimmunity against relevant tissues possessing the same antigenic markers.

Gonzalez: In the case of malignant melanoma, the melanoma vaccine has had a positive impact, but even here the successes have been limited to either early stage disease or late-stage patients with a poor prognosis. Monoclonal antibodies have been used with certain types of lymphoma, although here again success has been limited. I don't mean to downplay the successes where they've occurred. Every advance is an important one. But we're just not seeing any results that place cancer immunotherapy firmly on the map.

Vojdani: I think vaccination will be very promising if we can also harness the full potential of cytokines. Jeffrey Schlom and his National Cancer Institute colleagues took human carcinoembryonic antigen (CEA), the tumor cell antigen in colorectal cancer, lung cancer, and certain other cancers. Schlom's group placed the tumor antigen in vaccinia virus and added IL-2. By adding the IL-2, they obtained 10-fold improvement in prevention of tumor cell development compared to using the vaccine alone. Why did this occur? IL-2 must be increasing the activity of the immune cells. I think that natural agents such as vitamins C and E (which happen to be synergistic with one another) may play a similarly complementary role with cancer vaccines.

Vaccines should best be regarded as one part of a multifaceted approach to the treatment and long-range management of cancer. Again, I believe vaccines work best in conjunction with conventional treatment and with immune-enhancing strategies that target NK cells in particular.

Point 5.

Might the immune system play a role in spontaneous remissions of cancer? If so, what mechanisms might be at work? If not, are there other mechanisms that you can point out that could contribute to such remissions?

Boyd: Spontaneous remissions have been described in certain malignancies at a significantly higher frequency than in others. Those include renal cell cancer, melanoma, and lymphomas, all of which possess a higher level of immune recognition and, as noted in previous answers, have been responsive to specific immunotherapies. A well-known example is the unpredictable and frequent spontaneous remissions that can occur in low-grade lymphomas. In addition, there have been examples of rapid and unpredictable progression of these malignancies in a much more aggressive fashion than is characteristic of epithelial cancers. In both cases, it is likely that the immune system plays a significant role, although the mechanism for the repetitive change remains uncertain. In several cases, the patients have been exposed to immune adjuvants or have had infections, which have presumably led to a nonspecific increased immune response

and a marked decrease in tumor size. In other cases, the exact mechanism of or stimulus to either immune enhancement or immune suppression has not been evident. It is nevertheless likely that those cases are based on alterations in immune surveillance of the selected cancers. Other mechanisms that might explain these observations include rapid progression because of the acquisition by selected clones of more rapidly proliferating populations of cells. However, the sudden and rapid remission of cancers by inherent tumor characteristics has not been adequate to explain these effects.

Gonzalez: I mentioned earlier that a recently published clinical trial showed that IL-2 by itself in kidney cancer worked about as well as placebo. The study showed that about 6% of patients receiving IL-2 had a significant regression. In the control group, 6% of patients on placebo had a significant regression. This was a lead story in the *New England Journal of Medicine*. So the study concludes that IL-2 was no better than placebo, but perhaps more interesting is the fact that placebo patients had a significant regression in 6 out of 100 people. That's a lot of people with no therapy, basically being given sugar water, having a significant regression in tumor growth.

What might be going on here? I don't think it's the immune system primarily. The main anticancer element in our approach is not antioxidants, which, like immune system functioning, receive the most publicity in the alternative and orthodox media. It's not the vitamins or antioxidants, it's the pancreatic enzymes. Just as important, it's manipulation of the sympathetic and parasympathetic system. Based on the work of Francis Pottinger in the 1920s and 1930s, it was proposed that certain tumors, particularly the classic solid tumors such as tumors of the lung, pancreas, and colon, occurred in people who had a strong sympathetic system and a very weak parasympathetic system. On the other hand, the immune system tumors such as leukemia, lymphoma, and multiple myeloma arose in people who have a very strong parasympathetic system and a weak sympathetic system. Micronutrient supplements are used in this therapeutic approach for one purpose: to bring the autonomic nervous system into balance. When the autonomic nervous system is in balance, the disease, whatever it is, from toenail fungus to a tumor, will tend to improve. Of course, with cancer we also need the enzymes to knock out the tumor.

The sympathetic system is the classic stress system, and it does certain things. First, it knocks out the entire digestive system, including the pancreas. So when the sympathetic system is strong, the pancreas tends not to produce pancreatic enzymes. If we're correct in saying that the pancreatic enzymes play a crucial role in the defense against cancer, then the strong sympathetic nervous system will knock out one of the main protective elements. In addition, the sympathetic nervous system, when it fires, also throws down immune function. I still feel this is secondary, but it's still part of the picture. When you bring this system back into balance, that is, by strengthening the parasympathetic system, the pancreas works better, pancreatic enzymes work better, and the immune system works better. The major anticancer elements all work more effectively. Through dietary modification and meditation, for example, it is possible to tone down an overly strong sympathetic system and build up the weak parasympathetic. When that occurs, I believe at times tumors will go away.

In patients with an overly strong parasympathetic system, we find the problem isn't that they have inadequate amounts of enzymes. They produce plenty of pancreatic enzymes. The trouble is that they're very susceptible to viral infections. The parasympathetic activity is too strong, and there's a whole metabolic milieu that develops that allows these viral infections to occur and that may be involved in leukemia. But most important, even orthodox immunologists now know that lymphocytes in the spleen and thymus have receptors for parasympathetic neurotransmitters. When the parasympathetic system is too strong, the immune response is actually too strong, even toward mild infections and what should be mild inflammation. In these patients, you actually want to turn down the immune system. We believe that leukemia, lymphoma, and myeloma actually result from an overly active immune system. What Rituxan® does, as a monoclonal antibody, is knock out lymphocytes. It attacks a specific CD20 antigen for a specific subset of lymphocytes, and it basically neutralizes the lymphocytes. With a monoclonal antibody, you're neutralizing an immune aspect using that particular medication. We can accomplish a similar feat, more broadly, but turning off the immune system, using various dietary and supplement strategies. When this occurs, again, tumors can disappear.

Vojdani: The immune system very likely plays a role in this situation, and I think it is the most plausible explanation. For this to occur, however, there has to be some way that the immune system bypasses the cancer's ability to evade immune recognition and attack. Although we don't yet know the precise mechanisms, it stands to reason that the immune system contributes to the occurrence of spontaneous remission. Herberman says that the ability of A-NK cells to identify abnormal cells may determine, to a large extent, an individual's potential for controlling spontaneously arising tumor cells.

Point 6.

Many cancer patients seek out integrative and alternative therapies with a specific interest in mobilizing their immune systems to fight malignancies. Are you aware of any potential contributions that diet, exercise, supplements, or herbal medicines might make in facilitating the role of the immune system in cancer treatment and management? Cancer patients also seek out integrative and alternative therapies to help their immune systems recover from

the suppressive effects of conventional therapies. Are you aware of any potential contributions that diet, supplements, or herbal medicines might make in the recovery of white blood cells, NK cells, and other immune components during or after chemotherapy treatment?

Boyd: Many patients indeed seek alternative or complementary therapies and may actually avoid conventional and potentially effective regimens because of fear of suppressing their immune system. The comment "I want to build up my immune system" is heard frequently among patients coming for advice with regard to using complementary care with conventional treatment. Numerous mainstream publications in the field of complementary and integrative care of the cancer patient frame potential therapeutic benefits in terms of improved immune function. Indeed, many integrative modalities—diet, nutritional supplements, and herbal or natural products, as well as stress-reducing approaches—contribute to an improved immune status. It remains unclear, however, what role these changes in various immune parameters may play in controlling existing advanced malignancy or preventing recurrence, based on previously noted limitations in the immune response. Some malignancies, including melanoma, renal cell cancer, and lymphoma, are particularly sensitive to the patient's immune status. What effect a simple alteration in effector immune cell number or function will have on their clinical status remains unclear. As noted, it is conceivable that a simple manipulation of the immune system with various complementary therapies can, in fact, increase the activity of the CD4+ immune suppressor mechanism, thereby reducing and not enhancing tumor immunity, leading to cancer progression. Thus, any recommendations must be accepted with caution. One example is a patient who recently was placed by a naturopath on echinacea for a known malignant melanoma and subsequently developed a rapid disease progression. While it is unclear whether this immune-stimulating herbal product may have contributed to this outcome, the possible role of the herb remains a concern.

