The Interrelationship of the Immune Response and Cancer

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The Interrelationship of the Immune Response and Cancer

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Foreward

For many years physicians treating cancer have observed the seemingly impossible – arrest, regression, and even disappearance of highly malignant tumors in the absence of treatment or with minimal treatment. The body's natural resistance has been repeatedly cited as playing an important role in the therapeutics of cancer.

Within the last ten years important laboratory data coupled with clinical observations have evolved, placing immunology in the forefront of today's cancer research. What is the state of the science today? What relationship has immunology to the cancer patient of today as well as of tomorrow? This highly stimulating cancer symposium held in San Francisco October 15 and 16, 1971, explored many of the multiple facets of immunology. The proceedings are presented to you as Volume 7 of the 'Frontiers of Radiation Therapy and Oncology'.

JEROME M. VAETH, M. D.
Director
West Coast Cancer Foundation

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Introductory Remarks on Immunology and Oncology

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One of the remarkable aspects of American medicine in the past has been the simple fact that oncology has never been a serious specialty here. Radiologists, internists, surgeons, neurologists, etc., spend part of their time dealling with cancer patients, but few, if any, have devoted their professional lives to the study and treatment of cancer in man. The reasons are quite obvious. Very little was known in terms of basic principles about the causation or treatment of cancer. Therapeutic approaches were almost entirely empirical: radiation therapy, surgery, chemotherapy, etc. – each mode of treatment of each type of tumor with its own statistical probability of success. And the truth was that without understanding of principles upon which more rational procedures could be based, the empirical treatment of cancer was frustrating and unrewarding and, therefore, physicians chose naturally to see patients with other diseases who had much better prognoses.

It seems to me that there is now a new climate, and a new generation of physicians is now contributing to the creation of the field of oncology. Such a development implies a number of things: a beginning to understand some basic general principles in regard to the mechanisms of viral, if not chemical, carcinogenesis; a sense of disciplined approach to a common problem as opposed to separate entities; and, most important of all, a feeling of optimism that principles only just emerging represent the basis for effective prevention and treatment.

Among the most fundamental principles or generalizations regarding cancer is the importance of the relationship between the immune response of the host and antigenically altered neoplastic cells. Stemming from the work of GEORGE and EVA KLEIN and RICHMOND PREHN, it became apparent that most tumors have some lesion of the cell membrane which permits them to

be distinguished from normal cells by the immune system. Through the work of OLD and BOYCE and the HELLSTRÖMS, as well as many other laboratories, it became clear that tumor cells in a variety of experimental systems can be rejected by the cell-mediated immune response. BURNET and THOMAS postulated that the positive selective value permitting the cellular immune response to survive over 300 million years of evolution was to provide a mechanism for 'immunological surveillance', i.e., the systematic and continuous rejection of body cells which have become altered antigenically, primarily as a result of neoplastic transformation. The lymphoid cell responsible for this cytotoxicity is known to be a lymphocyte, probably thymus-derived, and possible chemical mediators of the biological effects produced by these cells, such as migration inhibitory factor, lymphotoxin, proliferation inhibitory factor, blastogenic factor, interferon, etc., are actively being studied in many laboratories. We have found that the maximum number of sensitized lymphocytes in the peripheral blood of humans exquisitely sensitive to tuberculin is of the order of 5/1,000, so one can imagine how few would be committed to a tumor antigen. And yet this small number can be extraordinarily effective. Curiously, although antibodies to tumor antigens may be developed in some circumstances, and are often capable of complement-mediated cytotoxicity *in vitro*, it has remained problematic why antibodies do not more often exert a tumorcidal effect *in vivo*. To render the situation even more complex, one must further consider that there exist, in tumor-bearing animals and human patients, factors in the serum which have the capacity to block the ability of sensitized lymphocytes to destroy *in vitro*, and presumably *in vivo* as well, the tumor cells to which they are sensitized.

These basic principles imply that, were the immunologists and oncologists able to manipulate it with precision, the immune system has enormous potential to bring about the destruction of existing tumor cells, and perhaps to prevent the development of new tumor cells. The realities of the situation, however, are that indeed the immune system in the form of blocking factors may play a significant role in permitting tumors to grow by protecting them from the natural mechanisms of cell-mediated immunity or surveillance.

