Relationships of Immunology to Cancer: A Review*

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I. INTRODUCTION
The term immunology brings to my mind the word glory, for glory is the word concerning which Humpty Dumpty exclaimed “a word means just what I want it to mean—neither more nor less.” The term immunology will be used here to embrace all those biological mechanisms by which a metazoan organism resists the pathogenicity of any noxious foreign thing. This broad definition is stressed because the term immunology is sometimes used as synonymous with serology or even to refer to antigen-antibody phenomena alone. In considering immunology as related to oncology we must not restrict our survey, because we are still groping for the mechanisms of resistance to cancer; in fact, we are still searching for proof that defense mechanisms against the neoplastic process do exist. Although our knowledge of immunology as related to cancer is imprecise and often speculative, it is nevertheless worthy of our consideration if for no better reason than that it demands the recognition of cancer as not merely a tissue or a cell but as a disease. Disease results from the interaction of a host and a pathogenic force, and thus any consideration of immunology in relation to cancer carries with it the implication that the host (the cancer patient) is not necessarily a passive supporter and victim of the neoplastic growth but may react to its presence. Any reaction of the host which tends to be detrimental to the continued growth of the cancer may be considered a defense

* Based on a talk presented at the Division of Medicinal Chemistry at the 134th meeting of The American Chemical Society, Chicago, September 11, 1958.

Received for publication October 5, 1959.
mechanism and comes within the broad field of immunology.

This review will attempt to consider this entire field. In such an undertaking omissions are inevitable, and inequities in emphasis are unavoidable because of the personal interests and prejudice of the author. For such, tolerance is requested. Since references to such a massive literature cannot be complete, the attempt has been to include such references as will in turn guide the interested reader to a more ample coverage of the literature. References to previous reviews are therefore frequently made, and references to original work are used for more recent or less extensively surveyed reports, or when documentation of details seems necessary.

II. REVIEW OF HOST DEFENSE MECHANISMS

A. General

The mechanisms by which a host organism reacts so as to produce a condition detrimental to an invading pathogen and, hence, conductive to the continued survival of the host are of many types. They may be chemical, as so well exemplified in antibodies which form chemical union with portions of the pathogens; or physical, as in the formation of dense barriers by the building up of scar and inflammatory tissue which inhibit the spread of a pathogen into new areas, and by fever which inhibits an invading pathogen by creating a temperature which is unsuitable for continued propagation of the pathogen while not detrimental to the host. They may be specific, i.e., directed against that specific pathogen; or, nonspecific, i.e., equally effective against a variety of pathogens. They may be cellular or humoral, i.e., mediated by cells or by noncellular "humors."

B. Cellular Defense Mechanisms

The polymorphonuclear neutrophilic granulocytes ("polys") are the most dramatically defensive cell. They can readily be observed to engulf bacteria and other particulate matter. They accumulate in tremendous concentration locally and in the blood in response to acute inflammation. The tissue macrophages which may be the same as or closely related to the monocytes of blood and lymph nodes are less theatrical but possibly even more efficient as a defense mechanism, since they too concentrate in inflammatory areas, engulf debris, and stay around to finish the job which the polys so dramatically initiate. Even the erythrocyte may function indirectly in host defense by adsorbing onto its surface viruses or bacteria which are thereby rendered more susceptible to phagocytosis (128). The fibroblast is an impressive but mysterious cell which, like Zorro or Superman, is inconspicuous or even unidentifiable in ordinary life but jumps into effective action when need arises, surrounding areas of injury by an increasingly dense tissue barrier or capsule which mechanically limits the extent of pathology. Lymphocytes or plasma cells or both are producers of antibodies. They do not directly attack foreign agents but probably accept into themselves particles of the foreign material (antigen) and may synthesize or modify a pre-existing globulin molecule in such a way that it will combine specifically with and usually to the detriment of that foreign substance. The basophilic and eosinophilic granulocytes of the blood and tissue remain a puzzle. The fact of their concentration in certain areas of inflammation suggests that they have a defensive role, and yet they are not phagocytic nor are they sources of antibody. The eosinophil is a major producer of histamine, and the basophil (or at least the rather similar tissue mast cell) produces both serotonin and histamine. These facts, as well as their occurrence in allergic type hyperimmune reactions, seem adequate evidence that they are in some way involved in host-pathogen interrelationships, although the exact mechanism and importance of these cell types remains obscure.

C. Noncellular Defense Mechanisms

1. Nonspecific mechanisms.—Noncellular factors are mostly humoral. The usage of this term has evolved through the days of Hippocrates and Galen and Samuel Bulwer, so that now it is essentially synonymous with extracellular fluid. From the standpoint of laboratory investigation human factors are serum factors, but the broader term is significant because it recognizes a broader field of distribution and reaction for such factors and the possibility that serum may not provide a sample which is representative of the whole.

The nonspecific humoral defense mechanisms include complement, properdin, certain hormone-like factors, and quite probably a whole host of as yet unknown factors. There is no doubt of the participation of nonspecific humoral factors in host-pathogen interactions, but the accomplishment of such reactions in terms of host welfare remains obscure. The activity of the complement system is most clearly demonstrated in antibody hemolysis. The reaction of antibody with the erythrocytes occurs whether complement is present or absent, but, if absent, cell destruction does not ensue. It is difficult to see how red cell destruction can be a defense mechanism; but this perhaps artificial phenomenon is the easiest to work with in the labora-
Complement (40, 105, 152) is a complex of at least four and probably 6 or more (13, 28, 106) components which are unromantically known as C1, C2, C3, C4, etc. They are distinguished on the basis of biochemical characteristics such as destruction by ammonia (C4), adsorption onto zymosan (C3), and precipitation (C1) or failure to precipitate (C2) when dialyzed against water. C1 is a proesterase (106) and is the component which is combined (fixed) first in the reaction of complement with an antigen-antibody complex. The proenzyme is activated in this process. C4 reacts into the complex next, followed by C2, and in the process they are said to be irreversibly destroyed by the C1 esterase. Finally, C3 reacts into this antigen-antibody-complement complex (148), and it is only after all the components of complement have reacted that the characteristic antigen-antibody-complement reaction (e.g., hemolysis) is seen. The presence of magnesium ions is an absolute requirement for these reactions, and calcium ions are required for maximal reaction.

