The Immunologic Status of Patients with Nonlymphomatous Cancer

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SUMMARY

It is firmly established that many cancer patients have impaired immune responses. Iatrogenic immunosuppression contributes to this impairment in many patients, but the data indicate that there is also an impairment which is related to the neoplastic disease per se. The defect appears to be in responses requiring the mediation of cells, rather than in those which are dependent upon the production and reaction of serum antibodies. The immunologic deficiency is most frequent and most severe in patients with widespread and debilitating cancer, but it is not a consequence of debility alone. There is no present evidence that abnormal immune responsiveness precedes the development of the cancer, but since the methods for evaluating immune responses are crude and insensitive, this possibility cannot be excluded.

INTRODUCTION

The detection of cancer-specific antigens in many tumors has been achieved. The tumor-inhibiting effects of immune reaction directed against such cancer-specific antigens is now well documented. The mechanisms by which host reactions influence the growth of autochthonous and syngeneic tumors are gradually being elucidated. Each of these areas has been considered by previous participants in this symposium. But it is axiomatic that if an immunologic response is to be effective against disease, the patient must be capable of producing an appropriate and adequate response. Therefore, it is appropriate that, in this symposium on cancer antigens, we also consider the immunologic capability of the cancer patient.

There is no simple test of overall immune status. The approach to evaluation of a patient’s immunologic status is, therefore, the measurement of the quantity and quality of as many as possible of the factors and the reactions which participate in or contribute to immune responses. The results of such tests provide what can be called an immunologic profile of the patient. It is convenient to subdivide the immunologic profile into four main categories: (a) serum antibodies, (b) serum factors other than antibody which participate in antigen-antibody reactions or other host defenses, (c) specific immune reactions which are mediated directly by lymphocytes or other

“immunocytes,” and (d) nonspecific cellular mechanisms which may be involved directly in host defenses or which may participate in the process of antibody formation or cell-mediated specific immunity.

In a group of cancer patients there may be great variation in types of cancer, general clinical status, extent and location and rate of tumor growth, and type and intensity of treatment. Each of these variables may have an influence on the patient’s immune status. Radiotherapy and most chemotherapeutic agents are known to have immunosuppressive effects, and it is necessary to distinguish these iatrogenic effects from results of the neoplastic disease itself. In this paper only the nonlymphomatous types of cancer will be considered because primary neoplastic diseases of the reticuloendothelial system present immunologic problems which set them apart, and because this group is considered elsewhere in this symposium by Miller (30).

SPECIFIC SERUM FACTORS

The production of circulating antibodies seems to be unimpaired in patients with nonlymphomatous neoplasms who are not receiving immunosuppressive forms of anticancer treatment, even in patients with extensive and debilitating disease. Patients with advanced cancer of a wide variety of histologic types and metastatic patterns who were infected with West Nile and other oncolytic viruses as an experimental therapeutic procedure produced serum antibodies as promptly and to similar titers as occur in natural infections with these viruses (51, 53). In order to obtain a direct comparison of the primary antibody response in healthy persons and cancer patients and to study the types of antibody globulins which are produced, Levin and others in my laboratory (unpublished data) recently immunized a group of cancer patients and healthy controls with yellow fever vaccine. The diagnoses of the 27 cancer patients were predominantly adenocarcinoma of the breast and epidermoid carcinoma of the oral cavity. The extent of disease and clinical status varied widely, but a majority of the patients were terminally ill with widespread metastases. Blood was collected weekly, and antibody titers were measured by hemagglutination inhibition in untreated serum and in serum which had been treated with mercaptoethanol to inactivate 19 S globulins. It was assumed that antibody activity which persisted after mercaptoethanol treatment was associated with the 7 S globulins and that lost by the treatment was 19 S macroglobulin. The validity of this assumption was confirmed in selected early
and late phase sera by the use of diethylaminoethyl cellulose column fractionation. Antibody levels were just as high in the cancer patients as in the healthy controls. The mercaptoethanol studies demonstrated that the pattern of 7 S and 19 S response varied greatly within the control group and also among the cancer patients, but there was no consistent difference in this respect between the two groups. Mean titers in patients and controls are shown in Chart 1.