Nonetheless, multiple complementary and nonconventional approaches have been shown to increase immune function. Acupuncture, electroacupuncture, and moxibustion have been studied extensively for immune function effects, both in China and elsewhere. Numerous studies demonstrate an increase in cellular immunity, in NK-cell number, and in cytotoxicity, and in several studies specific selected acupuncture points were associated with immune effects. In most studies, the effects were paralleled by an increase in β-endorphin level and an associated increase in IL-2 production subsequent to the acupuncture procedure. In addition, an increase in macrophage phagocytic activity has been demonstrated with acupuncture.

Massage therapy has been extensively studied at the Touch Research Institute at the University of Miami in various patient populations, including HIV and breast cancer populations. In one large study in the HIV population, 1 month of daily massage therapy produced a significant increase in NK-cell number and cytotoxicity, as well as an increase in total and cytotoxic CD8 cell number. This was accompanied by a significant decrease in plasma cortisol levels. A subjective decrease in anxiety and an increase in relaxation were significantly correlated with the improvement in NK-cell numbers found.

Similarly, qigong practice has been assessed for a variety of immune functional changes. Alterations include an increase in IL-6 and TNF-α, as well as interferon-γ secretion and decrease in IL-10. These changes were similarly paralleled by a decrease in cortisol levels.

Acute high-intensity exercise may briefly impair immune function. This has been attributed to an acute increase in neural endocrine effectors including norepinephrine and cortisol. This transient impairment may be attenuated by an increase in carbohydrate intake prior to exercise as well as supplemental glutamine and antioxidant vitamins. In contrast, frequent moderate aerobic exercise may actually improve innate immune function, with a rise in NK-cell activity. Of note, in a population of breast cancer patients undergoing peripheral stem cell transplant in an in-hospital setting, a randomized trial of aerobic exercise daily versus routine in-hospital activity was undertaken. Those who exercised daily were noted to have a reduction in the duration of hospital stay, a significant reduction in complications, and a more rapid recovery from chemotherapy-induced cytopenia. Whether this translated into improvement in immune function was not evaluated.

Numerous nutritional interventions have significant immune benefits. Antioxidants may be important in oxidative radical generation by immune effector cells due to the need for efficient endogenous antioxidant mechanisms to protect these cells. Dietary supplements with ascorbic acid and vitamin A in older women, those either in good health or with coronary artery disease or severe depression, have been demonstrated to produce a significant enhancement in lymphocyte proliferation to mitogens and an increased phagocytosis of polymorphonuclear leukocytes, accompanied by a decrease in lipid peroxidation and reduction in serum cortisol levels. Other studies have demonstrated an antioxidant-induced increase in macrophage phagocytosis. Ascorbate depletion results in an impaired mitogen response and reduction in IL-2 production, which is restored with vitamin C repletion. This has been suggested to indicate an adverse effect of decreased vitamin C on interleukin gene expression. In several animal studies of ultraviolet-induced immunosuppression, vitamins C and E systemically and topically were effective in reversing the immune suppressive effects of ultraviolet radiation. Reduced levels of β-carotene in older populations have been correlated

with a reduction in cellular immunity, which in several studies has been reversed by supplementation.

In addition to antioxidant vitamins, micronutrients, particularly zinc, have been linked to immunodeficiency. Older patients with zinc deficiency have impaired cellular immunity that is restored with physiologic supplementation with zinc for 1 to 2 months. The dietary zinc deficiency syndrome has been characterized by both lymphocytopenia and an impaired cell-mediated immunity. This may reflect a defect in early thymocyte maturation with increased apoptosis, similarly seen with significant caloric restriction in animal studies. The clinical manifestation of zinc deficiency in human populations includes growth retardation, diarrhea, and increased susceptibility to infection. However, the immune abnormalities common in zinc deficiency include an impairment in interferon-γ and IL-2 production along with a decrease in NK-cell lytic activity and T-cell cytotoxicity. Most studies indicate a specific impairment in T-helper 1 (TH-1) cell cytokine activity versus T-helper 2 (TH-2) cytokine, differentially affecting cellular immunity (through a decrease in IL-2 and interferon-γ) and humoral immunity.

Zinc deficiency has been linked most closely to squamous carcinomas of the head and neck as well as the esophagus, with the zinc depletion markedly enhancing experimental chemical carcinogenesis. In head and neck and esophageal cancer patients, cellular zinc deficiency is common (up to 50%), accompanied by an alteration in T-cell and NK-cell activity. Despite this clear-cut immune abnormality, numerous animal studies indicate that zinc deficiency tumorigenesis is caused by a zinc-deficient increase in cell proliferation as well as an impairment in DNA repair mechanisms. A recent study from the Kimmel Cancer Institute published in the *Journal of the National Cancer Institute* demonstrated rapid response to zinc repletion in the NMBA (nitrosomethylbenzamine) esophageal tumor model: a marked increase in apoptosis was observed within 48 hours as well as a reduction in esophageal cancer production. Although zinc deficiency affects cellular immune function and has been linked to squamous cancers, the major antitumor effect of zinc may be through alternative nonimmune mechanisms such as enhanced apoptosis and improved DNA repair mechanisms.

It is worth noting that deficiencies of numerous other micronutrients may shift the TH-1/TH-2 balance away from cellular immunity, including methionine, arginine, vitamin A, vitamin E, and selenium, in part acting through glutathione and other antioxidant-related enzyme systems.

In addition to micronutrients and vitamins, macronutrient status may also affect immune function. Long-standing observations indicate that significant protein deficiency affects cellular immunity. Furthermore, an increase in caloric intake or fat in both animal and human studies has been shown to alter or inhibit immune response. This effect may depend on fatty acid composition, particularly in the polysaturated fat component of the diet. Eicosapentenoic acid (EPA) derived from fish oil has been of particular interest, resulting in an extensive literature on its immunomodulatory effects. Most studies in both animals and humans suggest a significant anti-inflammatory effect, with a reduction in both T- and B-cell mitogenic responses and a decrease in T-cell cytokine production (including TNF, IL-1, and IL-2). However, some human studies in the setting of advanced malignancy or in the preoperative supplementation of patients with gastrointestinal malignancy have demonstrated an enhancement in cellular immunity as well as a reduction in surgical complications with EPA supplementation. Some of these studies have used an immune-enhancing combination including arginine, RNA, and EPA-supplemented enteral feedings. Most but not all studies in the perioperative period have shown an improvement in immune function and reduction in infectious complications. Much of the beneficial effect in autoimmune and inflammatory states of EPA supplementation may reflect the attenuation in cytokine production and reduction in inflammatory mediators due to changes in eicosanoid/prostaglandin E_2 production. Most animal studies indicate a significant antitumor effect with EPA (N3) versus N6 fatty acid supplementation, despite this variable effect of EPA on cellular immune function. Some researchers have suggested that the high EPA intake may increase lipid peroxidation, which may be partly responsible for an altered immune function and may be reduced by vitamin E supplements.

There are, also, multiple natural products that may have significant and positive effects on immune function. Alkylglycerol-derived compounds in shark liver oil are potent immunostimulants for both humoral and cellular immune function and are particularly powerful stimulants to NK-cell activity. Interestingly, probiotic supplements with shark liver oil are markedly synergistic in increasing immune function in animal studies.

Various polysaccharide-protein complexes including lentinan, schizophylide, and protein-bound polysaccharide, which are derived from several mushroom species, have been used in Asia as antitumor agents and have been demonstrated to have potent effects on cell-mediated immunity including an increase in cytotoxic T cells as well as an increase in cytokine production. Work is ongoing in terms of tumor-specific effects of these compounds and the determination of the exact antitumor mechanism.

