THE YALE JOURNAL OF BIOLOGY AND MEDICINE 55 (1982), 329-333

On Immunosurveillance in Human Cancer

LEWIS THOMAS, M.D.

Memorial Sloan-Kettering Cancer Center, New York, New York

Received May 12, 1982

The extraordinarily high incidence of cancers of many different varieties—carcinomas and lymphomas—in organ-transplant patients being maintained for long periods of time with immunosuppressive drugs is briefly reviewed. The role of immunosurveillance as a *primary* defense mechanism against cancer in human beings is consistent with these observations and is in need of further investigation. Conceivably, this mechanism may play a somewhat different role in humans from what has been observed in most experimental animal models.

Twenty-five years ago, about all that was known about cellular immunity or, as it was then called, delayed type hypersensitivity, was that it was, in general, a bad thing. The tuberculin reaction was the paradigm, a violent, often corrosive response in the tissues of infected animals, probably mediating the destruction of lung tissue but of arguable protective value. The lesions of leprosy were thought to be similarly mediated. Louis Dienes had discovered in the 1920s that tissues involved in the tuberculin reaction were peculiarly hyperreactive to other antigens injected into the reacting sites, and Jules Freund, about ten years later on (the field moved slowly in those days) applied this observation for the development of the mixed salad of killed tubercle bacilli, mineral oil, and antigen, known as Freund's adjuvants; this was of course a highly useful aspect of cellular immunity, but only useful for experimental pathologists. As it turned out, Freund's adjuvants were indispensable for the induction of allergic encephalomyelitis, the earliest experimental model for autoimmune disease, characterized by dense aggregates of lymphocytes around foci of myelin destruction. Later, others produced by the same method a series of other autoimmune disorders involving lymphocytes and macrophages and involving, selectively, thyroid, testis, liver, skin, adrenal, and other organs—all testifying to the likely involvement of cellular immunity as a centrally placed mechanism for destroying one's own organs and tissues, with a high degree of specificity. The field of inquiry was given the term "immunopathology," and it has been influencing our views of human disease in medicine ever since, perhaps over-influencing and oversimplifying them as well. During all this time through the post-World War II period, nothing *beneficial* about this sort of immunologic reactivity had been adduced. The phenomenon of skin graft rejection, and the discovery of the role played by cellular immunity in histocompatibility and tolerance, opened the way for the understanding of what lymphocytes actually do for a living, but the teleological question remained hanging in mid-air. Tissue grafts could be selectively rejected with exquisite, surgical perfection, down to the last alien cell, one's own cells could be edited away using tissue an-

Address reprint requests to: Lewis Thomas, M.D., Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021

tigens and adjuvants, and lymphocytes were known to be primarily responsible, but what after all was this intended to accomplish in real life? Surely this intricate and powerful apparatus was not selected in evolution in order to provide experimental surgeons and pathologists with something to do for a living. The notion that perhaps cellular immunity had something to do with defense against viruses and some types of bacteria had not yet emerged.

This is where things stood in the late 1950s: an infallibly accurate device had been recognized for destroying autografts as well as recognizing and remembering the specific foreignness of individual populations of cells and destroying them more rapidly the second time around, but no one knew what it was good for.

In the circumstance, the phenomenon of cellular immunity was fair game for loose speculation. The possibility was then raised [1] that it might have been designed as a useful and effective mechanism for the early sensing and early elimination of neoplastic cells, on two assumptions: that cancer cells might be arising in small clones, in one organ or another, all the time, and that they might always have something foreign displayed at their surfaces indicating their alien nature. The notion was proposed at a New York symposium in 1957, and, sometime later, Burnet [2] developed the concept in detail and gave it the name "immunosurveillance."