The production of isoantibody to homografts of human tissue-cultured cell lines by cancer patients and healthy persons has also been studied in my laboratory using several serologic technics (2, 18, 19, 58, 59). More than 20 cancer patients and 30 healthy persons were studied after a primary homotransplant. About half of both groups had detectable antibody at titers of 1:10 to 1:80. In spite of the fact that rejection of the homotransplants was markedly delayed in many of the cancer patients (see below), there was no difference between patients and controls in the frequency of detectable antibody, time of appearance of antibody, or maximum antibody titers. There was a striking difference in the persistence of antibody, but it was in those patients whose ability to reject the homotransplant was impaired that the isoantibody persisted longest (19, 59). In both cancer patients and normals, the antibody activity in sera collected 2 to 4 weeks after homotransplantation was usually destroyed by mercaptoethanol, indicating that the isoantibody was predominantly 19 S globulin (and this presumption was checked by G200 Sephadex fractionation). The antibody titers detected by the immune adherence technic, which requires the first four components of complement (C1, 4, 2, 3c), and those obtained by the passive hemagglutination technic, which does not require complement, were parallel in the two groups (58). Thus, we have found no evidence of abnormality in quantity or quality of the primary antibody response to virus infections or to allogeneic tissue antigens in cancer patients. Several other studies of serum antibody production by nonlymphomatous cancer patients have been published; most agree that there is no abnormality attributable to the cancer per se.

Leskowits et al. (22) studied production of serum antibodies in patients with cancer (types not specified but presumably gynecologic carcinomas) using pneumococcal polysaccharides, diphtheria toxoid, and tetanus toxoid as antigens. The cancer patients developed higher antibody titers to the polysaccharide antigens than did the controls. The antitoxin responses were not significantly different in the two groups.

Lyttton and Hughes (28) also studied antibody response to tetanus toxoid in patients with carcinoma and, contrary to the above results, found that their cancer patients had a significantly poorer antitoxin response than did the controls. The cancer patients had not received radiotherapy or anticancer chemotherapy, and surgery was excluded as the cause of diminished antibody response. In both of these studies the controls were patients with non-neoplastic diseases.

Levin et al. (26) studied antibody responses to tularemia and E. coli antigens in 10 patients with metastatic cancer. Six who were being treated with 6-mercaptopurine had little or no antibody response, but the four patients who were not receiving chemotherapy all produced antibody at apparently normal levels.

Balch (4) studied the anamnestic responses to diphtheria vaccine in a group of cachectic cancer patients and found it no different from the response of healthy controls and well-nourished noncancer patients.

Electrophoresis and immunoelectrophoresis have been used extensively in recent years to study serum proteins in all types of disease. In nonlymphomatous cancer the only deviations from normal that occur with any frequency are increased concentrations of beta globulins, which are not known to have immunologic functions, and the decreased albumen concentrations which occurs in any condition in which there is chronic nutritional depletion. Gamma globulins are apparently normal in patients with nonlymphomatous cancer (39, 60).

**NONSPECIFIC SERUM FACTORS**

Serum complement levels of cancer patients as judged by total hemolytic activity or immune adherence were within the normal range or higher (29, 50, 61). Levels of the second component of complement were normal (57), and in a recent study of all nine serum complement components by Mc Kenzie *et al.* (29), C8 and C9 were usually higher in cancer patients than in healthy controls.

