Harnessing the Immunity System: From Potential to Reality

The Editor interviews:
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Editor: You have previously stated that cancers occur not once in a lifetime but perhaps once every week. Do you still believe this to be true, and why?

Dr. Good: My statement was based on the concept, originally proposed by Paul Ehrlich and later by Lewis Thomas in 1958, that the body has an immunosurveillance system directed against cells or tissues which, arising de novo in the body, are recognized as foreign and destroyed. The concept has had to be modified in the light of more recent experimental and clinical data. We no longer think that cancers occur as often as once a week, for instance, but certainly they develop more frequently than manifested by clinical disease.

Editor: This implies that patients with cancer are immunologically deficient in some way.

Dr. Good: Exactly. At the time Thomas expressed the concept of immunosurveillance, we were working on a corollary theory which postulated that patients with primary immunodeficiency diseases should have far more cancers than immunologically competent individuals. And indeed this was correct. We also found that the incidence of cancer was six to 100 times higher in patients receiving immunodepressive agents, such as those undergoing kidney transplants, than in the general population.

In addition, scientists at the National Cancer Institute and Sloan-Kettering Institute noted marked immunologic depression accompanying the development of cancer of the head and neck, certain forms of uterine cancer and breast cancer.

Editor: What is the nature of these deficiencies?
Dr. Good: As you know, lymphocytes produced in the bone marrow and, to a lesser extent, in the yolk sac and fetal liver, differentiate into two distinct types of cells, T- and B-cells. The T-cells are responsible for directly attacking foreign matter, including cancer. The B-cells form antibodies which combine with antigens, thus becoming susceptible to macrophage attack and destruction. These separate but interacting T- and B-cell systems are responsible for cellular and humoral immunity, respectively. Indeed, not only can these T- and B-cells interact positively but suppressor cells for both T- and B-functions have been found to be an important component of the T-cell population.

In studying patients with primary immunodeficiency disorders, we found various types of dysfunction. For instance, patients with Bruton-type agammaglobulinemia lack B-cells as well as plasma cells and often cannot form antibody even in response to repeated and intense antigenic stimulation. Their cellular immunity and T-cell numbers are at least normal. On the other hand, patients with Wiskott-Aldrich syndrome have frequent and progressive deficiency of cell-mediated immunity.
Editor: What about patients with cancer?

Dr. Good: We also see different patterns of immunologic deficiency in patients with cancer. The clearest evidence is found in cancers that involve the immunity system itself, such as Hodgkin's disease, multiple myeloma, the leukemias and lymphosarcomas. As an example, patients with Hodgkin's disease exhibit a deficiency of T-cell functions, while patients with multiple myeloma have deficient B-cell immunity. In those with chronic lymphatic leukemia, both T- and B-cell immunities are deficient early in the course of disease.

Editor: Do these differences in immunologic function exist in the more common cancer killers as well?

Dr. Good: Yes, and this is extremely interesting. In patients with head and neck cancer, immunologic deficiencies occur early in the course of disease and get worse as the disease progresses. In women with breast cancer, generalized deficiency of immunologic function is very difficult to demonstrate early in the disease, but
HUMAN LEUKEMIC LYMPHOCYTE WITH A LARGE NUMBER OF MICROVILLI. PRESUMABLY A B-CELL.

becomes pronounced as the cancer extends. The same is true of colon cancer. In patients with lung cancer it's striking to me how little immunodeficiency exists even when the disease is advanced. From retrospective double-blind analysis, we've even been able to define which patterns, especially in the lymph nodes draining the cancer, are associated with a good prognosis and which with a poor one.

Editor: Are the tumors found in patients with primary or secondary immunodeficiency disorders representative of the population at large?

Dr. Good: Overall, these patients develop cancers which are not characteristic of those found in the general population of the same age. Patients with primary immunodeficiency diseases have a high incidence of leukemias, lymphoreticular cancers, reticulum cell sarcomas as well as cancers of the stomach and colon. In those receiving immunosuppressive agents we again see a predominance of cancers of the lymphoreticular system although many other kinds of tumors have also been observed.
Editor: What's the direct evidence for the relationship between the immune system and cancer?