It seemed to me then, and still does, that some such built-in immunologic mechanism *ought* to exist for natural defense against cancer in humans. It had already been solidly established that experimental animals could be immunized against syngeneic transplantable tumors, especially tumors known to be caused by viruses. To be sure, immunization was a tricky business, as likely to cause increased vulnerability by the phenomenon of enhancement as to produce solid resistance, depending on the dosage and timing of tumor antigens. What was not known then, and remains unclear still, was whether preexisting immunity could bring about resistance to the development of *spontaneous* cancer in animals. However, there was, and is, abundant evidence that some strains of inbred mice were much more susceptible to spontaneous tumors, including tumors caused both by viruses and chemical carcinogens. Recently, North [3] has found that syngeneic sarcomas in mice can be eliminated by passive transfer of immune T-lymphocytes, provided that the population of specific T-suppressor cells is eliminated at the same time.

The idea that differences in genetic resistance might be based on different degrees of immunologic response seemed reasonable enough 25 years ago, and it seemed a short step to extrapolate the possibility to humans. There are such things as "cancer families" in which the incidence of various neoplasms runs considerably higher than in the general population. Moreover, it has long been known that there are cancer-prone individuals, in whom two or more quite different types of cancer will occur in a lifetime; indeed, a study at Memorial Hospital [4] has revealed that patients with any given type of cancer are, as a group, statistically much more liable than normal people to develop a second or even a third tumor of a different kind after they are surgically cured of the first growth. This is not to be confused with the possible carcinogenic effects of chemotherapy: the observation of multiple cancers long antedates chemotherapy. Children with various types of congenital immunodeficiency are highly vulnerable to neoplasia, mostly leukemia and lymphomas.

The overall incidence of cancer in different human societies, living under altogether different environmental conditions, also suggests the existence of some fairly stable form of natural resistance. By and large, around 25 percent of human beings will develop cancer in a full lifetime in our kind of society. The figures have

been skewed somewhat in recent decades because of the increased incidence of lung cancer in cigarette smokers, but, even so, it seems to happen that around 75 percent of us are, somehow or other, naturally protected against cancer.

There are a few forms of human cancer in which something like immune defense seems to be operating in the natural course of the disease. One form of skin cancer, keratoacanthoma, which seems on histological grounds to be a genuine cancer, regresses spontaneously and vanishes altogether a few weeks or months after its appearance, without any kind of treatment. Lymphocyte aggregation around the tumor is a conspicuous feature of the pathology of this tumor. Spontaneous regression has also been observed, although much less frequently, in other tumors, notably choriocarcinoma and, less often, malignant melanomas; Klein [5], of Buffalo, has shown that regression of melanomas confined to the skin can be induced by local injections of BCG into the tumors; skin melanomas at remote sites may regress at the same time, although internal metastases are not affected. From time to time, rarely but in well-documented circumstances [6], spontaneous regression has been observed in extensive, metastatic malignancies involving the lungs, liver, and peritoneal cavity; there are several hundred such cases now recorded in the world literature—people who have been found at laparotomy to have extensive cancer in the bowel and liver, been sewed up and sent home to die, and then turn up a few years later free of cancer. It is not known how such things happen, but the mobilization of cellular immunity against the neoplasm is as reasonable a possibility as any other to be thought of.

What is needed, of course, is a series of human experiments, planned and executed in order to answer the sort of question which automatically raises itself: what would happen if you were to remove the putative defense mechanism of cellular immunity in human beings? Would this affect either the incidence or clinical course of cancer? As it happens, the experiments have already been done, and continue today.

Malignancies have been occurring with astonishing frequency in patients receiving grafts of kidneys and hearts in recent years, and the only plausible explanation for this is the routine, mandatory use of immunosuppressive drugs. At first—in the case of kidney grafts—these seemed to be the result of using grafts from donors who themselves had cancer; it was thought that a few stray cancer cells had somehow come along with the graft. Later on, however, it became clear that a very substantial number of brand new cancers were occurring in the course of the intensive treatment of the graft recipients with immunosuppressive drugs. The cancers have been of all types, carcinomas, sarcomas, and lymphomas. Some have appeared in or near the graft area, others at distant sites. The most remarkable feature of the phenomenon, apart from the cancers themselves, has been that a few of these spontaneous tumors have regressed when the immunosuppressive drugs were discontinued. On a few occasions, malignant growths the size of a hen's egg or larger, some with already established lymph node metastases, have been reported to melt away after stopping the drugs.