The purpose of this first session will be to define the various roles played by these three known immune mechanisms in tumor immunity, and to consider possible means by which these principles can lead us to more effective rational modes of diagnosis and treatment.

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Some Aspects of Human Tumor Immunity and their Possible Implications for Tumor Prevention and Therapy[1]

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Summary of Some Existing Findings

Human cancers have been shown to possess antigens [5, 6, 8, 10, 11, 17, 19, 21, 23, 26, 28, 29, 32, 33, 34, 37, 38, 39, 47, 50] which are either not detected at all [34], or are detected only in small amounts [38], in normal cells from adult human tissues. These antigens are often referred to as tumor-associated antigens (TAA).

A crucial question is whether TAA can induce an immunological defense against cancer that is beneficial to the patients or can be made to be beneficial. *A priori,* it seems to be a good chance to be so: patients who have been immunosuppressed have a vastly increased frequency of cancer [40], suggesting that the immunosuppression has hampered a normally occurring immunological surveillance mechanism, capable of eliminating neoplastic cells. Furthermore, lymphocytes from patients who either have, or have had cancer, can destroy cultivated neoplastic cells of the respective types, while normal cells from the same patients are not affected [5, 8, 10, 17, 19, 21, 23, 26, 27, 28, 29, 32, 47].

One of the most striking observations made when studying human tumor immunity is that tumors of the same histological type cross-react antigenically, while tumors of different types do not. For example, lymphocytes from a patient with a colon carcinoma are cytotoxic to colon carcinoma cells

1 This paper summarizes information given and thoughts expressed in two presentations at the Symposium, one by KARL ERIK HELLSTRÖM and one by INGEGERD HELLSTRÖM. The work of the applicants was supported by NIH grants CA 10188 and CA 10189, by grant T-453 from Amer. Cancer Soc. and by contract NIH-NCI-71-2171 within the Special Virus-Cancer Program of the National Cancer Institute, NIH, PHS.

both from the same patient and from other patients but not to other kinds of tumor cells, e.g. to breast carcinoma cells [23]. Groups within which such cross-reactions have been detected are constituted by neuroblastomas, malignant melanomas, sarcomas, seminomas, and by carcinomas of the colon, breast, ovary, endometrium, uterine cervix, bladder, kidney. Analogous findings can be obtained when studying serum antibodies that are cytotoxic to tumor cells in the presence of complement, although fewer groups of tumors have been studied that way [6, 10, 19, 21, 50]. Most likely, individually tumor-specific antigens exist in addition to the common TAA. The evidence for this is particularly strong with respect to malignant melanomas [10, 37].

Lymphocytes can destroy animal and human tumor cells *in vitro* also when the neoplasms grow progressively *in vivo* [5, 6, 8, 10, 23, 32]. This conclusion is of course, compatible with the demonstration that some patients with widespread neoplastic disease have less reactive lymphocytes than do patients with small amounts of tumor, as can be detected when titrations are made of the minimum lymphocyte – target cell ratio needed to produce a significant cytotoxic effect. The fact that tumor cells can grow *in vivo* also when they are killed by the tumor-bearing individuals' lymphocytes *in vitro,* may be at least partially explained by the demonstration that sera from individuals with growing tumors, but not sera from tumor free (cured?) ones, can block destruction of the same individuals' tumor cells by lymphocytes immune to their TAA [6, 18, 26, 32]. The blocking effect of serum was first demonstrated in animal tumor systems and there interpreted as an *in vitro* counterpart of the *in vivo* phenomenon of immunological enhancement [27]. It can be seen both when standard microcytoxicity and colony inhibition tests [16] are performed, and when the macrophage migration inhibition assay is employed [12]. The latter is interesting because it indicates that blocking factors can interfere with either MIF production or macrophage reactivity, both probably important for rejection of antigenic tumor cells *in vivo*.

There have been exceptions [26], where a blocking serum effect was seen also in the absence of detectable tumor growth *in vivo*. However, the majority of experimental animals, as well as human patients, in which this was seen, shortly afterwards developed recurrences.

One may interpret the demonstration of blocking serum activity in patients with growing tumors as a consequence rather than a cause of tumor growth. This interpretation is correct to the extent that the blocking activity appears after antigens have been released from the neoplastic cells and stimulated the formation of antibodies against them, the blocking factors most likely being complexes between tumor antigens and their antibodies [45].