In 1954 further confusion was introduced and further interest was aroused in nonspecific serological factors by the discovery of properdin by the late Dr. Louis Pillemer (139, 142). Properdin, like the complement components, is a serum protein; but, unlike complement, properdin is not known to participate in any antigen-antibody reaction. It does react with a rather wide variety of neutral polysaccharides of microbial, animal, and plant origin, including the yeast product "zymosan" (142). Its discovery was so long delayed because its separation from C3 depends on incubation with zymosan at 15°—17° C. instead of 37° C. Properdin is not an antibody in the usual sense of that word. It is a constantly present serum component which is not specific in the choice of polysaccharides with which it will react; nor is its level influenced (except transiently) by the administration of polysaccharides. However, the reaction of properdin with zymosan bears an interesting parallel to antigen-antibody reactions in that the properdin-zymosan complex will also fix complement components in the same order and with almost the same characteristics as does an antigen-antibody complex. In fact all the known reactions of properdin necessitate the participation of the four components of complement and magnesium ions. This resemblance to antigen-antibody reactions prompted Pillemer to refer to properdin as perhaps "a Primordial type of ‘antibody’" (138); and more recently Nelson (129) has considered it a "natural antibody." The properdin system (i.e., properdin plus complement plus the divalent ions), upon reacting with certain viruses (9, 53, 56, 86), bacteria (202), and protozoa (48), causes destruction of the microorganisms, and thus the properdin system merits inclusion in our catalog of host defense mechanisms. Excellent reviews of properdin have recently been published by Eyquem (45) and by Isliker (82).

Another nonspecific humoral factor is leukotaxine, described by Menkin (190) as a material produced in inflammatory tissue, presumably during the process of cell necrosis, which has the capacity of causing leukocytosis, increasing vascular permeability in the region of the inflammation, and thereby concentrating the leukocytes in the inflammatory area. The material has not, to my knowledge, been studied by other investigators. Other, even less well understood, factors are known to exist. Kidd discovered a tumor-inhibiting effect of guinea pig serum which is neither properdin nor any of the four recognized components of complement (76, 90). Some human sera contain a heat-labile factor which enhances certain virus-neutralizing antibody reactions. This effect is apparently not due to specific antibody or complement or properdin (174).

The amorphous ground substance of connective tissue is an extracellular material, viscous in consistency and of high polysaccharide content. Its importance in the interplay of host and pathogen was clearly demonstrated in the studies of Duran-Reynals which demonstrated that "spreading factor" (hyaluronidase and perhaps other enzymes which diminish the viscosity of connective tissue ground substance) enhanced the spread of tumor-causing and other viruses from a subcutaneous inoculation site (39).

2. Specific mechanisms.—Antibody is serum gamma globulin which has been specifically modified as a result of the intrusion into the body of a foreign material (antigen)—modified in such a way that it will react specifically with that same foreign material and no other. The degree of this specificity is extremely fine. It would seem axiomatic that the determinant of antibody specificity is chemical structure, although there is little knowledge concerning precisely what changes in globulin structure determine this specificity. There are examples of antibody reacting (cross-reacting) with a material of completely different source than the stimulating antigen. For example, if rabbits are given injections of a suspension of a guinea pig kidney, the resulting antibody will react not only with guinea pig kidney but also with sheep erythro-
cytes, with mouse brain, and even with some strains of pneumococci. These are called heterophile antibody reactions (literature reviewed in reference 173) and are thought not to violate the rule of specificity, but rather to indicate that there are identical antigenic groups in each of these materials of diverse origin. Most known antigens are protein, but some polysaccharides are antigenic (72), and lipides (15), nucleic acids (137), and even simpler compounds (96, 97) may function as haptenes, i.e., when administered together with a protein they may dictate the limits of specificity.

It seems well established that more than one type of antibody molecule may be produced in response to a single antigen, but these differences are very slight (85). For present purposes it is sufficient to assume that all antibodies produced in response to a single antigen will react only with the appropriate antigen. Antibody may be detected however, by a variety of reactions which vary greatly in type and sensitivity. Consequently, antibodies are often referred to according to the detection technic as if they were of many different types. For example: agglutins (or agglutinating antibodies), precipitins, lysins (or cytolysins, or hemolysins), opsonins, complement-fixing antibodies, neutralizing antibodies, protective antibodies, antitoxins, agglutination-inhibiting antibodies. Antibodies circulating in the blood stream reach almost every part of the body and thus can react with extracellular antigens. The prophylactic and therapeutic effect of specific antibody for many infectious diseases is common knowledge.

In addition to the well known concepts of passive immunity (conferred by administration of antiserum) and active immunity (produced in response to administered antigen), the concept of "adoptive immunity" has recently been introduced. Adoptive immunity is continued production of antibodies by lymphoid cells transplanted from an actively immunized donor to a recipient never directly exposed to that antigen (59, 123, 154).