All of the transplanted patients who developed neoplasms were routinely maintained on immunosuppressive drugs, usually a combination of azathioprine and prednisone. Krikorian [7] summarized the results of the Stanford experience with heart transplants three years ago. Out of 143 transplanted patients who survived for three months or longer, ten developed cancer: six lymphomas, three carcinomas, and one acute leukemia. All of these patients were under 40 years of age, which indicates that the incidence of de novo cancer was really extraordinarily high. For renal

transplant recipients, it has been estimated that cancer develops at more than 100 times the expected rate for the ages involved. In one series of kidney transplants reviewed by Israel Penn [8] in 1977, 5–6 percent of the patients developed cancer during the next three to four years. The average age of the recipents was 38. There were 453 de novo cancers in 432 recipients, meaning multiple cancers in 20 patients. Over 65 percent of the cancers were epithelial in origin—including skin, lip, uterus, colon, bladder, lung, breast, kidney, while the other 35 percent were mesenchymal, principally reticulum cell sarcomas and some leukemias. Less than 1 percent were Hodgkins.

In another study reported from Australia in 1981, by Sheil et al. [9], 459 patients received cadaveric renal grafts and were maintained on azothioprine and prednisone. Within one year, 108 (26 percent) developed neoplasms, chiefly squamous cell cancer of the skin (80 percent of the affected group); in nine of these patients, the skin cancers exhibited metastases. A smaller cluster (181 patients) were followed over a five-year period, with a cancer incidence of 43 percent.

Zisbrod [10] reported one patient who developed extensive and rapidly growing Kaposi's sarcoma eight months after renal transplantation, involving both skin and gastrointestinal tract. The immunosuppressive drugs were discontinued and replaced by a rather mild course of anti-cancer drugs, and all of the Kaposi lesions vanished. It has been reported that the skin lesions of Kaposi's sarcoma will sometimes regress, although it is a rare event, but this, according to Zisbrod, is the only reported case to have had total remission of visceral Kaposi's.

Spees [11] reported a patient with an ocular melanoma which appeared one year after kidney transplantation. As it happened, the kidney transplant was unsuccessful and the drugs were stopped. The patient was maintained on dialysis, and the tumor remained quiescent for the following 13 months. Then a new renal transplant was put in place and the drugs resumed. Within three months the melanoma grew so rapidly that the eye had to be enucleated. In addition, there is a small group of renal transplant patients in the literature who were known to have had cancer beforehand, thought to have been cured, in whom recurrence of the cancer with metastases and death occurred during immunosuppressive therapy.

The greatest trouble with the idea of immunosurveillance is that it cannot be shown to exist in experimental animals, with the exception of tumors caused by viruses in which an early immune response either to the virus itself or to antigens coded by the virus has been shown to be protective. Nude mice, and thymectomized mice, are no more susceptible to carcinogen-induced cancers, or to spontaneous cancers, than are normal mice. However, the mechanism responsible for the distinct difference in susceptibility between different genetic lines of mice remains to be clarified. There is evidence that at least part of the difference is due to the activity of cytocidal natural killer lymphocytes, under control of a strong H-2 linked factor in resistant animals [12]. However, it is by no means clear that the situation in mice—either with chemical carcinogens, tumor viruses, or transplanted tumors—is comparable to the situation in man which must exist when the very first nest of neoplastic cells turns up in a given tissue, long before this microneoplasia has had time to begin replicating new cells with modulated surface antigens. The frequency with which small clusters of cells resembling cancer cells are encountered in routine human autopsy specimens on patients, mostly elderly patients, not suspected of having cancer (the ambiguous and long-debated "carcinomas-in-situ") suggests the possibility that transformation may be a much more frequent event in human beings