However, animal studies indicate that the blocking factors come early during the natural history of a neoplasm and are present already when a detectable cell-mediated antitumor immunity first appears [22, 27, 43, 45]. The prevailing situation is thus acceptable from the growing tumor's 'point of view': no blocking factors are needed until there is a cell-mediated antitumor immunity that has to be blocked.

The blocking serum activity, as detected *in vitro,* correlates well with the *in vivo* response of animals to their tumors: rabbits with persistent Shope papillomas have blocking sera and are susceptible to new papilloma induction with Shope virus DNA, while rabbits whose papillomas have regressed lack blocking factors and are not susceptible to papilloma induction with DNA [13]; splenectomy decreases the formation of blocking factors and increases antitumor resistance [22]; mice and rats with growing tumors have, *in vitro,* reactive lymphocytes and blocking sera [7, 13, 14, 15, 22, 43, 45] and are, *in vivo,* relatively susceptible to inoculation of the respective neoplasms [43, 48]; if their tumors are removed (or have regressed), the blocking serum activity disappears, while the lymphocyte effect remains [14, 15, 22, 43], and an increased resistance to tumor grafting can be detected [43]; blocking factors can be eluted from tumors growing *in vitro* [2, 42]; sera and eluates blocking tumor cell destruction *in vitro* can enhance tumor growth *in vivo* [2, 42].

'Unblocking' serum factors (probably antibodies) can be detected in mice whose Moloney sarcomas have regressed [15, 28], and in rats immunized against polyoma virus-induced tumors [3, 4]. They are defined, operationally, by their ability to specifically cancel the blocking effect of sera from animals bearing the respective tumors, when added to them *in vitro.* Animals inoculated with unblocking sera often respond with an arrested tumor growth [20, 43], and apparent cures have been obtained in 30 % of mice with primary Moloney virus-induced sarcomas [20, 28], in rats with transplanted polyoma virus-induced tumors [3], and in a few rats with primary such neoplasms [4]. In the last case, it could be shown that inoculation of unblocking antibodies decreased the blocking activity of serum from tumor-bearing animals, concomitantly with having an antitumor effect *in vivo* [3, 4].

Unblocking antibodies have been recently demonstrated in sera from some human patients cured of breast carcinomas or kidney carcinomas (hypernephromas), in serum from a patient whose malignant melanoma had spontaneously disappeared, and in serum from a patient whose metastasized colonic carcinoma had regressed following a course of chemotherapy which was considered unlikely, by itself, to be able to destroy all of the growing tumor [24] (tables I–IV).

Table I. Unblocking tests with breast carcinoma target cells

Serum of J.H. with metastatic breast cancer[1]	Serum of 'cured' breast cancer patient J.C.	Lymphocyte cytotoxicity[2], %	Blocking[2], %
–/1:2.5 NS	–	30.0	
1:5/1:5 NS	–	– 2.5	>100
–	1:5/1:5 NS	48.0	– 60.0
1:5	1:5	33.0	– 10.0
1:5	1:10/1:10 NS	19.5	35.0
1:5	1:20/1:7 NS	27.0	10.0
1:5	–/M.D. melanoma 1:5 [3]	5.1	83.0
1:5	–/F.R.L. colon cancer 1:5 [3]	– 2.0	>100

1 NS = Normal serum from adult healthy donor.
2 Percentage of lymphocyte cytotoxicity calculated by comparing number of target tumor cells/well with respective serum mixtures in the presence of specifically immune and control lymphocytes. The blocking effect of serum was calculated by comparing the percentage lymphocyte cytotoxicity in the presence of various serum mixtures by that seen in the presence of control serum (and immune lymphocytes).
3 Results with sera from patients M.D. and F.R.L. show that the unblocking effect is specific.

Table II. Unblocking tests with malignant melanoma target cells[1]

Serum of M.G. with metastatic melanoma	Serum of symptom-free melanoma patient M.D.	Lymphocyte cytotoxicity, %	Blocking, %
–/1:2.5 NS	–	25.1	
1:5/1:5 NS	–	16.7	33.5
–	1:5/1:5 NS	34.9	–39.0
1:5	1:5	30.8	–22.7
1:5	1:10/1:10 NS	34.7	–38.2
1:5	1:20/1:7 NS	11.7	53.4

1 See footnotes to table I.

Altogether, the data summarized indicate that the *in vitro* tests so far used provide a meaningful correlate of the antitumor immune response *in vivo*. Furthermore, they suggest that procedures capable of decreasing the formation and/or action of blocking factors may be therapeutically beneficial [27].