About 12 years ago, Pillemer (40) described a complement-fixing reaction between serum globulins and zymosan (a preparation of yeast consisting largely of polysaccharides) which
he attributed to "a primordial type of antibody" which he named properdin. Serum reactions which caused lysis of various Gram-negative bacteria and which neutralized T-2 bacteriophage were thought to be due to the same material. He postulated that this serum protein represented a nonspecific host defense mechanism which could react with a wide variety of potentially pathogenic microorganisms. During a period of acrimonious debate concerning the nature of this "properdin reaction," it gradually became evident (34, 36) that much properdin activity is due to classic antibodies ("natural antibodies") which react specifically with antigenic materials such as polysaccharides, which are widely distributed in nature and have an identical or cross-reacting antigenic structure. Thus, it appeared that the properdin reaction was not due to a non-specific "primordial antibody" but rather, to paraphrase Pillemer's words, was the reaction of classic antibody with a primordial antigen. Recent data support the concept that there is indeed a unique serum protein that participates in the properdin reaction which is neither classic antibody nor complement (37), that is, true properdin. Nevertheless it seems quite certain that most tests of properdin activity have measured antibody rather than this unique protein.

Although it may now be inappropriate to discuss studies of serum properdin reaction under the heading of nonspecific serum factors, the data are clearly pertinent to the present discussion to the immune status of cancer patients because the serum of many cancer patients fails to give this reaction. In tests performed by Pillemer using his zymosan technic (41) on coded sera from healthy persons and cancer patients, many of the latter had no detectable properdin activity, and the absence of this reaction was correlated with an impaired ability to reject homotransplants (56). Subsequent studies in my laboratory using Pillemer's technic showed that nearly 40% of patients with advanced cancer had no detectable properdin activity (less than 1 unit per ml) and 54% had less than 4 units per ml. Only 5% of our healthy controls gave negative results and only 23% had titers of less than 4 units per ml (47). These data are summarized by diagnostic categories in Table 1. Sera of cancer patients also showed a "zone" reaction, that is, less than 1 unit per ml, and 54% had less than 4 units per ml (47). This term is used to reject homotransplants (56). Subsequent studies in my laboratory using Pillemer's technic showed that nearly 40% of patients with advanced cancer had no detectable properdin activity (less than 1 unit per ml) and 54% had less than 4 units per ml. Only 5% of our healthy controls gave negative results and only 23% had titers of less than 4 units per ml (47). These data are summarized by diagnostic categories in Table 1. Sera of cancer patients also showed a "zone" reaction more frequently than the controls. This term is used for sera which had properdin activity when diluted but not when undiluted. Such a result suggests the presence of some type of inhibitor which is effective only in undiluted serum. It is possible that negative properdin tests were due to greater concentration of such inhibitors rather than actual absence of properdin. This interpretation is also consistent with the observation (47) that, when large amounts of serum globulin with extremely high properdin activity were administered to patients with properdin titers of zero, the properdin activity disappeared very rapidly, although when the same preparations were administered to patients with detectable levels of serum properdin, their titers were increased and remained elevated for a time consistent with a normal metabolic breakdown of human globulins.

The European literature contains numerous papers reporting low properdin activity in cancer patients, usually based on bacteriolytic or bacteriophage neutralization tests. It now seems certain that these various tests of "properdin" activity did not measure a single serum factor, but regardless of the identity or significance of these reactions, it is clear that many cancer patients are deficient in certain serum factors which react with microorganisms and microbial products.

### SPECIFIC CELL-MEDIATED IMMUNE MECHANISMS

Laboratory technics for the study of cell-mediated specific immune reactions are currently under investigation in many laboratories, as described earlier in this symposium (5, 7). They have been successfully applied to several discrete problems but are not yet adequate for the evaluation of immunologic competence of individuals. Instead, a clinical evaluation of cell-mediated immunity requires direct participation of the patients in tests of delayed hypersensitivity or homograft rejection and often requires parallel tests on healthy controls as well.

As yet the only exception to this generalization is the blastic transformation of lymphocytes on exposure to phytohemagglutinin or antigens to which the lymphocyte donor is sensitized. This laboratory test has been used to study the responsiveness of lymphocytes from patients with leukemia and lymphoma and often reveals poor responses (30), but patients with other neoplastic diseases have not yet been studied, to my knowledge.