Allergy is characterized by a highly specific host reactivity for certain antigens (allergens), and in many allergic diseases such as hay fever, asthma, and serum sickness antibody which reacts specifically with the causative allergen can be demonstrated in the serum. In other allergic states, such as poison ivy sensitivity or tuberculin sensitivity, circulating antibodies are not demonstrable by present technics, but highly specific tissue sensitivity is demonstrable by skin tests. The tuberculin test is the prototype. It causes no immediate reaction but after a delay of 24-72 hours causes a local inflammatory lesion characterized by edema and infiltration of mononuclear eosinophile leukocytes and mast cells. This is known as the delayed hypersensitivity type of response. That this host reaction can function as an effective defense mechanism is demonstrated by the prophylactic value of BCG vaccination against tuberculosis. It seems possible that the mechanisms are similar to those in sensitivity states characterized by serum antibody, but that the antibodies are concentrated on or in cells such that no detectable excess escapes into the circulation. The presence of antibody-like activity on cells has been demonstrated by transmitting sensitivity to nonsensitized individuals by transfer of lymphocytes or blood leukocytes (97, 103, 154). In histologic appearance, in the absence of detectable circulating antibodies, and in transferability through cells, the delayed hypersensitivity reaction resembles the immune reaction to tissues such as is seen in second set tumor transplant. These parallels (104) suggest the possibility that the mechanisms of rejection of transplanted tumors may be the same as delayed hypersensitivity mechanisms, and thus the phenomenon becomes of interest to the oncologist.

Specific immune tolerance is a paradoxical phenomenon in which the exposure of a fetal or newborn animal to an antigenic material results in subsequent acceptance of that particular antigen as if it were a normal body constituent even though in actuality it is a foreign and possibly noxious agent (18, 19, 118). Although it may seem paradoxical to include such a phenomenon among immune mechanisms it appears that such reactions obey the rules of antigenic specificity as seen in more conventional types of immune phenomena. Most of the work with tolerance has concerned skin grafting procedures rather than nonliving antigens or microorganisms. However, it seems possible that a mechanism which will allow the acceptance of homotransplanted skin as if it were a normal body constituent might also permit the unopposed persistence, even propagation, of other tissues or microorganisms if the initial exposure occurred during embryonic or neonatal life. It is conceivable that some such phenomenon accounts for the persistence of viruses through successive generations of individuals, as is known to occur with Rickettsiae (84) and several oncogenic viruses (20, 21, 69).

The phenomenon of tolerance is an area of very active investigation by many laboratories at the present time and should yield interesting results of basic as well as clinical import in the next few years.
D. FACTORS INDIRECTLY INFLUENCING HOST DEFENSE

Several other factors which influence incidence, time of appearance, or rate of progression of cancer in humans or experimental animals are known. They are worthy of mention in the present discussion because some or all of them may have these effects because they exert influences upon host defense mechanisms. It seems probable that none of these is in itself a mechanism of host defense, but rather that the effects are mediated through the cellular and humoral mechanisms discussed above.

1. Heredity.—Genetic factors clearly influence susceptibility to infection and to other toxic agents. The classical experiments of Webster (204) by which the PRI (Princeton Rockefeller Institute) resistant and susceptible lines of mice were bred by selection from a common stock illustrate the importance of genetics in resistance to bacterial and viral disease. It is common knowledge that various inbred lines of mice have different susceptibility to oncogenic viruses such as Bittner’s milk factor, Gross’ leukemia, and Friend’s leukemia. In clinical medicine, various racial groups have marked differences in incidence of certain types of cancer, even when living in the same geographic area (148, 186, 212). While such differences in racial incidence of cancer may result from cultural factors influencing exposure to carcinogetic substances, genetically determined differences in susceptibility have not been excluded. Genetic studies of cancer in human families suggest that genetic as well as environmental factors influence cancer risk (182, 200). The genetic makeup of an individual cannot, of course, be altered, and hence this factor appears to have little bearing on the problem of cancer therapy or prophylaxis in man.

2. Hormones.—Hormones are also known to play a role in host resistance. The most obvious example is the greater propagation and pathogenicity of certain bacteria and viruses in a variety of experimental animals after intensive treatment with adrenocortical steroids or adrenocorticotropin (ACTH) (195). Agosin et al. reported that cortisone treatment induced metastases of a transplanted mouse tumor (2). It is known that the adrenal steroids and ACTH cause depression of lymphocytes and eosinophils (73), inhibit antibody formation (134) and phagocytosis (150), and retard healing of wounds (147) and abscesses (181). Cortisone has no apparent effect upon the rate of growth of Bunyamwera virus or cytopathogenesis in human fibroblast tissue cultures where no defense mechanisms are operative. Therefore, while it is conceivable that cortisone and possibly other hormones have a direct influence upon the susceptibility of cells to damage by viruses or other noxious agents, it seems more probable that they affect host-pathogen relationships through the previously discussed cellular and humoral defense mechanisms.

3. Nutrition.—Nutrition affects host defense mechanisms. Many vitamin deficiency states decrease antibody-forming capacity in experimental animals (8). Serum complement levels are reduced in rats with pyridoxine deficiency (8). Vitamin A deficiency diminishes resistance to infections due to epithelial changes (17). Vitamin antagonists or restricted diets which bring about deficiency states of folic acid (190), pyridoxine (191), or riboflavin (187) inhibit growth of various mouse tumors. Dietary restriction is said to decrease frequency and retard time of onset of spontaneous tumors in mice (131). In experimental animals, protein depletion may diminish the rate of growth of transplantable tumors but does not prevent the progressive course (198). Folic acid antagonists are therapeutically useful in the chemotherapy of acute leukemia in man. No causal relationship of diet to the spontaneous occurrence of tumors in man or animals has been recognized, but the possibility that nutritional factors may be related to differences in cancer incidence patterns in different geographical, racial, or religious groups cannot be excluded.