Thus, as noted, numerous nutritional as well as other complementary modalities have significant immune-related effects. Their impact on the prognosis and progression of cancer, however, remains uncertain.

Gonzalez: Diet, exercise, and supplements all have their place in modulating the immune system, but I don't see that they have much value in cancer therapy per se

without first attending to the imbalances in autonomic functioning that underlie the abnormal immune responses that we see in leukemia, lymphoma, and myeloma. As I alluded to above, the goal is try to turn off the immune system because of the overly active parasympathetic system. There's a case in which stimulating the immune system is probably the worst thing you can do, because the system is already overactive. I have patients with leukemia, lymphoma, and myeloma who are trying the natural immune stimulants—the mushroom extracts, for example—and they're getting worse.

The way that we quiet down the immune system in such cases is by using vitamins and minerals that stimulate sympathetic activity. Beginning with Pottinger nearly a century ago, Kelley a few decades ago, and our own work today, it seems clear that whatever vitamins, minerals, and foods do, they're all able to influence autonomic physiology. Certain vitamins and minerals such as magnesium and potassium will shut down sympathetic activity and stimulate parasympathetic activity. B vitamins such as thiamine, riboflavin, niacin, and folic acid tend to tone down sympathetic and stimulate parasympathetic activity. On the other hand, other B vitamins such as pantothenic acid and vitamin B12 stimulate sympathetic activity, as do certain minerals such as calcium. So you can use vitamins and minerals reproducibly and with very great precision to affect autonomic function. That's how we use diet, vitamins, and minerals.

Vegetarian diets tend to slow down sympathetic activity; they're very alkalizing and in an alkaline environment, the sympathetic system doesn't fire as well. They tend to tone down sympathetic activity and stimulate parasympathetic activity. With high-meat diets, which are very acid forming, certain nutrients such as phosphates and sulfates tend to stimulate sympathetic activity and tone down parasympathetic activity. So if we have a patient with a strong sympathetic nervous system, we put him on a vegetarian diet with large doses of B vitamins, magnesium, and potassium. If we have a parasympathetic-dominant patient (leukemia and lymphoma), we put him on a red-meat diet—horror of horrors to all vegetarian advocates—but these people are like Eskimos. They thrive on red meat. The fattier the better. We avoid thiamine, riboflavin, and niacin, and we give them large doses of B12 and pantothenic acid but absolutely no potassium or magnesium. Despite the enthusiasm to give everyone in America large doses of magnesium, these patients do terribly with magnesium. So we give them large doses of calcium instead, along with large doses of zinc and selenium. What this does is bring the out-of-balance autonomic system into balance.

So we don't address immune function directly. We're affecting nervous system function. Along with that, we're providing large doses of pancreatic enzymes. In a sense, then, we're redefining the concept of cancer immunity or cancer resistance. We're saying the problem is centered in the nervous system, and that the immune system plays a secondary role. From this perspective on the anticancer defenses, immune function is no more important than liver function. For example, when the sympathetic system is too strong, the liver doesn't work well. This means that all the 10,000 detoxification processes that normally occur in the liver are very inefficient. Sympathetic-dominant people are very susceptible to toxic exposures, and they don't detoxify chemicals very efficiently. Because the sympathetic system is too strong, they don't produce a lot of pancreatic enzymes. They're too acidic. Because pancreatic enzymes only work in an alkaline environment anyway, the enzymes they do produce don't work well, increasing their susceptibility to cancer. In sympathetic-dominant cancer patients, which is to say most solid-tumor patients, the immune system doesn't work well either. The sympathetic system, or what might be called the stress nervous system, tends to suppress immune function when it is overactive. The liver, pancreas, and entire gut function poorly when the stress system is overactive. Sympathetic-dominant patients are very inefficient at breaking down, absorbing, and utilizing nutrients and foodstuffs. They have a whole cascade of inefficiencies that must very quickly be addressed. When we have a patient present with a hard tumor, we have to get the liver to work better and we have to get the patient to absorb and utilize food better. So the immune system is one part of a broad multifactorial picture. It's not the main problem. The main problem is getting the autonomic nervous system into balance.

I should also comment on a third category: the more balanced metabolizers. These are people who have a genetically and metabolically balanced autonomic nervous system, so they're balanced between the sympathetic and parasympathetic systems, between left brain and right brain. All their tissues and organ systems work in balance and quite efficiently. They don't tend to get sick. Instead, either through stress or wrong diet, they get artificially pushed toward either sympathetic or parasympathetic dominance. They are susceptible to either solid tumors (with sympathetic dominance) or to immune system tumors (with parasympathetic dominance). How can this happen? A balanced person should eat a smorgasbord diet—that is, fruits, vegetables, nuts, seeds, grains, fish, poultry, and some red meat. If they eat what they read—let's say, an Atkins™-type diet, where they eat red meat 4 times a day, with and no fruits and vegetables—they'll push themselves much too far toward sympathetic dominance, and develop a solid tumor. If they get caught in the vegetarian, Ornish diet, they may become far too parasympathetic dominant and develop any one of the immune system cancers. Thus, they develop either type of cancer through artificially pushing themselves in the wrong direction. But as long as they stay balanced, they tend to stay *immune* to the common cancers in our experience.

As far as contributing to recovery from immune-suppressive cancer therapies, diet and supplements

all have their place and may alleviate some of the immune suppression, but again I think they play a more fundamental role in modulating autonomic function, which can then direct immune activity in an appropriate manner. More vigorous aerobic exercise is great for sympathetic dominance, particularly since the aerobic metabolism of sympathetic-dominant people tends to be very inefficient. Also, sympathetic-dominant people can burn off adrenaline when they exercise, which is why they feel relaxed and high after exercising. Aggressive aerobic exercise or jogging is basically wearing out the sympathetic system, so they feel more relaxed and not as edgy or angry. On the other hand, parasympathetic patients would not do well undertaking these activities. They should walk, jump on a trampoline, swim, or ride bicycles. However, vigorous aerobic exercise such as running will often stress them out. Parasympathetic-dominant people don't have the strength to handle more intensive exercise.

Vojdani: As I said earlier, I think conventional treatment needs to be used in conjunction with immune-modulating strategies. Surgery and immunotherapy in particular can work well together.

Over the past 20 years, we have found that patients who have had toxic chemical exposures in the past often go on to develop fibromyalgia and chronic fatigue syndrome. The majority of these patients have low NK-cell activity. In the oncologic setting, chemotherapy has a similar impact. Although chemotherapy and radiotherapy may also be used to lower the tumor burden, both can be immunosuppressive. High-dose chemotherapy in particular can be very immunosuppressive. Chemotherapy involves toxic chemicals, so it is important to study how toxic chemicals suppress the immune system and how we can reverse such suppression. One of our studies attempted to address this issue.[27] We focused on the use of vitamin C after exposure to toxic chemicals and found that vitamin C could indeed help patients recover their NK activity after toxic exposure.

Dr Gunnar Heuser, a coauthor of the article I just mentioned, is an internal medicine specialist who sees patients who have been exposed to toxic chemicals. Over the course of a year, he sent me patients for testing of NK-cell function, as well as T- and B-cell function. I was unaware at the time that these patients were part of a study, so I was effectively blinded while doing the immune evaluations. After 1 year, a total of 55 patients (39 women and 16 men) had been referred by Dr Heuser for immunologic evaluations. All 55 patients had well-documented evidence of exposure to toxic chemicals such as formaldehyde, organic solvents, pesticides, and heavy metals. After the first blood draw, the patients immediately ingested granulated buffered vitamin C in water at a dosage of 60 mg/kg body weight. Exactly 24 hours later, the blood was again drawn for follow-up measurements of NK-, T-, and B-cell function.