than can be accounted for by the incidence of successful bona fide cancers. Boyd [6] summarized the evidence for latent, nonprogressive, possibly transient cancers in human beings in 1966. The most remarkable observations concern cancer of the prostate. In men over 50, dying from other causes, 25 percent were found to have small, histologically unquestionable cancer in their prostate glands. In men over 80, the figure was 50 percent. These incidences are so far in excess of the known occurrence of clinical cancer in this organ that it must be assumed that many of the cancers either failed to grow or later regressed. I believe it is true that we, unlike inbred mice, are constantly producing small nests of transformed cells in one organ after another, under environmental or endocrine or viral influences, and getting rid of them efficiently most of the time. Approximately 25 percent of us fail to do this.

It will be of great interest to see what happens in the increasing population of organ-transplanted patients now undergoing immunosuppression with Cyclosporin-A. This substance seems to be providing a high degree of protection against graft rejection by its relatively selective action on T-helper lymphocytes. To date, most of the cases of cancer in grafted patients have occurred during treatment with aziothioprine, and it is possible that some of the effect of this drug may be the result of its own mutagenic and carcinogenic properties (although it is difficult to use this explanation for the appearance of tumors within so short a time after beginning its administration). In the case of Cyclosporin-A, there is no evidence for carcinogenicity; it seems generally accepted that its principal action is directed against T-lymphocytes. Thus far, five cases of lymphoma have been reported among 300 recipients of kidney grafts maintained on Cyclosporin-A [13]. If other neoplasms, especially the epithelial carcinomas reported in such high incidence among azothioprine-treated patients, begin to occur in patients receiving Cyclosporin-A, this can be taken, in my view, as additional evidence for the notion of immunosurveillance as a natural protective mechanism against neoplasia in human beings.

REFERENCES

1. Thomas L: Discussion. In Cellular and Humoral Aspects of the Hypersensitive States. Edited by HS Lawrence. New York, Hoeber-Harper, 1959, pp 529–532
2. Burnet FM: Immunological Surveillance. New York, Oxford University Press, 1970
3. North RJ: Cyclophosphamide-facilitated adoptive immunotherapy of an established tumor depends on elimination of tumor-induced suppressor T cells. J Exp Med 155: 1063–1074, 1982
4. Cahan WG: Multiple primary cancers of the lung, esophagus and other sites. Cancer 40: 1954–1960, 1977
5. Klein E, Holtermann OA, Helm F, et al: Immunologic approaches to the management of primary and secondary tumors involving the skin and soft tissues: Review of a ten-year program. Transplant Proc 7:297–315, 1975
6. Body W: The Spontaneous Regression of Cancer. Springfield, IL. Charles C Thomas, 1966
7. Krikorian GG, Anderson JL, Bieber CP, et al: Malignant neoplasms following cardiac transplantation. JAMA 240:639–643, 1978
8. Penn I: Development of cancer as a complication of clinical transplantation. Transplant Proc 9:1121–1127, 1977
9. Sheil AGR, Mahony JF, Horvath JS, et al: Cancer following successful cadaveric donor renal transplantation. Transplant Proc 13:733–735, 1981
10. Zisbrod Z: Kaposi's sarcoma after kidney transplantation. Transplantation 30:383–384, 1980
11. Spees EK, Kramer KK, Light JA, et al: Reactivation of ocular malignant melanoma after renal transplantation. Transplantation 29:421–424, 1980
12. Greenberg AH, Greene M: Non-adoptive rejection of small tumor inocula as a model of immune surveillance. Nature 264:356–359, 1976
13. Morris PJ: Cyclosporin A. Transplantation 32:349–354, 1981