Dr. Good: Whenever they can be effectively studied in experimental animals, malignant cells and tumors can be shown to have antigens at their surface that are foreign to the host. Similarly, tumor antigens are being found in man that ought to be recognized as foreign and should lead to the destruction of the cancer.

Editor: Are these antigens normally present in the host?

Dr. Good: In several experimental studies, many have found what seem to be neoantigens, not normally present on the surface of normal, adult cells. However, some of these substances may have once appeared on normal cells and become lost or hidden as the cells matured. It has been most difficult to demonstrate these neoantigens in human cancer, and this is one of the central challenges.
facing the immunologist today. I don’t believe that man is different from the animals, he’s just harder to investigate.

Editor: If antigens behave as if they were foreign to the host, what prevents them from being recognized and destroyed?

Dr. Good: This area is also receiving intense study. One theory is that cancer induces antibodies which coat the cell’s surface and protect it from attack by the T-cells. We know that such enhancing or blocking antibodies exist. But we think that more often, the protective substances are either antigens or antigen-antibody complexes that somehow, perhaps like a smoke screen, interfere with effective cellular or antibody assault on the tumor. Another explanation is that antigens shed their surfaces—so-called antigenic modulation—to confound the T-cell function directly.

Editor: Wouldn’t the fact that antigens shed their surfaces provide a basis for detecting cancer at an early, localized stage?
Dr. Good: Yes, this is precisely what we’re looking for. One kind of antigen that tumor cells shed is the carcinoembryonic antigen. Unfortunately, the original hope that CEA would have a high degree of specificity for cancer has not been realized. Nonetheless, ability to detect CEA will prove to be most useful clinically.

Editor: Should one speak in terms of tumor-associated rather than tumor-specific antigens?

Dr. Good: Yes, that’s preferable for now. But there almost certainly will be antigens that are specific for a particular cancer which can be detected even in very small quantities. Many have found tumor-specific antigens in experimental animals, and we’re searching for them in man.

In addition, we are looking for etiologic agents of cancer and tracking them with immunological techniques that detect antigen-antibody complexes in the circulation. Since certain cancers in animals exhibit such complexes long before the disease is evident, these methods may be extremely useful in anticipating and ultimately preventing cancer. In fact, immunological means of diagnosing and even preventing cancer may be possible within the next five to 10 years. We’re not there yet, but I think it’s coming very quickly.

Editor: Are the prospects for immunotherapy as encouraging?

Dr. Good: We can cure cancer in animals by immunological techniques and there is no question that immunotherapy can be of benefit to man. But all approaches are still experimental and continuing success depends on many factors, especially on our ever-developing understanding of the immunity system and its relationship to cancer. We must proceed with caution, however, as there is already some evidence of possible deleterious effects following immunologic manipulation, such as immune enhancement. Each step should be thoroughly analyzed, each mistake immediately corrected, but the work should be vigorously pursued because the promise is great.

Editor: What approaches to immunotherapy are currently being studied?

Dr. Good: Many centers are experimenting with extremely crude forms of what will ultimately be a refined technique. One area of investigation is based on experimental evidence demonstrating that the immunity system can be nonspecifically stimulated with bacillus Calmette-Guérin (BCG), killed vaccines such as Corynebacterium parvum and mixed bacterial vaccines that attempt to mimic the beneficial effects that infections sometimes have on cancer. The field of passive immunotherapy has enormously exciting potential.

Another approach involves active immunization with the patient’s own cancer cells. This has been beneficial experimentally,
and we are trying to discover in what clinical situations it may also be useful.