We then compared the before and after measurements of immune function. Vitamin C in high oral dose enhanced NK activity up to 10-fold in 8 out of every 10 patients (78%). Also, the lymphocyte blastogenic responses to T- and B-cell mitogens were restored to their normal level after vitamin C ingestion. The improvement in immune functions correlated with increased protein kinase C (PKC) activity in the immune cells. Our conclusion was that immune function abnormalities could be restored after toxic chemical exposure by oral supplementation with vitamin C.

The study's findings may be relevant to cancer patients receiving chemotherapy, a highly toxic and often immunosuppressive form of chemical exposure. Chemotherapy is somewhat different, however, because it entails 1 large exposure in a short period of time. If you spread the chemotherapy out over 1 month, it would be more analogous to the study's findings. At any rate, we do know that chemotherapy tends to destroy NK cells along with many other immune functions. My own observations indicate that cancer patients receiving chemotherapy do recover their immune competence much more rapidly with vitamin C. The NK-, B-, and T-cell function all improve dramatically after chemotherapy if they received vitamin C. The patients must receive the vitamins before, during, and after. Vitamin C and other antioxidants can prevent immunosuppressive effects, selectively protecting immune cells while leaving cancer cells unprotected.

In other studies, we tried to determine the time frame in which vitamin C modulated NK activity. We examined not only NK cells but also T-cell and B-cell functioning. The laboratories that were doing the testing for this study were blinded—they did not know a study was in progress, nor did they know where the blood was coming from. Twenty-four hours after the initial blood draw, subjects had a repeat blood draw. Then, 8 months later, we compared the files and found that 70% to 80% of those who took vitamin C had significant enhancement in NK activity but not in number. What does it mean to have enhanced NK activity after exposure to toxic chemicals? We know from the literature that people who have been exposed to toxic chemicals are more prone to develop cancer. So, at the level of prevention, it seems likely that people will become more resistant to cancer if their NK activity is increased following toxic exposure. Also, people who are smoking or eating excess nitrosamine-containing canned foods are more likely to have cancers of the lung and colon, respectively. Giving these people vitamin C should help them prevent such cancers.

As you may know, there was a short article in *Nature* a few years ago that proclaimed vitamin C a prooxidant rather than an antioxidant.[28] This article created quite an uproar, but it was based only on limited laboratory research. To test its premise in humans, we

took 25 individuals and gave them either 500 mg, 1000 mg, 2000 mg, or 5000 mg of vitamin C for 1 week. I included myself in the 5000 group to demonstrate my firm conviction that vitamin C was safe and would not harm the DNA. We also wanted to know whether this short period of time would increase NK activity or number, and whether we could improve apoptosis (programmed cell death). When we have oxidative stress in our system, the resulting surge of free radicals can damage DNA and mitochondria. Any of this damage can initiate the apoptotic program in cells, so that they commit suicide. This is a way that the cell protects the genetic code—it self-destructs upon exposure to toxic chemicals, to prevent passing on the bad genes to other cells. Finally, we wanted to know whether we could prevent DNA damage, as measured by 8-hydroxyguanosine, using these doses of vitamin C.

Our findings were as follows.[29] For 500 mg to 5000 mg, we did not see any evidence of DNA damage. Moreover, this full range of vitamin C intake significantly increased NK activity while reducing apoptosis in the immune cells, meaning that more of those cells were alive and kicking. After giving the cells vitamin C, we found that more immune cells went from the apoptotic signal to the mitotic signal, which of course means that we were able to get more of an immune response. We were essentially able to reverse functionality of the cells using vitamin C. Doses of 500 mg to 1000 mg produce results similar to 5000 mg. Therefore, we really don't need to take more than 1 g to enhance the functionality of the immune system. By the same token, however, there was no harm caused by taking 5 g. Overall, the findings are clear-cut in showing that the vitamin enhances cellular function without harming DNA. I personally take 1000 mg of vitamin C each day, and I recommend this amount to everyone.

There are of course many other antioxidants that work together with vitamin C, such as bioflavonoids. I have focused primarily on vitamin C. In another study, we found that enhancement of NK activity starts at 8 hours after receiving vitamin C, peaks at 16 hours, and then reaches a plateau to 24 hours, after which it drops steadily; by 48 hours, it is back to baseline. At a minimum, then, people should take vitamin C every other day. However, for maximum protection, I would advise taking it every day.

Finally, let me say that the role of diet in combating cancer is still grossly undervalued by the medical community. In 1999, *Toxicological Sciences* published an excellent article on the role of diet in cancer prevention by Gary Williams and colleagues of New York Medical College and the American Health Foundation in Valhalla, New York.[30] As I said earlier, many of the principles of cancer development also apply to the cancer patient after a diagnosis of cancer, because the mechanisms of prevention may encompass the progressive growth and spread of cancer. Ideally, of course, we would want to begin a healthy diet and lifestyle very early in life, but even in later life, I feel that adopting a healthy diet may help many people. About 60% of cancers are induced by environmental factors and can be prevented by diet and lifestyle factors such as avoidance of tobacco and alcohol. The main point is that diet must be optimized to reduce caloric intake and especially the dietary fat component. In the typical American diet, fat constitutes about 60% of calories, which is far too much. People who eat less fat and more fiber have better immunity. There's good preclinical evidence, as well as some clinical evidence, that this amount of fat is harmful to immunity and moreover that it directly promotes tumor growth and metastasis. Many of these fats contain chemicals that are metabolized into toxic or carcinogenic compounds.

Point 7.

What role, if any, can stress reduction (imagery, self-hypnosis, etc) and body-centered strategies (eg, massage, qigong) play in supporting anticancer immune mechanisms? What role, if any, can stress reduction and body-centered strategies play in reducing the immune-suppressive burden of conventional treatments (as well as the disease, which exerts a background influence in this instance)?

Boyd: Significant research indicates a relationship between stress and cancer. This is complicated by the difficulty of determining the mechanism as well as the significance of stress in its relationship to cancer etiology and progression. Numerous studies have examined the interaction between stressful life events and cancer incidence and prognosis, as well as the relationship of cancer with self-reported stress. A significant controversy exists with regard to the significance of these interactions. Most striking is the divergent opinions of the public and health care professionals. A majority of individuals, particularly cancer patients, believe that stress plays a significant role in the development and progression of their disease, whereas physicians generally dismiss any association. Thus, these issues are often overlooked in patient care and represent an important focus of integrative therapies.

One widely reported study by David Spiegel published by *Lancet* in the late 1980s described the use of an expressive-supportive group therapy in patients with metastatic breast cancer. This unexpectedly led to a significant increase in survival of the members participating in the supportive care in contrast to the control arm of that study. A similar study at the University of California, Los Angeles, on malignant melanoma showed an overall improvement in survival and reduction in recurrence. Both groups reported an accompanying improvement in immune parameters in the study group, particularly an increase in NK cell number and activity. Several other smaller studies have reported an improvement in survival with group support. These studies led to speculation that the statistically significant findings might be explained by the improvement noted in cellular immune function.

These effects have been explained by the well-known impact of chronic stress through an alteration in the hypothalamic-pituitary-adrenal axis (HPA) and consequent abnormal cortisol rhythm on immune function.

There is an extensive literature documenting the bidirectional effects of immune-nervous system interactions and the deleterious effects of stress on immune function mediated by neural-humoral mechanisms involving sympathetic and HPA axis alterations. Spiegel, in an additional study of women with metastatic breast cancer, demonstrated that those patients who had an abnormal diurnal cortisol pattern (manifested by flattened salivary cortisol levels) had a significantly worse outcome than women with a normal cortisol rhythm. This was attributed to the impact of stress on diurnal cortisol and subsequent prognosis. A recent multicentered trial conducted by Pamela Goodwin and colleagues in Toronto, comparing weekly supportive-expressive group therapy versus no intervention in patients with metastatic breast cancer, failed to show a significant improvement in survival, although there was reduction in levels of stress and pain. To date, half of the studies on supportive-expressive group therapy have shown no survival benefit, including this large multicentered trial. This has been used to support arguments that stress reduction has little likelihood of affecting survival outcomes in cancer patients.