4. Age.—The age of a mother at the time of parturition may influence cancer susceptibility of the offspring. Strong (188) presented data indicating a decreased susceptibility to chemically induced sarcomas in mice born in late litters. Law (102) reported that frequency of spontaneous leukemia was lower and time of onset later in mice born of old mothers. No study relating human cancer to maternal age has yet been published. The incidence of acute leukemia is increased in children with mongolism (85), and the frequency of mongolism increases directly with age of the mother at time of delivery (150), but it does not necessarily follow that there is any causal relationship between maternal age and leukemia. If any such relationship does exist in man these observations suggest that it might be the reverse of that reported for mice.

III. ANTIGENIC ANALYSIS

In basic research, antibody technics provide poorly understood but extremely sensitive tools for the detection of biochemical differences. If differ-
ences between normal and neoplastic cells were detected by these technics, the exploitation of such differences to achieve specific antineoplastic effects would be attempted by all available methods. Such methods would include but would not be limited to specific immune mechanisms. It is conceivable, for example, that antigenic analysis might reveal differences in polysaccharide, amino acid, or nucleic acid haptenes against which specific antimetabolites might be prepared.

Antigenic analysis is an old approach to cancer research—a much traveled path liberally littered with a voluminous literature. The older work can be brusquely evaluated as revealing no qualitative and no consistent quantitative differences between cancer tissue and comparable normal control tissue (11, 71, 182, 210, 217). The problems in antigenic analysis of tissues are great and are readily apparent. Cancer tissue is a mixture of cancer cells, normal cells, and noncellular constituents. The choice of a normal tissue as a control for tumor is difficult if not impossible because of marked differences between normal and neoplastic tissues in absolute concentration and relative proportion of each of these constituents. Even within a single cancer cell there are normal constituents which may obscure the cancer antigen in both in vitro tests and when used for antiserum production. Current renewal of interest in this area derives from the development of technics which may circumvent these difficulties.

A. METHODS OF ANTIGENIC ANALYSIS

1. Immunologic technics.—One approach is the use of new, more sensitive, and more discriminating technics for the detection of antigens and antibodies. The adsorption of antitumor antisera with normal tissues to remove antinormal components of the antiserum is a relatively recent concept which is now used almost routinely. Using this technic and standard complement-fixation methods Korosteleva (93) reported that specific cancer antigens were demonstrable in human tumors and that the same cancer-specific antigen was sometimes demonstrable in tumors of different individuals, but that there was no cancer antigen common to all human cancers. The extremely sensitive hemagglutination technic of Boyden (25) utilizes antigens adsorbed onto tannic acid-treated erythrocytes to make visible antigen-antibody reactions which are often undetectable by older methods. The Ouchterlony technic (29, 70, 92) separates and identifies antigens on the basis of differential diffusion through an agar gel. An electrophoretic separation of antigens is accomplished by the gelelectrophoresis technic (215). The radioiodine-labeled (145, 207) and the fluorescein-labeled (78, 130, 205) antibody technics are not more discriminating in an immunologic sense but offer previously unavailable accuracy in the anatomical localization of antigens in tissues and cells. Zilber (218) reported on use of the phenomenon of immunologic tolerance to render an experimental animal nonresponsive to normal tissue antigens but still capable of producing antibodies to abnormal cancer antigens. This ingenious approach for differentiation of closely associated antigens deserves further study but will probably prove difficult of application. In this laboratory it has been very difficult to induce tolerance to heterologous tissues. Tissue cultures were used for detection of cytotoxic antibodies as early as 1927 (110), but this approach became practicable only with the advent of stable cell lines (58, 117, 128, 169). This technic offers the advantage of a single cell type, thus reducing somewhat the complexity of antigens to be expected in whole tissue preparations. Salk (162) introduced the time-saving modification of indirect detection of cytopathology through pH differences instead of microscopic examination. Zilber (216) has also used anaphylaxis in guinea pigs after desensitization to normal tissues as a means of detecting specific cancer antigens, and others (30, 63, 119) have used the basically similar Schulz-Dale technic. Takeda (192) has utilized rate of rejection of repeat ("second set") heterotransplants to study antigenic relationships between various tumor lines. Theoretically these last three technics, based on the active immune status of an experimental host, should not be more discriminating than previously used methods; but final evaluation awaits further studies.

2. Purification of antigens.—A second approach is the better separation of cancer antigens from normal antigens prior to injection into animals for antibody production, or prior to use in tests in vitro. Rapport and Graf (149) have extracted a nonphosphorus-containing lipide (sphigmo lipide) which appears to be a haptene in that it does not react as an antigen by itself but does exhibit antigenic specificity when mixed with other lipides and protein in a complement-fixation test. These studies are not yet sufficiently advanced to permit final evaluation of qualitative specificity or the degree of cross-reaction between various normal and tumor tissues, but the normal tissues studied thus far contained little or none of the "cytolipin II" found in several types of human cancer. Recent studies from Japan report isolation of a phosphorus-containing lipide haptene from cancer tissue, but detailed data are not yet available (94). A phospholipid haptene has also been demon-
The selective concentration of cancer-specific antigens is illustrated by the studies of Toolan (198), who separated the transplantable human epidermoid carcinoma #3 (H.Ep. #3) into five subcellular fractions by differential sedimentation techniques. Her results indicate a high degree of antigenicity in the "fluffy layer," which appears to consist principally of endoplasmic reticulum (ergastoplasm). Similar studies with mouse tumors (38, 113) also revealed antigenic activity in cytoplasmic factors. These observations point to cytoplasmic rather than nuclear constituents as a likely site in which to look for antigenic components characteristic of the neoplastic cell. The fact that these fractions are thought to have a high lipoprotein and low nucleic acid content is of particular interest in view of the lipide antigens obtained by chemical separation technique.