Table III. Unblocking tests with colon carcinoma target cells[1]

Serum of A.A. with metastatic colon cancer	Serum of 'cured' colon cancer patient F.R.L.	Lymphocyte cytotoxicity, %	Blocking, %
–/1:2.5 NS	–	28.0	
1:5/1:5 NS	–	7.5	73.2
–	1:5/1:5 NS	39.0	– 39.3
1:5	1:10/1:10 NS	16.8	40.0
1:5	1:20/1:7 NS	– 4.0	>100

1 See footnotes to table I.

Table IV. Unblocking tests with kidney carcinoma target cells[1]

Serum of B.L. with metastatic kidney cancer	Serum of 'cured' kidney cancer patient B.F.	Lymphocyte cytotoxicity, %	Blocking, %
–/1:2.5 NS	–	34.1	
1:5/1:5 NS	–	– 1.4	>100
–	1:5/1:5 NS	39.1	– 14.7
1:5	1:5	32.2	5.6
1:5	1:10/1:10 NS	29.0	15.0
1:5	1:20/1:7 NS	15.1	55.7

1 See footnotes to table I.

Implications for Tumor Prevention

As already pointed out, human tumors of the same histological type have common antigens, which can elicit a lymphocyte-mediated response leading to tumor cell destruction *in vitro*. This suggests that a similar type of reaction might be induced *in vivo* and there be capable of destroying neoplastic cells as they appear (following 'spontaneous' mutation, contact with carcinogen, etc.), thus preventing tumor formation. One could argue, however, that it is questionable whether an immunity to the common 'tissue-type-specific' TAA of the kind seen in human neoplasms can be established at all and that, if it can, normal cells of the tissues against whose tumors one would try to 'vaccinate' may be destroyed as well.

If common TAA of the 'tissue-type-specific' kind characteristic for human neoplasms can be demonstrated in some animals tumors, such as carcinomas of the bladder or colon, one may have the possibility to test whether at least some common TAA are transplantation antigens, capable of invoking a reaction which can kill transplanted neoplastic cells of the respective types.If that would, indeed, be the case, one could then study whether properly immunized animals become more resistant to carcinogenesis in the respective tissue (and whether any autoimmune reactions to normal cells would develop following immunization with the TAA).

One step towards this goal may have been achieved by the recent demonstration that lymph node cells from mice transplanted with chemically induced bladder carcinomas are cytotoxic to cultivated mouse bladder carcinoma cells, derived either from the same tumor or from other bladder carcinomas [49]. Analogous results have been obtained when studying carcinomas and papillomas of rat bladder, using peripheral blood lymphocytes. It is unknown, so far, whether the common TAA of the bladder carcinomas can act as transplantation antigens *in vivo*. Preliminary experiments indicate, however, that the appearance of primary bladder papillomas in rats, chemically induced, is delayed in rats immunized against the common antigens of such tumors.

If it will be shown that one can, indeed, immunize animals with TAA and thereby make them more resistant against carcinogenesis (and it may not at all be so), there would be a rationale for ultimately trying similar immunizing procedures against some selected type of human cancer in some groups of human subjects. One must realize, however, that there might be considerable risks of either inducing tumor enhancement, or autoimmunity to normal tissues, as well as of infecting healthy persons with viruses, and that these risks would have to be controlled for extremely well.

Implications for Tumor Therapy

Probably the most important consequence of the recent findings is that techniques now exist by which one can study to what extent already existing forms of cancer therapy influence some parameters of the immune response to TAA. For example, certain regimens of chemotherapy are likely to decrease both cell-mediated and humoral immunity to TAA, and the effects on different immune parameters (tumor cell destruction by immune lymphocytes, cytotoxic antibody formation, blocking and unblocking serum acti-

vities, etc.) need to be worked out, as well as how these effects might correlate with the patients' clinical response. Furthermore, the correlation seen in animal systems between the presence of unblocking antibodies and good tumor resistance *in vivo*, corroborated by recent human findings, would make it meaningful to follow unblocking serum titers in cancer patients in relation to tumor therapy of various kinds. Information obtained on such points may have a rather immediate clinical value.