Several points must be addressed with regard to the issue of stress reduction and the studies previously noted. It is likely that a small subset of patients may be particularly vulnerable to stress, particularly those with the helplessness/hopelessness response to cancer as well as those with depression, as noted by Margaret Watson and others in England. Women with metastatic breast cancer who have this particular constellation of psychological responses to stress have been noted to have a particularly poor outcome. Although many women may not require or benefit from supportive care in terms of survival, this subset of women with depression and hopelessness may be particularly vulnerable to the effects of chronic stress and could derive benefit from supportive care. This is particularly true of patients who lack a significant social support network, as noted in other studies. This subset of patients may also be most likely to be affected by an alteration in diurnal cortisol rhythm through an alteration in HPA axis activity. In animal models, the generation of a model of helplessness in a variety of settings has been noted to produce the chronic stress response with an alternation in the HPA axis. Thus, despite the absence of a broad effect of supportive care in reducing stress and altering prognosis in metastatic breast cancer, there may be a subset of women who are particularly vulnerable and may experience a survival benefit from such interventions. Although studies indicate a significant alteration in cellular immune function, whether the effect of stress is an adequate explanation given the limited efficacy of immune recognition of most cancers remains to be demonstrated.

An attractive alternative explanation involves insulin and insulin-like growth factor (IGF). Recent evidence suggests an important effect of the insulin-IGF pathway on both carcinogenesis and, more recently, tumor progression, particularly for epithelial cancers (colon, breast, prostate, and pancreas). The insulin and IGF receptors are present in most epithelial tissues and are expressed at higher levels in malignant cells. IGF-1 as well as insulin have been associated with an increase in cell proliferation in multiple in vitro and in vivo studies in animals as well as human populations. Epidemiologically, they have been associated with increased risk for a variety of epithelial cancers. Insulin is likely to act as a pro-proliferative tumor promoter enhancing progression to the malignant state and further progression to a more advanced and aggressive phenotype. Recent epidemiologic studies indicate that insulin resistance, which is growing in frequency within Western populations, in addition to being associated with an increase in cardiovascular mortality is associated with an increase in cancer mortality. Insulin resistance and its surrogate, abdominal obesity, is linked to increased incidence of colon, pancreatic, postmenopausal breast, esophageal, endometrial, and prostate cancer.

Goodwin and others have recently shown that fasting insulin level is an independent prognostic factor associated with both distant recurrence and mortality from breast cancer. Similar effects have been reported with C-peptide, a marker of hyperinsulinism. The biological rationale for these effects is the selective growth advantage associated with the insulin mitogenic effect via the insulin-IGF receptor pathway. In addition, insulin resistance and accompanying hyperinsulinism have been associated with a significant proinflammatory state, with increases in IL-6, C-reactive protein, and NF kappa-B level. This provides an additional pathway enhancing tumor progression. The insulin-IGF effect may be seen as an alternative explanation for the purported effect of chronic stress on cancer outcomes and the beneficial impact of stress reduction methods as well as a variety of additional complementary approaches including nutrition and dietary supplements. It has been demonstrated that chronic stress, with secondary perturbation in the HPA axis, is a significant factor in the development of abdominal/visceral obesity, leading to hyperinsulinism and the insulin-resistant state, mediated by an abnormal diurnal cortisol rhythm. Thus, patients under chronic stress, including those with cancer-related depression and the helplessness/hopelessness response, may be expected to be at a higher risk for this perturbation and a consequent elevation in basal insulin level.

Of interest is the well-known phenomenon of insulin resistance in advanced malignancy. Within our program, up to 45% of newly diagnosed cancer patients and 75% of advanced cancer patients show

evidence of the insulin-resistant state, with elevations in levels of fasting insulin and C-peptide, as well as hypertriglyceridemia. We are currently actively addressing this problem with a combination of nutritional support, dietary supplements, exercise, and targeted stress reduction. Our feeling is that the insulin resistance syndrome and the concurrent elevation in fasting insulin level is a more biologically plausible explanation for the adverse effects of chronic stress on tumor progression and prognosis. Interestingly, many of the beneficial effects on immune function noted through a variety of dietary approaches, including antioxidant vitamins, low-fat diet, omega-3 supplements, and nutriceuticals, as well as the stress reduction effects of a variety of behavioral interventions, may improve fasting insulin level and in many cases may reverse the abnormal HPA axis and circulating cortisol level. Despite the high frequency of these insulin-related abnormalities in the cancer population, this remains an as yet unaddressed but extremely important phenomenon.

Most notably, it is a biologically plausible explanation for many of these associations and provides a firm scientific foundation for the introduction of many integrative approaches. No longer should an oncologist or other health care professional say he or she sees no rationale for patients seeking these integrative approaches in their cancer care.

Gonzalez: Stress reduction techniques do come into play in a very important way. As I said, the sympathetic nervous system is the stress system. These are patients who, even when they're well, never sleep very well. They overreact to stress and get angry too fast. Those with a strong sympathetic system tend to think clearly, are good at mathematical calculations, and are more left-brain dominant. Because they have plenty of adrenaline, they tend to be more assertive and aggressive, more fearless and authoritative. The problem, as I discussed, is that their digestive system will be weak because the liver, pancreas, and intestinal tract all function poorly under the influence of stress hormones. They're not getting the nutrition they need, so in many ways they're set up to get cancer. For these people, stress management is critical. Even orthodox doctors are realizing that we humans have a mind and that our physiology affects the mind. Just as we use vitamins, minerals, trace elements, and diet to try and change the sympathetic dominance, the mind can do that too through relaxation techniques. Sympathetic-dominant patients thrive on relaxation as well as exercise, which raises endorphin levels and tends to cuts down their stress hyperactivity. According to Benson of Harvard University, meditation, biofeedback, guided imagery, and other relaxation techniques are all ways to tone down the sympathetic system. After meditation, the sympathetic and parasympathetic systems are more in balance.

Leukemia, lymphoma, and multiple myeloma patients are parasympathetic dominant—their right brain axis is already too strong. If anything, they're too relaxed. These are people that are very prone to severe depression. They can't get out of bed. They're so lethargic they can't do anything but turn on the television and drink a bottle of beer. They have no ambition or motivation to take measures to change their condition. In the worst cases, they fall into cataclysmic and suicidal depressions.

In 1981, when I was a medical student, I recall meeting a patient with lymphoma who had obvious parasympathetic dominance, as Kelley had described it. This patient was obviously very relaxed, even somewhat lethargic. I was big on meditation even then. But Kelley said that a patient like that should not be meditating. We want to have them watch war movies or give them something that turns on their stress system, because it's weak. Their immune system is too strong because of their parasympathetic dominance. The parasympathetic system—the opposite of the stress or sympathetic system—is the one that turns on at night when we're asleep. It's involved in utilization of nutrients and repair of damage, a process in which the immune system plays a prominent role. In a patient whose parasympathetic system is too strong—these are the people with leukemia and lymphoma—the parasympathetic is out of control. We want them to be more angry, feisty, assertive, and aggressive. People who display sympathetic dominance need meditation and relaxation techniques, whereas parasympathetic-dominant individuals are already in a state of alpha just when they wake up. They need to have this shut off, perhaps with the image of John Wayne leading the troops. They need tasks or situations that make them more assertive, ambitious, and aggressive, and less relaxed and lethargic. We use meditation very selectively, mainly because we believe everyone is different and not everyone has a strong sympathetic system, which is where meditation and relaxation techniques may be very valuable.

Also, along these lines, certainly a variety of stress reduction techniques may be used to reduce some of the immune suppression caused by conventional treatments. As I noted in my answer to an earlier question, these techniques play a pivotal role by quieting the sympathetic activity in sympathetic-dominant people while raising the parasympathetic activity so that the person is more capable of deep relaxation. This, in turn, would tend to support immune function in people who tend to operate in a more stressful fashion. For parasympathetic-dominant people, however, relaxation techniques are almost redundant.