Bjorklund (22) has suggested and applied the interesting concept that if cancer tissues contain cancer-specific antigens in common, such antigens would not be diluted in a tissue pool, whereas antigens unique to individuals would be diluted in proportion to the number of individuals represented in the pool. Thus, if the basic concept is correct, a pool of many human cancers would in effect accomplish a selective concentration of cancer-specific antigens.

The development of mass tissue culture techniques and the development of twenty or more human cell lines which can be grown in continuous passage promise to solve the problem of mixed tissue by providing a cell mass consisting of a single cell type. Exploration of this source of tissue for immunological studies has barely been initiated because of production problems and difficulty of obtaining adequate normal cell cultures for controls.

3. Choice of experimental host.—Another method of improving antigenic analysis studies is better experimental control of the host in which antibodies are produced. The use of the same species for the source of both antigens and antibodies simplifies antigenic analysis because it eliminates reactions to all those antigens which are common to all the individuals of a species. Even within a species, the complexity of reactions can be further reduced by the use of animals which are genetically (and hence antigenically) very similar. This approach is illustrated by the studies with the EL4 and EL5 mouse leukemias (60), which indicate that the leukemic cells contain antigens which are not present in normal tissues of the host (C57BL mice) but which are common to the two lines of leukemia. Contrariwise, studies of this type by Sachs and Feldman (161) with several tumors of C3H and DBA mice failed to reveal any antigens in tumor which were not also present in normal tissues of the hosts. The studies of Hirsch et al. (79) using low passage tumors of inbred mice also suggest that tumors may contain antigens foreign to their isologous host. For the study of human cancer this approach is possible only through the cooperation of human volunteers. In such studies (175) it has been found that there is cross-antigenicity between the few human cancer cell lines which have been studied, and the very limited studies of normal cells showed no evidence of common antigens between normal (fibroblast) and neoplastic (epidermoid) cell lines. These studies are not sufficiently extensive or intensive to permit uncritical acceptance, but the results to date are consistent with the hypothesis that there may be unique cancer antigens—even in human cancer—and that such antigens may be common to cancer of different individuals.

IV. ARE THERE HOST DEFENSES AGAINST CANCER?

The most basic problem upon which rests all hope for clinical applications of immunological methods is whether host defense mechanisms against cancer actually exist. As yet there is no answer to this question, but both clinical and experimental observations seem to indicate that man may indeed have mechanisms by which he resists neoplastic disease.

A. CLINICAL OBSERVATIONS SUGGESTIVE OF HOST DEFENSES AGAINST CANCER

There is marked variation in the clinical behavior of cancer even within a single histopathologic type and within groups of patients which are apparently homogeneous as to sex, age, and race. There is frequently a lack of correlation between the clinical course of cancer and the estimated "grade of malignancy" as judged by histopathologic criteria. Some cancers have a prolonged preclinical stage. This was documented for lung cancer by Rigler's (153) retrospective study which revealed identifiable lesions as long as 5 years before clinically apparent disease. A similar situation for
cancer of the prostate is indicated by the fact that it is at least 4 and possibly 10 times more frequent at autopsy than is apparent from clinical evidences of the disease (80). Cancer metastases (thyroid and breast cancer are good examples) may lie dormant or latent for years and even decades before exhibiting a growth spurt with resulting clinical disease. In situ carcinoma of the cervix may apparently undergo spontaneous regression as judged by disappearance of histologically proved lesions (914). Spontaneous remissions will occasionally occur even in widely disseminated cancer (7, 48, 52, 88, 151, 185). Recent cytologic studies have indicated that cancer cells are present in blood (42, 144, 168, 165), lymph (308), pleural and peritoneal fluids (188) and in operative wounds (168) much more frequently than the subsequent development of metastases would indicate, indicating that not all loose cancer cells are capable of establishing a metastatic lesion.

Occasional cancers are accompanied by a marked inflammatory infiltrate, for example in inflammatory carcinoma of the breast and occasionally in prostate carcinoma. This is a local host reaction to the presence of tumor which might be interpreted as defensive. Berg (16) presented evidence that in human breast cancer the presence of a plasma-cell reaction is prognostic of a favorable clinical course. Lymphoid (184) or eosinophilic (218) infiltrations are stated to be favorable prognostic signs in gastric cancer.

Grace and Dao (61) reported that skin tests with antigen prepared from their own tumor tissue produced wheal formation in patients with inflammatory breast cancer (indicative of serum antibodies) but not in patients with noninflammatory cancer. Graham and Graham (65) reported that complement-fixing antibody against their own tumor antigens was demonstrable in serum of patients with gynecological cancers of favorable prognosis.

B. EXPERIMENTAL STUDIES SUGGESTIVE OF HOST DEFENSES AGAINST CANCER

The growth of a human neoplasm when transplanted to experimental animals or human volunteers does not always parallel its aggressiveness in the original patient. Toolan’s human sarcoma #1 (H.S. #1) grows rapidly in conditioned rats and hamsters and in chick embryos, whereas it was a circumscribed lesion in the patient and has not recurred 6 years after local excision (35, 198, 197). Conversely, most highly malignant human tumors have not been transplantable at all in a heterologous host. (This does not deny the fact that some tumors do show parallel growth potentials in original hosts and on transplantation, as illustrated by Toolan’s H.Ep. #3 tumor (196) and by the extensive studies of Greene (67)). If, however, the relative growth capacity of a series of transplanted cancers does not parallel their growth characteristics in their original hosts, it is clear that factors other than innate capacity for reproduction must be operative and that these factors must either be resident in the host or must have arisen after transplantation.