Delayed hypersensitivity reactions of patients with nonlymphomatous cancer have been studied by several investigators using tuberculin and other microbial antigens. Positive reactions to these tests require not only the immunologic capacity to respond but prior exposure to the antigen, and this exposure is usually left to chance. When the occurrence, intensity, and time of exposure are unknowns, the absence of positive reaction to any one antigen cannot be interpreted as an immunologic defect for any individual, but failure to react to any of a group of frequently encountered antigens is indicative of anergy, and even in studies with a single test antigen, response rates in different populations can be compared. Studies of this type permit the general conclusion that there is a deficiency of delayed hypersensitivity reactions among patients who have advanced nonlymphomatous cancer, although this deficiency is not as marked as among lymphoma patients. In our study (24) only 30% of patients with nonlymphomatous cancer and 12% of lymphoma patients had positive tuberculin tests to middle strength PPD, whereas 72% of patients with nonneoplastic nontuberculur diseases had positive reactions. In two studies (9, 27) tuberculin response rates were not significantly different in carcinoma patients, but Hughes and Mackay (17) found a distinct relationship to the extent of the disease. In their group of patients with generalized or regional spread of cancer, only 35% and 47% respectively had positive tests, while those with only local cancer reacted like the noncancer control group (75% and 81% respectively). Solowey and Rapaport (46) used a battery of 5 microbial antigens of which streptokinase and streptodornase gave the most positive reactions; they found that 73% of the cancer patients were anergic to this antigen preparation in contrast to only 24% of the controls. They also found that the degree of reaction was generally less in the cancer patients. Lamb et al. (21)
<table>
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<th>4-8</th>
<th>&gt;8</th>
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Serum "properdin" activity in healthy persons and patients with cancer or other diseases. Assayed by the zymosan technic of Pillemer (41). CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; LSA, lymphosarcoma; RSA, reticulum cell sarcoma.

used a similar battery of microbial antigens and also found that, among 32 patients “in poor condition” from carcinoma, 38% were anergic to all of the tested antigens whereas none of the 27 carcinoma patients “in good condition” were anergic. None of the patients in this study had received chemotherapy or hormonal therapy during the 4 weeks preceding the test. Hattler and Amos (14) had very similar results. Advanced cancer patients had a lower incidence of positive skin tests to all five test antigens than did their healthy relatives, and 5 of the 18 patients, but none of the controls, had complete anergy. Logan (27) found only 29% positive skin tests with mumps antigen in patients with advanced carcinoma but 82% in patients with early cancer and about the same in healthy controls.

A more significant measure of immune responsiveness is obtained if the initial exposure to the test antigen is controlled as part of the investigative procedure, for a preexisting immunity might persist in a patient who is no longer capable of initiating an immune response. This requires use of a test antigen with which patients would not normally have any contact. We (24) conducted a study of this type by sensitizing patients and normal subjects with a primary dose of dinitrofluorobenzene (DNFB) and testing 14 days later for a delayed-type hypersensitivity. Seventy-five percent of the healthy persons and the same proportion of patients with nonneoplastic diseases had positive reactions, but only 23% of the patients with cancer reacted. (Only 11% of lymphoma patients responded in this test.)

Several methods have been used to study the homograft rejection reaction in man. The most extensive studies in cancer patients were done with subcutaneous homotransplants of cell suspensions of tissue-cultured lines of human cells. This technic gives reproducibility of quantity, quality, and antigenic composition of the graft which cannot be achieved with solid tissue grafts or with direct homografts from donor to recipient. The procedure is technically simple, is easy to explain to both patients and healthy volunteers, and was readily accepted by them. Unfortunately, cell lines derived from normal tissues (amnion or fibroblast cells) proved unsatisfactory for this purpose because they did not produce a detectable growth or host reaction in any recipient. Certain of the cancer cell lines, notably the epidermoid carcinoma lines HEp3 and HEp2 (31) and the osteogenic sarcoma line RPMI-41 (32), were ideal.
because, in healthy recipients, limited propagation of the transplanted cells together with the rejection reaction of the recipient produced a palpable subcutaneous nodule which increased to a maximum of 2 to 5 cm by 12 to 14 days and regressed rapidly thereafter. This behavior in healthy recipients provides a base line against which deviations from the normal rejection pattern can be evaluated.