Of course, assessments do play an important role in determining where the emphasis should be placed. Based on a comprehensive questionnaire, Kelley divided patients into 3 metabolic types: parasympathetic, sympathetic, or balanced. He then used this metabolic typing to guide the dietary choices of individual cancer patients, the overall dietary pattern matching each patient's metabolic type. Sympathetic-dominant individuals are slow oxidizers and thus cannot handle animal products; they need more plant-

based diet. Fast-oxidizing parasympathetic-dominant individuals require more meats and fatty foods. After observing Kelley work with patients for 5 years, and looking through his records, I began to get a good sense of who was sympathetic dominant and who was parasympathetic dominant. Simply by one's history and behavioral tendencies, one can get this sense. Sympathetic dominants have plenty of adrenaline. They feel great with just 4 or 5 hours of sleep. They never sleep restfully but have more energy than anyone else. They get up early in the morning and are at work by 7 AM. They are asleep in the evenings at 9 or 10 PM. They tend to be assertive, aggressive, and ambitious. In contrast, parasympathetic-dominant individuals tend to do terribly in the morning and do great in the later evening. They start waking up around 2 or 3 in the afternoon. These are people who shouldn't even go to school until 2 or 3 PM, because that's when their brains are waking up. Ernest Hemingway was a classic parasympathetic dominant. They're not very disciplined or organized, but they tend to be very creative. They do terribly as accountants, but they do well as writers, artists, or composers. They're very creative. They don't fit into highly regimented or disciplined situations. If you have a parasympathetic dominant working for you, you want to make sure you set up different times when they can come in, when they function more efficiently. They function wonderfully in the latter part of the day.

The bottom line is that assessments need not be too technically oriented. You can tell what the tendency is from a combination of history, psychology, and the foods people crave or covet in private. People cater to certain diets because of what they read; however, if you ask them, sympathetic dominants will admit to you that they hate red meat. They feel tired and fatigued after eating it; they love eating fruits and vegetables, so much so that they get very self-righteous about it and will tell you the whole world should eat what they say. In contrast, many parasympathetic dominants, because of the general climate against red meat, tend to force themselves to eat a predominantly vegetarian diet. But they will tell you that they wake up in the middle of the night dreaming of pot roast with gravy, dreaming of steak and prime rib. Their mouth gets into this big smile as they talk about it, and they think it's a sin to eat it.

Vojdani: There is no doubt in my mind that psychological stress represents a potent influence on the pathogenesis of cancer. In an early set of studies conducted in our laboratory, we placed mice under stressful conditions before exposing them to a specified amount of carcinogen. We then compared tumor growth rates for stressed mice versus mice that were not exposed to stress. The results were dramatically different between the 2 groups. The mice exposed to stress developed cancers almost 50% faster than nonstressed mice. Tumor numbers and size were consistently bigger than in the nonstressed group. I think this clearly demonstrates the tight relationship between stress and immune dysfunction in the genesis of cancer.

There is a growing body of evidence from psychoneuroimmunology (PNI) studies indicating a strong interrelationship between immune function and emotional distress. Meditation, relaxation techniques, and other stress reduction methods that enhance the mind-body connection should play an important role in maintaining optimal NK activity and other anticancer immune functions. Currently, PNI researchers are trying to identify the mechanisms responsible for low NK activity in individuals who have difficulties in handling stress and in individuals suffering from behavioral disorders. By retraining an individual's reaction to stressful situations such as a cancer diagnosis or relapse, NK activity will be more adequately sustained. For this, please learn to "live, love, laugh, learn, sing praises, and exercise."

In terms of body-centered strategies, exercise is certainly proving itself to be a valuable way to support NK activity and immune functioning more broadly. Briefly, the research suggests that extremes in exercise patterns—either too little activity or overly strenuous activity levels—may be harmful, whereas moderate amounts may be beneficial to NK functioning.

I feel that the potentially adverse effects of intensive exercise on immune function may be modified by antioxidants such as vitamin C. The main effect of intensive or strenuous exercise is to increase oxidative stress. In 1993, we reported the results of a placebo-controlled study in which we gave vitamin C to healthy athletes to assess the effects on NK activity. We showed that one could further enhance NK activity in athletes with a dose of about 1 g of vitamin C. This was followed by another study in which we compared vitamin C to a buffered form of vitamin C. We found that the absorption of the buffered form was 20% better; however, there was no difference in stimulation of NK activity—both stimulated NK activity. It's worth mentioning that 30% of the population, because of their stomach acidity, cannot adequately absorb the unbuffered form and thus must take the buffered form to obtain the antioxidant benefit.

In closing, it would seem clinically reasonable to monitor the extent and duration of suppression of NK activity following cytotoxic treatment such as chemotherapy. There are 2 vantage points on this issue. One is that it may be advantageous to use chemotherapy protocols that minimize the suppression of NK activity. The other is that one would want to take steps to stimulate NK activity using biological response modifiers such as vitamin C, plant lectins, and plant extracts, as well as using moderate exercise and stress management strategies.

The strength of this approach will most certainly grow as researchers continue to identify promising new chemoprevention agents and clinical trials begin to provide insight into these substances' effect on humans. With the further advancement of these investigations and our great understanding of cancer,

nutritional prevention will undoubtedly play a major role in reducing the incidence of cancer, as well as in reducing the number of deaths caused by the disease.

Integrative Clinical Perspective

In presenting the 3 panelists in this Point-Counterpoint, we have accessed 3 very different approaches to the questions we pose. Dr Boyd is a clinician with an active interest in the evolving knowledge of cancer immunology. Dr Vojdani, on the other hand, is a bench scientist, quite active in basic and applied research in immunology, specializing in the study of NK cells. In presenting the views of Dr Gonzalez, we are pursuing this journal's commitment to giving a voice to the alternative cancer community in a place accessible to both conventional and alternative practitioners, as well as its commitment to promoting a more thorough knowledge of both systems for clinicians and patients alike.

Our panelists offer contrasting perspectives on the role of immunologic intervention in cancer care. Whereas Boyd provides a broad overview of cancer immunology, Vojdani focuses almost exclusively on the role of NK cells and the importance of cytokines. There is reason for enthusiasm about the potential therapeutic contribution of NK cell activity, given that a number of studies have demonstrated significant correlations between NK cell activity (including intratumoral infiltration), fewer metastases, and longer survival rates.[31-35] Gonzalez dismisses practical applications in immune modulation at this time, mainly on the grounds that IL-2 therapy has not proven efficacious and that decades of research in cancer immunology have not yielded major advances in this area. He advocates an approach that supports the use of pancreatic enzymes and the modulation of the sympathetic and parasympathetic nervous system as the central means of combating malignancy.

Immune System Support for Cancer Recovery

Boyd discusses the many limitations of immune surveillance, based on a wide variety of studies on the functioning of the immune system in cancer. Some of the most interesting data he discusses arise from observations of patients with specific immune deficits, who are in some instances susceptible to particular types of cancers. These cancers are not, however, the common solid tumors but, rather, virally related cancers, implying that the increased susceptibility to malignancy results from failure of recognition of specific viruses. He posits that tumor progression in common malignancies arises not from progressive immune failure but from the clonal evolution of tumors, which lose their sensitivity to growth inhibitory signals, evade apoptosis, and acquire greater invasive potential. Additionally, he points out a profound truth: the real clinical importance of the immune system in cancer patient care is the very high risk of secondary infections in this immune-suppressed population. In spite of doubts about the ability of immune cells to retard cancer growth and recurrence, all clinicians must continually grapple with the problem of susceptibility to infectious disease and the associated life-threatening risks.