The administration of neutral polysaccharides of diverse plant, animal, and microbial origins to experimental animals profoundly affects resistance to bacterial infection and growth of tumor transplants. Large doses of zymosan (a crude polysaccharide from yeast) or bacterial polysaccharides transiently decreases resistance of mice to gram-negative bacterial infections (140, 160) and causes increased growth and lethality of Sarcoma 180 in mice (27), human epidermoid carcinoma #3 in rats (135), and a human intestinal adenocarcinoma in rats (74). Conversely small doses of polysaccharides increase resistance of mice to infection (81, 98, 99, 100, 158, 160) and increase rejection of Sarcoma 180 (26, 27) and Sarcoma 37 (114) in mice, Yoshida sarcoma in rats (91), and human sarcoma #1 in conditioned rats. The effect of polysaccharides on susceptibility to infection and tumor growth varies inversely as its effect upon serum properdin levels (26, 98, 99, 141), suggesting the possibility that properdin or some other defense mechanisms which fluctuate in parallel with properdin may be directly involved in the tumor rejection mechanism.

Kidd has demonstrated in guinea pig serum a nonspecific humoral factor which inhibits the growth of a rat lymphosarcoma (90). This work, which has recently been confirmed (8, 76), suggests participation of humoral factors other than properdin or complement in tumor rejection.

In recent studies with established lines of human cancer cells (176), homotransplants in healthy recipients elicited an acute inflammatory reaction and were promptly rejected after a brief


M. Aizawa and J. Palm, personal communication.

period of propagation, as would be expected. In contrast, the same type of transplants in patients with advanced cancer did not elicit an inflammatory reaction and continued to propagate for 4–6 weeks and often longer before rejection started. When rejection did occur, the cellular response was of the mononuclear type. Apparent delay of rejection of direct homotransplants of human cancer tissue (rather than established human cell lines) and of human adult or embryonic skin has also been reported by Grace (68) and by Snyderman (170). These observations are interpreted as indicating that the patient with advanced neoplastic disease is deficient in certain mechanisms by which homotransplanted tissues are rejected. The postulated defect does not appear to be in ability to produce circulating antibodies or to mobilize a leukocyte reaction (176). Collateral studies indicate that these same patients have a deficiency of serum properdin (178), but there is no evidence that the properdin deficiency is the cause of the defective rejection response.

None of these experimental studies proves that there is host resistance to spontaneous cancer, because each deals with transplanted rather than spontaneous cancer, and it must not be assumed, although the hypothesis is worthy of consideration, that the same mechanisms which participate in the rejection of transplanted tumors can also restrain spontaneous neoplasms.

In spite of the complete absence of proof, the existence of so many suggestive bits of clinical and experimental data sustains the working hypothesis that cancer is not a wholly autonomous growth but may be susceptible to restraint by host mechanisms.

V. IMPLICATIONS OF IMMUNOLOGY FOR CLINICAL ONCOLOGY

The implications of immunology for problems of clinical cancer are many and are intriguing. At present, however, they are theoretical at best and often purely speculative. Under the headings of prevention, detection, prognosis, and treatment we will consider first theoretical aspects and then experimental studies at laboratory and clinical levels.

A. CANCER PREVENTION—THEORETICAL CONSIDERATIONS

The possible implications of immunology for cancer prevention reside in the possibilities of increasing the efficacy of postulated nonspecific defense mechanisms, or inducing specific active immunity. Active immunization against transplantable tumors in experimental animals has been accomplished many times, but most of this work has no carry-over to the problem of human cancer, because heterologous or homologous cancer transplants are obviously foreign to and hence antigenic in the recipient. The possibility of inducing specific active immunity against the development of spontaneous cancer in man demands that there exist unique human cancer antigens. These might reside in the neoplastic tissue or in the oncogenic agent which might or might not persist within the cancer which it induces. It further demands that the number of these hypothetical cancer antigens be sufficiently small so that immunization of a population against a manageable number of these antigens would provide immunity against the development of a considerable proportion of possible antigenic types of cancer. These unique antigens would not necessarily be protein nor complete antigens. The possibility exists that haptenes which are unique to cancer could be made antigenic by combining them with suitable carrier antigens. One exciting aspect of the virus theory of cancer etiology is its implication for specific immune prophylaxis. It is clear that if a finite number of viruses were the causative agents for any considerable proportion of human cancer, then these viruses would satisfy the requirements for specific cancer antigens. Last, however, there should be any over-optimism in interpretation of this suggestion, it should be recalled that to attempt immunization against a large number of specific cancer antigens would be analogous to attempting simultaneous immunization against a wide variety of infectious diseases. A final note of pessimism is impelled by the knowledge that, if active immunization against spontaneous cancer is achieved at the laboratory level, the clinical field trials which would be necessary to establish its validity in the general population might well require more than two decades of observation to permit adequate evaluation. There has apparently been little research work aimed directly at this approach to the cancer problem, although such studies could be undertaken in experimental animals such as mice which develop spontaneous cancer. The cancer homotransplantation studies performed at the Ohio State Penitentiary (175, 176), although not designed with this objective in mind, will be evaluated from this standpoint by comparing the eventual cancer incidence in men who have been inoculated with a variety of human cancer cells and in a parallel group of paired controls.