The cancer cell homograft studies (6, 48, 54, 55, 56) revealed that many cancer patients have an impaired immune reaction to the foreign cells and a delay in rejection of the resulting subcutaneous nodule. Prolonged growth of the homotransplants never occurred among 164 healthy persons who received one or more of the human cancer cell lines, in 19 patients with debilitating non-neoplastic diseases, or in patients with cured cancer or early disseminated cancer. However, persistence and growth of homotransplant nodules beyond the six to eight weeks required for complete rejection by the healthy recipients occurred frequently in patients with advanced cancer (Table 2). Of the 195 evaluable studies in cancer patients, rejection was strikingly delayed in 31%. That is, regression of the nodule did not start until 6 weeks or longer after transplantation. Only 42% of the cancer patients rejected their homotransplants as promptly as did the controls. Many of these patients, of course, received immunosuppressive types of anticancer therapy which might have caused or contributed to the impairment of rejection mechanisms, but many of them were not receiving any chemotherapy or radiotherapy at the time of, or for many weeks preceding, the transplants (23). Thus, the immunologic inadequacy of some cancer patients must be attributed to the cancer per se.

Homografts of cancer tissue directly from patient to recipient have also been studied in a few cancer patients, but the evaluation of graft rejection was usually not the primary objective. The composition and growth potential of the inoculum is variable and is not reproducible. In our studies (49) such homografts were usually rejected promptly, and the protracted growth that occurred in two patients was probably attributable to the concurrent use of immunosuppressive drugs rather than cancer per se. Grace and Kondo (13) studied direct homografts of cancer in 20 patients. A few had a somewhat longer persistence of the nodule than might have been expected, but all were rejected as soon or sooner than simultaneous homografts of normal skin.

Isotopic skin homografts have also been used to study homograft reactions in man. The rejection reaction can be followed by macroscopic examination and by histologic examination of small biopsies. Use of this method for clinical research requires a surgical procedure for both donor and recipient, and reproducibility is limited by the number of studies that the skin donor will tolerate.

Gardner and Preston (10) found that in some patients with advanced debilitating carcinoma rejection of skin homografts was impaired. Mean rejection time among 23 carcinoma patients was 24 days, and in 5, rejection took 30 to 50 days. In contrast, rejection time averaged 17 days in patients with cirrhosis and 12 days in other patients, and maximum rejection times in these control groups were 38 and 12 days respectively. They also noted that there was less inflammatory response to the homografts in the cancer patients.

Robinson et al. (43) studied skin homograft rejection in 25 cancer patients (one Hodgkin's disease, but all others were nonlymphomatous) and found that 19 of the 25 rejected skin of healthy donors (mostly children) in 6 to 18 days, but in the other six, rejection required 28 to 35 days. Rejection of simultaneous skin grafts from donors who had cancer was usually slower—12 to 28 days in the 19 prompt rejectors and 26 to more than 55 days in the slow rejectors. No healthy recipients were included in the study, but it seems clear that 6 of these patients did have impaired homograft rejection.

In two other studies (12, 26), skin homografts were used to demonstrate the immunosuppressive effect of cancer chemotherapy, but the untreated cancer patients rejected their grafts promptly.
The lymphocyte transfer test is a special case of the homograft reaction in that the transplant is composed of immunologically reactive cells. Therefore, there may be a reaction of the graft against the recipient’s tissues in addition to the reaction of the recipient against the graft. However, the total reaction is small and persists only a few days.