Gonzalez also mentions the capacity of cancer cells to evade immune surveillance but emphasizes instead the first aspect of his alternative approach that he explicates in this article, the importance of pancreatic enzymes as the primary anticancer system in the body. Based on the work of Beard early in the last century and on the clinical application of this work by Kelley, the application of pancreatic enzymes in cancer has received substantial attention in the alternative cancer community and has attracted government funding. Gonzalez points out some of the preliminary laboratory work on pancreatic enzymes in cell culture systems that is now ongoing.

Vojdani emphasizes the role of NK cells, his main area of research interest. These cells are most likely to be effective in the cancer prevention stage or in the earliest stages of cancer. Vojdani points out the potential applicability of prevention research to cancer treatment and emphasizes the potential usefulness of immune modulation (primarily in terms of NK activity) as an aspect of secondary prevention. This latter emphasis, a focus on remission maintenance in the posttreatment period, is usually disregarded in both conventional and alternative cancer practices. Interesting data are adduced on the ability of NK cells to distinguish tumor cells spontaneously and on their responsiveness to a complex array of receptors on the cell surface. Animal data indicate the correlation of NK cell destruction with the development of melanoma in experimental systems (melanoma is, of course, one of the more immunogenic tumors, as pointed out by Boyd). Both the importance of NK cells in cancer prevention and their potential importance in more advanced cancers as a follow-up to conventional treatment are discussed.

Clinically Effective Means of Promoting Immune System Responsiveness to Cancer

The fairly short responses by all 3 panelists to this question are, perhaps, an indication of how little we know about how to promote an immune response to cancer. Boyd points out the potentials of therapies such as lymphokine-activated NK cells, IL-2, interferon, and biochemotherapy in the treatment of the more immunogenic cancers, such as melanoma, lymphoma, and renal cell cancer. Gonzalez mentions the

potential of the European cancer enzyme product WobEnzym to affect the fibrin coat of tumors—an intriguing possibility for which some data exist, although they are not conclusive at this time.

Vojdani points out the complexity of immune response to cancer: T cells, NK cells, macrophages, and a "symphony" of cytokines; this very complexity may explain the relatively small progress in this area that we have seen to date. Other complications are the suppressive factors secreted by tumors that hinder the ability of even NK cells to identify cancer cells as hostile elements, allowing the tumor to gain the upper hand and grow beyond the size that the cellular immune response can control. Vojdani points out the importance of reducing tumor mass through conventional treatments that debulk the disease, leaving only minimal residual disease. At this time, enhanced NK cells or cancer vaccines may be helpful in mounting an immune response to eliminate residual disease and prevent the development of micrometastases. The identification of this critical point in treatment for effectively promoting the activity of the immune system, whether through conventional means such as vaccines or through integrative approaches ranging from meditation to herbal formulas, is an important consideration in our attempts to develop effective immune responses to cancer.

Cancers That Are Most Responsive to Immunologic Interventions

All 3 panelists point out our current ability to effect immune-related improvements in renal cancer, melanoma, and lymphoma. Vojdani also points out the existence of tumor cell antigens, capable of stimulating the production of cytotoxic T cells. This antigenicity is present in the earliest stages of many tumors but disappears as tumors evolve evasion mechanisms, presenting substantial challenges to the development of immune-based treatments.

Effectiveness of Conventional Immunotherapy (Cancer Vaccines and Monoclonal Antibodies)

Boyd points out the success of monoclonal antibodies directed against specific cell surface receptors in lymphoma and breast cancer (trastuzumab and rituximab), actively used in the treatment of patients today, and the studies of other cell surface receptor antibodies including the EGF receptor. Work is also in progress toward cancer vaccines, for example, whole tumor cell–based vaccines, working in conjunction with the BCG vaccine in colorectal cancer. Dendritic cell vaccines, aimed at enhancing the presence of antigen-presenting cell populations, are also in the works. Allogeneic lymphocyte therapy is showing some promise in hematological malignancies; this is limited because of the presence of tumor-associated antigens on normal tissue and the possibilities of autoimmune reactions. Vojdani points out that the use of cancer vaccines may be improved by joining them to methods that harness the potential of cytokines, and refers to studies of Schlom that use the CEA tumor antigen in vaccinia virus in addition to IL-2. He also states that natural agents such as vitamins C and E may play a complementary role with cancer vaccines, an interesting area for investigation by integrative cancer therapy researchers.

Role of the Immune System in Spontaneous Remissions of Cancer

Boyd points out that renal cell cancer, melanoma, and lymphomas are among the cancer types that have higher frequencies of spontaneous remission—as well as cases of rapid progressions of disease unpredicted by typical medical assessments. The potential linkage with the enhancement or collapse of immune surveillance in these cancers that are known to be immunogenic is obvious. In several cases, patients who have had remissions have been exposed to immune adjuvants or have had infections, presumably stimulating a nonspecific immune response. Vojdani also feels that the immune system is likely to play a role in spontaneous remissions. Harnessing the factors that have led to spontaneous remissions into clinically reproducible treatments is thus the challenge faced by immune therapy researchers.

Gonzalez, on the other hand, feels that cancer remissions are not based on the functioning of the immune system but, rather, on the balance of the sympathetic and parasympathetic nervous systems. In his response to this question, Gonzalez outlines one of the bases of his alternative approach to cancer medicine. Not unlike many alternative medicine approaches, the work of Kelley and Gonzalez is based on early scientific observations, those of Pottinger, who proposed that persons with a dominant sympathetic nervous system were more susceptible to solid tumors (lung, pancreas, colon), whereas those with a dominant parasympathetic system were more susceptible to leukemias, lymphoma, and myeloma. The diet, enzyme, and supplement interventions that are part of the Gonzalez approach to cancer revolve around the concept of balancing the sympathetic and parasympathetic systems. When these systems are in balance, according to Gonzalez, all diseases will improve. Strategies for suppressing the overactive sympathetic system include such interventions as low-fat vegetarian-type diets, whereas the overactive parasympathetic system would be treated with a diet rich in

meats; all cancer patients are also given pancreatic enzyme supplements as the other foundation of cancer treatment.

Viewing this system in the context of alternative medicine, it is interesting to note the clear-cut and relatively straightforward concept of causality in Gonzalez's work, which appeals to many patients because it is easier to understand than the complexity that we see miring the more science-based approaches of Boyd and Vojdani. It is also difficult to avoid noticing the more engaging and personal style of explanation that Gonzalez adopts in this interview, which may certainly appeal to many patients more than the technical explanations of multisyllabic monoclonal antibodies and endless acronyms that are common in current scientific discourse on the immune system. Little scientific work has gone into the validation of the Kelley-Gonzalez approach until recently; again, this is typical with alternative medicine approaches which were regarded as outside the scientific paradigm before the last decade.

With the initiation of the National Center for Complementary and Alternative Medicine in the National Institutes of Health, however, the level of scientific exploration of alternative medicine has increased dramatically. The Kelley-Gonzalez approach was the first of the alternative cancer therapies to have received major funding for a large-scale randomized trial. The trial was based on a set of case reports of extended survival of pancreatic cancer patients published by Gonzalez: the study was designed to randomly assign recently diagnosed pancreatic cancer patients with very limited extent of metastatic spread to either chemotherapy treatment with gemcitabine or treatment with Gonzalez using pancreatic enzymes in the framework of the Kelley-Gonzalez theory on the sympathetic and parasympathetic nervous systems. It is somewhat disappointing in terms of evaluating this important dichotomy in the theory that the cancer chosen for study was a solid tumor. Because this is associated with the dominant sympathetic nervous system, the dietary intervention (and, as we see in later responses to questions, lifestyle modification) would be that typically associated with many alternative and integrative cancer approaches: a low-fat vegetarian-type diet. Although the use of this diet type in the trial may help to validate the mainstream of alternative/integrative cancer therapy, it does not provide data that might be used to shed light on the purported effects of the nervous system on cancer development. The trial could, however, shed some light on the use of pancreatic enzymes.