B. CANCER DETECTION

The application of immunologic methods to cancer detection is theoretically possible (a) by the
detection of cancer-specific antibody in serum, (b) by the detection of cancer-specific immune reactions of tissue (e.g., skin tests), or conversely (c) by the demonstration of cancer-specific antigen or hapten in a readily sampled material such as serum or urine, and finally (d) by the detection through immunologic technics of changes in body composition or reactivity which indirectly indicate the presence of cancer. Many past and present investigations fall into these categories.

1. Serum antibody.—Sporadic attempts have been made to demonstrate cancer antibodies in the serum of cancer patients, with the use of various crude preparations of human cancer tissue as antigen. Reports concerning the detection and significance of such reactions have been presented with various degrees of enthusiasm but quite uniformly without conviction (see bibliography in reference 66). A clinically useful test would require a widely distributed cancer antigen, specificity of the reaction for cancer, and a high degree of sensitivity. The prospects for such a test seem discouraging at present, but studies using more purified antigens or more discriminating serological reactions (as discussed under "antigenic analysis") will continue to be of interest.

2. Skin tests.—Skin tests for cancer diagnosis by detection of sensitivity to cancer antigens have not been investigated to the knowledge of this writer. The skin testing technic presents the same problems of antigenic specificity as do in vitro techniques and has as disadvantages the necessity of patient participation and the possibility of detrimental reactions. It does, however, offer the possibility of detecting tissue-fixed antibody through the delayed hypersensitivity type of reaction, which is usually unaccompanied by detectable serum antibodies.

3. Circulating antigens.—Since a search for antibodies—whether in serum or tissue—presupposes that the cancer patient has been exposed to cancer antigens and has reacted with development of specific antibodies, it might be supposed that this approach is doomed to failure, since such a test would necessarily fail to detect those patients who do not produce an adequate antibody response to their developing cancer. It seems logical, then, to attempt to detect a cancer-specific antigen which might be released from the cryptic cancer into serum or other body fluid. This approach was attempted with suggestive results by Mann and Welker (115) by a precipitin technic and a rabbit antihuman cancer serum. Makari (112) and Burrows (30) have recently reported on this same type of study, with the sensitive but cumbersome Schulz-Dale technic used for detection of the antigen-antibody reaction. They reported data interpreted as indicating circulating cancer antigens or haptenes in a very high percentage of cancer patients and rarely in patients without cancer. The specificity and sensitivity of these technics for cancer, and its possible use for cancer detection, cannot yet be evaluated but certainly merit further investigation.

4. Indirect immunologic technics.—The fourth approach has likewise failed to yield any test for cancer detection, but is illustrated by studies of Kahn’s “universal serological reaction” (109), heterophile reactions (178), trichina precipitins (180), C-reactive protein (64, 211), and Abderhalden reaction (89), and the current studies of serum properdin (side infra).

An admission of pessimism seems appropriate, because a cancer test which is based on immunologic (or chemical) methods will be positive only if the cancer is liberating something into or removing something from extracellular fluid in quantities sufficient to yield a detectable abnormality. It seems unlikely that this would occur sufficiently early in the course of disease in most people to permit detection in time for effective treatment. However, the need for better cancer detection methods is so great that studies in this direction certainly will and should continue.

C. Prognostic Tests in Cancer

It is somewhat easier to conceive of useful immunologic methods for cancer prognosis, for the very reason that they seem unlikely for cancer detection. As cancer grows, no matter how inaccessible its location, it would be expected to liberate or to remove various materials which might be immunologically detectable in direct proportion to the total cancer mass, and thus the fact of demonstrability and the degree of such changes would roughly correlate with prognosis—i.e., they would correlate with prognosis to the same extent that cancer mass correlates with prognosis, which is not necessarily close. Studies of serum properdin levels1 (44, 47, 127, 157, 159, 178) suggest such a correlation, but the data are not yet sufficient for one to hazard a guess concerning the possible prognostic importance of properdin determinations in cancer patients.

D. Immunologic Approaches to the Treatment of Cancer

1. By specific immunologic mechanisms.—The utilization of specific immune mechanisms for cancer treatment rests on the possibility that there may be a unique cancer antigen—otherwise, spe-
specic immune mechanisms would react detrimentally against normal as well as tumor cells. It is also necessary that every individual's cancer be not unique, but rather that cancer fall into a finite number of antigenic groups, comparable to the causative agents of infectious disease. A third necessity is that the unique cancer antigen persists in or on every cancer cell throughout the course of the disease. If some human cancer were found to be caused by a virus and if a specific antibody against that virus could be prepared, it would not be effective if (as has been suggested) the virus disappeared after the neoplastic transformation had occurred, or if the virus reverted to an incomplete form such as nucleic acid which was incapable of reacting with antibodies. Still another problem is the possibility that the hypothetical unique cancer antigen against which the antibody must act is situated intracellularly, and thus may be inaccessible to the action of antibodies. There has been no clear demonstration of effective penetration of serum antibodies into a cell. The evidence from infectious diseases fits this pessimistic assumption. Administration of antiserum is therapeutically effective when the pathogenic antigen is extracellular—as occurs in many diseases due to bacteria or bacterial exotoxins; but if the pathogen is intracellular, as in virus infections, a specific antiserum is generally ineffective. This inability of circulating antigen to eliminate intracellular virus is illustrated in clinical experience by recurrent herpes simplex, and in the laboratory by the observation, according to the fluorescein-labeled antibody technic, that West Nile virus may persist (and presumably propagate) within cancer cells for weeks after circulating antibodies have appeared (177).

The approaches to cancer treatment by specific immune mechanisms might be by active or passive immunization. Active immunization attempts would require inoculation of the patient with material containing the unique cancer antigen. The source of such an antigen presents little problem in the patient who already has neoplastic disease because his own cancer tissue would presumably contain the cancer antigen and the normal tissue components within the cancer tissue would not be antigenic in the same individual. However, the theoretical objections are formidable.