**Editor:** *Is there evidence that immunotherapy can cause regression of cancer in man?*

**Dr. Good:** Yes. Controlled studies seem to indicate that advantage may be obtained from nonspecifically stimulating immunity function in certain patients with acute myeloid leukemias, melanomas and carcinomas. Immunologic manipulation can surely cause melanomas to regress as when BCG is injected into the tumor. Sometimes this effect extends even beyond the local tumor and can address distant metastases in the skin and, rarely, distant metastases at other sites. However, these are just small responses compared to the major effects of chemotherapy and, in my view, the very dramatic potential of bone marrow transplantation.

**Editor:** *Please discuss bone marrow transplantation as a means of correcting immunologic dysfunction.*

**Dr. Good:** It was found many years ago that if an animal that had leukemia undergoes a transplant with bone marrow identical to its own, syngeneic marrow, the host will after even fatal irradiation develop cancer all over again. But if the marrow is somewhat foreign, the cancer may never recur. Such resistance is, I am sure, immunologic.

In patients with primary immunodeficiency diseases we are now able to completely reconstitute the immunity system by transplanting bone marrow cells from matched donors—a process I call cellular engineering. We can also dramatically correct immunologic imbalance in patients with an absent or deficient thymus by an embryonic thymus transplant.

**Editor:** *Are you able to use cellular engineering for patients with cancer?*

**Dr. Good:** We’re just beginning to employ bone marrow transplants for the treatment of leukemias that cannot be satisfactorily managed by standard means. Donnell Thomas and his coworkers in Seattle have already presented some very promising results, and this is one of the most exciting areas now under study. I am certain this approach involving cellular engineering coupled with chemotherapy and total body irradiation can provide powerful new approaches to solid tissue cancers as well.

**Editor:** *To summarize, would you briefly outline the major avenues of investigation in immunology at the Sloan-Kettering Institute for Cancer Research.*

**Dr. Good:** We’re approaching these issues in many ways. We are analyzing the cellular and humoral immunologic parameters as indications of immunologic vigor in patients with all manner of cancers and
we are searching for and beginning to find, at the surface of
cancer cells, antigens that are definitive for various kinds of
cancer. We are able now to seek and find antigen-antibody
complexes and perturbation of the serum complement in patients
with both localized and generalized cancer. These seem important
leads. We are using immunological probes involving highly
purified antigens from animal cancer viruses to reveal antibodies
in normal and cancer patients—a most powerful approach. We
are investigating the distribution and control of differentiation
of lymphoid cells in the body, the influences of cancer antigens
and antibody complexes on immunity functions and the best
means of regularizing or strengthening immune responses of
patients with cancer. We are carrying out extensive studies of
nutritional factors in cancer and immunity functions, and the
effects of chemical carcinogens on immunity.

In addition, in both experimental and clinical situations, we
are trying to develop and analyze the basis of immunotherapy,
immunofacilitation and immunoregulation. One avenue of great
promise is the immunogenetic approach coming to fruition in
the clinic as well as in the laboratory. Over the past 20 years,
our Immunological Parameters Laboratory has developed the
capacity to quantify each of the known means by which man
immunologically resists infections and intoxications, as well as
cancer. We are studying the various patterns of immunodeficiency
that lead to and are consequent to cancers and how they
can be corrected. We are trying to determine whether immuno-
therapy can become a practical means of treating cancer.

Editor: If immunotherapy develops a high level of competence, will it
replace standard forms of treatment for cancer?

Dr. Good: That, of course, is our fond hope. At the present time, however,
our goal is to introduce another modality to improve treatment
that can be used with surgery, radiotherapy and chemotherapy
as part of a multimodality assault on cancer. Each benefits the
patient; each complements the other. We must, of course, bring
immunotherapy up to the very front of the modalities used if
it is to be effective. We now know many of the principles behind
harnessing the immunity system, but these are just the beginnings
which must be amplified and strengthened by clinical and addi-
tional laboratory investigation. It’s my estimate that within 25
years, immunology will be a very powerful tool in the analysis,
diagnosis, treatment and even the prevention of many forms of
human cancer.

Editor: Thank you, Dr. Good.