The progress of this trial to date is instructive for those interested in research on alternative medicine. Fairly early on in the study it became clear that, as in many more conventional studies, recruitment of patients into the 2 study arms was problematic. Interestingly, however, the recruitment into the alternative medicine arm was not the main problem. Instead, the patients who sought to enroll in the study refused to submit to random assignment to either the chemotherapy or alternative medicine group: they were only willing to participate in the alternative group and were unwilling to face the possibility of chemotherapy. The study was then altered to follow a series of pancreatic cancer patients undergoing the alternative intervention in a prospective manner.

Contributions of Diet, Exercise, and Supplements to Fighting Malignancy and Promoting Immune System Recovery After Conventional Therapy

Integrative and alternative practitioners hear patients assert that "I want to improve my immune system" through integrative interventions on a daily basis. Boyd details the effects of a number of specific alternative or integrative therapy approaches on the immune system, pointing out that acupuncture, massage, qigong, exercise, nutritional interventions, and supplements (especially EPA, mushroom polysaccharides, and shark alkylglycerol) do have positive effects on immune functioning. He also points out that it is not clear what effects immune stimulation arising from these interventions will actually have in controlling malignancies or preventing recurrences due to the complex nature of the immune system-tumor interaction. It is possible that these interventions may contribute to the important dimension of helping patients recover immune function during and after treatments and thus reduce the risk of secondary infection, but no data yet exist to support this.

Gonzalez details in his response to this question the type of dietary interventions that are appropriate for balancing patients with overly dominant sympathetic or parasympathetic nervous systems. Vegetarian diets slow the activity of the sympathetic system in the Kelley-Gonzalez theory, as do thiamine, riboflavin and niacin, magnesium, and potassium, and would thus be used with sympathetic-dominant patients with solid tumors. On the other hand, high-fat, meat-based diets and supplements of calcium, pantothenic acid, and vitamin B12 are appropriate for parasympathetic-dominant patients to bring them into balance. Some questions could be raised with regard to the increased oxidative impact of such dietary suggestions equally for cancers that are classified by Gonzalez as parasympathetic and for solid tumors he associates with the sympathetic system. Gonzalez also discusses the importance of vigorous aerobic exercise for sympathetic-dominant patients, who need to be

worn down and burn off adrenaline, whereas parasympathetic-dominant patients should not undertake vigorous exercise but should rather do mild exercise—walking, swimming, or bicycling. It is in the diet prescriptions for the parasympathetic-dominant patient that Gonzalez most dramatically departs from other typical alternative or integrative approaches to diet for cancer patients.

Vojdani discusses this question in terms of his work on the relevance of vitamin C supplementation in subjects who have suffered from toxic chemical exposures—which is, of course, what cytotoxic chemotherapy represents. In a 1997 study, Vojdani and Heuser found that 80% of patients exposed to toxic chemicals had improvements in NK cell activity after oral vitamin C. Vojdani recommends that patients receive vitamin C before, during, and after chemotherapy in order to protect immune cells. Vodjani was involved in the debunking of the pro-oxidant character of vitamin C asserted in a 1998 article in *Nature*. He and other experimental subjects took up to 5 g daily of vitamin C for a week, assessing apoptosis and DNA damage (using the standard assay of 8-hydroxyguanosine) before and after vitamin supplementation. He observed decreases in apoptosis of NK cells, increases in their activity, and no evidence of DNA damage in this human study.

Effects of Stress Reduction and Body-Centered Therapies to Fighting Malignancy and Promoting Immune System Recovery After Conventional Therapy

In addition to summarizing the current findings and controversies in research on psycho-oncology interventions and their rather questionable relevance to the immune system's ability to affect the progress of malignancy, Boyd mounts a spirited defense of many integrative and alternative therapies from a most interesting viewpoint—their relevance to reducing the tumor-promoting effects of insulin and IGF-1. The effects of hyperinsulinism on breast cancer survival were recently exposed in the work of Goodwin that Boyd mentions, where fasting insulin level predicted distant recurrence and mortality. Hyperinsulinism is associated with inflammation and is promoted by chronic stress, and insulin resistance is found in both newly diagnosed and advanced cancer patients. As Boyd points out, many of the interventions typical of integrative approaches to cancer care currently, such as the low-fat diet, antioxidant vitamins, omega-3 fatty acid supplements, and a variety of stress management techniques, are likely to have a beneficial effect on this state. There is a strong evidence base to support the effect of these interventions on insulin levels and the related cortisol levels. This evidence supports the utility of integrative interventions, and should be widely acceptable to conventional physicians.

In his discussion of stress effects, Gonzalez specifically rejects the need for "technically oriented" validation of methods of assigning patients to parasympathetic or sympathetic dominant classifications. Although Kelley originally used a comprehensive questionnaire for this assignment, Gonzalez feels that patient interviews and direct questioning about life habits and food preferences are sufficient for such assignments. This is not inconsistent with some approaches of alternative medicine, but it should be noted that in the search for acceptance by the medical community and an increasingly knowledgeable public, a standardized and reproducible method of detecting such an important variable, which could direct, for instance, assignment of patients to relevant groups for clinical trials, would be critical.

Vojdani points out the importance of PNI and moderate amounts of aerobic exercise as well as vitamin C supplementation in maintaining the efficiency of immune functioning in cancer patients. He also advocates clinical monitoring of the extent and duration of suppression of NK activity following chemotherapy in order to properly address the functioning of these important cells. Although monitoring immune function may have relevance to the battle against malignancy, we cannot say that we understand yet how this can be done. But it is certain that immune monitoring has an important role in maintaining resistance to secondary infections that plague so many cancer patients.

Conclusion

We cannot say that the panelists addressing our questions speak with a single voice on the question of the relevance of the immune system in cancer. Boyd takes a very broad scientific perspective in his critique of the potential of immune-based therapies for cancer, whereas Vojdani focuses more narrowly on the potentials of NK cells, especially as they relate to earlier disease stages. Gonzalez, on the other hand, presents a very different viewpoint rooted in his alternative approach to cancer.

At this point, it is unclear whether the immune system can be coaxed into a supportive role outside of the usual purview of immunotherapy (mainly for melanoma and renal cancer, in which spontaneous regressions have occurred). The value of maintaining immunocompetence in cancer patients is readily appreciated in the setting of treatment- or disease-induced granulocytopenia or mucosal damage due to

drugs or dehydration commonly seen in patients undergoing intensive treatment. The life-threatening infections seen in advanced-stage cancer represent another area that may benefit from immunologic intervention. Against the extremely immunosuppressed backdrop of advanced cachexia, it seems unlikely that most forms of immune modulation could promote adequate resistance to the microbial organisms that threaten survival of advanced-stage cancer patients. Certainly this is an area that deserves more intensive research attention, particularly in light of the large number of nutritional and botanical agents that are known to enhance resistance to infection.

In terms of improving survival, our roundtable discussion suggests that immunologic intervention may prove most efficacious in early-stage cancers and in the post-cytoreductive period of cancer treatment, after appropriate tumor debulking strategies have been employed. Maximal reduction of tumor burden may be needed before immune potentiation strategies can be reliably used to improve clinical outcomes for patients with the more common types of solid tumors. At the same time, increased efforts to counteract treatment-induced immunosuppression will be needed. In principle, this should be more feasible with surgery than with radiotherapy or chemotherapy. The immunosuppression associated with major surgery is thought to increase the risk of metastatic spread during and following surgical removal of tumors and to the increased risk of sepsis in the postoperative period. One intriguing possibility is that patients who maintain good health or optimal functioning will, in general, be more likely to maintain a sizable reservoir of NK cells and cytotoxic T cells that eventually might be called into action to destroy micrometastases as they arise. Performance status has consistently demonstrated strong predictive power in studies of cancer immunotherapy; thus, working to improve the patient's physical and psychological functioning could favorably impact immune-mediated strategies that are used as adjuncts to conventional treatment. If correct, this simple principle could have a profound impact on the future survival prospects of cancer patients, and would be an additional strong justification of the health-oriented interventions of integrative medicine.

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