Immunotherapy of tumors is a more distant goal. If it is carried out wrongly, it may be hazardous to the patients in several ways: enhancement to TAA may increase in magnitude, there may be risks for autoimmunity as well as for infection with various viruses, and graft-versus-host reactions may be induced with certain therapeutical programs. Furthermore, tumor immunology as a scientific field would be in risk of becoming confused. Immunotherapeutical protocols should, therefore, not be tried in man, unless there is evidence that they will work in at least some animal tumor systems, preferably ones in which primary tumors of spontaneous origin are studied. Work with transfer factor [36] has to form an exception in this respect, since, although the existence of transfer factor has been documented in man, it has not been unequivocally demonstrated in animals.

Since several reviews have been written covering what kinds of human immunotherapy have been done and what may be suitable to try (in view of our present knowledge [1, 9, 26, 29, 35], only a few aspects will be taken up here which directly relate to work of the type summarized above.

In general, it is likely that procedures capable of improving cell-mediated antitumor immunity will have beneficial effects [1, 26, 29], unless they have some concomitant, adverse action, for example by increasing the blocking serum activity. This is, of course, true both for those tumor-bearing patients who have a good tumor immunity and for those in which it is (more or less) depressed. Procedures to be tried should include attempts to increase the number of specifically reactive lymphocytes (by immunization, inoculation of immune cells – if a useful source is available –, injection of transfer factor or 'opsonizing' antibodies), and to improve macrophage reactivity as well as to free from restraint – by blocking serum factors – immune cells already present so they can kill their targets.

A new lead for tumor therapy may come from the recent demonstration that certain immune sera from animals and human patients are unblocking, and that inoculation of mice and rats with unblocking sera can have an immunotherapeutical effect (see above). The unblocking sera so far tested have not induced tumor enhancement the way they have been given; on the

contrary they have decreased it. It is encouraging that heteroimmune sera with unblocking activity can be prepared as well [3].

There is also some recent evidence that sera taken at the right time points from animals or human patients who have growing cancer or whose tumors have been removed, can specifically confer an ability on lymphocyte suspensions from nonimmunized donors to kill tumor cells having antigens of the respective types [6, 41]. A similar 'arming', 'opsonizing' or 'potentiating' effect is sometimes seen when unblocking sera (see above) are added to already reactive lymphocyte suspensions from patients with tumors [24]. The relationship between a serum's blocking, unblocking, and opsonizing (arming, potentiating) activities remains to be worked out.

Two recent attempts of Drs. L. and H. L. HORN [30, 31] to perform human immunotherapy, deserve comments in this context, since the rationale for doing them was, at least partially, based on the kind of work summarized here. One of the two patients studied had a clear cell kidney carcinoma (hypernephroma) which was surgically removed but soon metastasized to the lung [30]. The lung lobe with metastasis was removed, but there was at that time detectable tumor in some removed mediastinal lymph nodes and thus a probable spread to other nodes as well. Starting at this time, the patient was given repeated infusions, each consisting of 500 ml plasma from his uncle, who also had a hypernephroma which, however, had been removed two years earlier and not given any metastases. During the first three months, the plasma infusions were given weekly, and after that, biweekly. Today, 18 months after onset of the plasma infusions, the treated patient is clinically tumor-free. Serum from the donor of the plasma has been found to be unblocking *in vitro*, when tested together with blocking serum from patients with growing kidney carcinomas [31] (table IV) and serum from the treated patient has by now, no detectable blocking activity [31]. Serum taken before therapy was started had a blocking activity, indicating the presence of tumor at that time.

The same therapy protocol is presently tried by the Drs. HORN on another patient with a metastasized hypernephroma, using unblocking plasma from a donor freed of such a tumor by surgery two years ago. Serum taken before the onset of plasma infusion was blocking [31] while the blocking effect has been found to decrease significantly after inoculation of the unblocking plasma [31] (table V). Too short a time period has elapsed (three months) to know whether or not the plasma infusions will have any beneficial (or harmful) effects in that patient.

When interpreting the data from the two kidney carcinoma patients, extreme caution is needed. First, a possible therapeutic effect was seen only in