We performed lymphocyte transfer tests, using lymphocytes from the blood of healthy donors, in a series of 22 Hodgkin’s disease patients and 6 patients with nonlymphomatous neoplasms. We found no significant difference in response between healthy controls and cancer patients, even in those with lymphomas (25). Hattler and Amos (14) did find that their cancer patients had significantly smaller reactions to lymphocytes from healthy donors than did healthy persons, but their patients and controls were not studied simultaneously. Three groups of investigators (1, 14, 44) made the interesting observation that when the lymphocyte transfer test was performed with lymphocytes from blood of patients who had carcinoma or lymphoma there was less reaction than was produced by lymphocytes from healthy donors tested simultaneously. If, as these investigators believe, the reaction to allogeneic lymphocytes is in part a graft-versus-host reaction, such a diminished response suggests that the lymphocytes of patients with neoplastic diseases are functionally defective. If, on the other hand, the lymphocyte transfer test is purely a host-versus-graft reaction, then these results would imply that the lymphocytes of these patients are less able to stimulate immune responses in an allogeneic recipient than are cells from normal persons. These results resemble the observation that skin grafts from carcinoma patients are rejected more slowly than skin from healthy donors (3, 43).

**NONSPECIFIC CELLULAR REACTIONS**

The term nonspecific cellular reactions is used here to include the participation of cells in those steps of specific immune reactions which are not restricted to specific antigens and the direct participation of cells in host defense reactions which occur without relation to antigenic determinants. The first of these categories would include the uptake and transport of previously unencountered antigen by macrophages, as discussed by Nossal in this symposium (35), and various reactions that occur as a consequence of the reaction of antigen and antibody, such as degranulation of basophils and contraction of smooth muscle cells. The second category includes engulfment of foreign matter or necrotic tissue by fibroblastic cells and the engulfing and digestion of microbes by polymorphonuclear neutrophils and macrophages. It is often impossible to distinguish between these two roles because much is still unknown about nonspecific defense mechanisms, about the steps in the initiation and expression of specific immune reactions, and about the interconversion of various wandering cells such as fibroblasts and macrophages. It is not surprising then that this aspect of immunology has received little attention in clinical research and that methods for such investigations are not well developed.

Studies of the transfer of delayed hypersensitivity suggest the existence of intermediate steps in the expression of cell-mediated immune reactions and the need for investigation of such steps. Injection of lymphocytes from blood of donors who were highly sensitive to tuberculin resulted in the transfer of sensitivity to healthy recipients, as evidenced by a delayed response to tuberculin when injected into the same area where the lymphocytes had been deposited, but the transfer of these same lymphocytes into patients with Hodgkin’s disease failed to transfer the tuberculin sensitivity in almost all cases (20, 33). These results suggest that the Hodgkin’s disease patients lacked some mechanism which must participate in the interaction of tuberculin and immune lymphocytes to bring about the inflammatory reaction of delayed hypersensitivity. However, similar studies in patients with carcinoma (14, 33) indicate that this defect does not commonly occur in nonlymphomatous neoplasia.

The cellular response to a nonspecific stimulus has been studied in cancer patients by Reubuck “skin window” techniques, in which the skin is abraded sufficiently to cause a slight exudate which is collected on glass coverslips in the standard technic (42) or collected in isotonic salt solution in quantitative modifications of this technic (38, 52). By both of these techniques we (8, 11) found that patients with advanced cancer often display an unabated polymorphonuclear exudation for 24 hours or more, in contrast to the conversion to a predominantly mononuclear cell response which is characteristic of normal persons. Hersch et al. (15) had similar results in acute leukemia patients and in carcinoma patients who were receiving chemotherapy, but the three untreated cancer patients in his series had normal responses.

The nonspecific phagocytic activity of the reticuloendothelial system was determined by Salky et al. (45) by measuring the rate of clearance of a lipid emulsion from plasma after intravenous injection. Carcinoma patients showed higher-than-normal phagocytic activity.

**REFERENCES**

9. Fairley, G. H., and Matthias, J. Q. Cortisone and Skin Sensi-
Immunology and Nonlymphomatous Cancer


Southam, C. M., and Goldsmith, Y. Effect of Nitrogen
The Immunologic Status of Patients with Nonlymphomatous Cancer

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