To consider therapy of the cancer patient through active immunization demands the unlikely assumption that a patient who has cancer (and who therefore is already exposed to a maximal antigenic stimulus and has failed to produce an effective specific immune response) nevertheless still has the capacity of responding to a further stimula

treatment could be used in an early stage of cancer, as would be logical if an effective agent were available. The serum donor would presumably be an animal such as horse, sheep, or rabbit, and thus the patient’s treatment would be limited by sensitization to the heterologous serum protein. The latter problem could be minimized by production of the antiserum in humans, but even if such a procedure were justifiable on an experimental basis the probability of producing an effective antiserum seems poor because serum antibodies have usually not been detectable in recipients of homologous tissue antigens. Sumner and Foraker (191) reported regression of melanoma in a patient given whole blood transfusions from a donor who had experienced spontaneous remission of melanoma. If this was truly a cause-and-effect relationship it may represent a therapeutic effect of serum antibody or cell-fixed antibody against melanoma.

The experimental data concerning antibody response to tissue antigens and the effect of active immunity or antibody administration on the growth of tumors are voluminous, perplexing, and apparently conflicting. In considering this type of investigation, it is imperative to keep in mind the relationship between the transplanted tissue and the recipient. This relationship is termed heterologous when tissues of one species are transferred to a recipient of a different species. It is homologous when donor and recipient are genetically different individuals but of the same species. It is isologous when donor and recipient are genetically identical (at least phenotypically identical). This situation exists in identical twins and theoretically in closely inbred strains of mice. It is autologous when a tissue is transplanted from one location to another in the same individual. The term isologous is extended to include the relationship between individuals who are phenotypically but not genotypically identical. Thus, F₁ hybrids (progeny of a female of one inbred line and a male of another inbred line) are histocompatible with both parent lines. Transplantations from either parent line to such hybrids, or among such F₁ hybrids, are therefore considered isologous even though the recipient may carry recessive genes of histoincompatibility. In a truly isologous system reactions would be the same as in an autologous system, but it is difficult, if not impossible, to eliminate all genetic variations which might influence antigentic composition. In referring to antibody which is formed to tissue antigens, it seems best to use fully descriptive terms such as “antibody to isologous cells,” etc., because the term isoantibody, which would be a logical parallel to isograft transplantation, is established in serological literature to mean naturally occurring antibodies such as those reacting against the blood group substances, and the term “homologous antibodies” has sometimes been used in studies within an isologous system.

When an animal is exposed to heterologous tissues, whether alive or dead, neoplastic or normal, specific immune mechanisms come into play which subsequently render that animal specifically reactive to the antigens in the injected tissue and usually result in the appearance of antibodies in the circulating blood. The study of experimental tumors by this approach has produced a very voluminous literature which has been periodically and adequately reviewed (11, 71, 182, 210, 217). The continued interest in the serologic response to heterotransplanted tumors is evidenced by recent publications involving the use of fractionated tumor tissues (38, 194, 198), established lines of human cancer cells (78, 117, 132, 198), and improved methods of antibody purification (36, 145). It has been repeatedly demonstrated that antitumor sera thus prepared in heterologous hosts will inhibit growth of that tumor in vitro or if administered prophylactically to an animal just before implantation of the same type of tumor. Therapeutic results are also reported in some studies if treatment is started within 24 hours after tumor implantation. Of recent interest is the demonstration of such an antitumor effect with rabbit antiserum against the human carcinoma cell line HeLa growing in conditioned rats (117). Such studies, however, have no direct implications for human cancer, because the test tumor is transplanted in a host in which it is not completely compatible and hence is subject to host defense mechanisms (whether homologous as with the animal tumors or heterologous as in the HeLa cell experiments). Furthermore, in this situation the antiserum may be directed against normal components of the transplanted tumor rather than against an antigen unique to the neoplasm. The validity of this last criticism is supported by studies with Rous sarcoma in which it has been demonstrated that antiserum against normal chicken tissues neutralizes purified Rous sarcoma virus preparations (18).

When an experimental animal is exposed to homologous tumors, specific immunity is regularly produced as evidenced by failure of growth or accelerated rejection of subsequent implants of the same tumor (37, 107, 116). Antibodies may (60) or may not (111) be detectable in the serum of animals immunized against homologous recipients. Immune responses to homologous normal tissues are also well documented. The “second set” reaction to a second homograft of skin and sensitization of Rh-negative recipients by administration
of Rh-positive blood are well known examples in clinical medicine. Demyelating encephalomyelitis (88), peripheral neuritis (201), testicular degeneration (54), nephrosis (77), nephritis (166), sympathetic ophthalmia (32), thyroiditis (208, 209), hepatitis (14), and adrenalitis (38) have been produced in various experimental animals by repeated injections of the corresponding homologous tissue or an antiserum against such tissue. The pathology is attributed to the reaction of anti-tissue antibodies with antigen in the affected tissue. In these studies, utilizing "vaccines" of homologous normal tissues, it has rarely been possible to demonstrate circulating anti-tissue antibodies, but it must be emphasized that the serological technics used for detection of such antibodies may be completely inadequate.

Antibody produced against a homologous tumor may be prophylactic and sometimes therapeutic when administered to other animals bearing transplants of the same homologous tumor (60), but these studies are subject to all the criticisms mentioned for heterologous systems, since even in a homologous host the transplanted tumor is foreign to its host and with few exceptions is spontaneously rejected. No experimental animal studies are reported in which a homologous animal was used to produce serum for treatment of a spontaneous neoplasm.

Homotransplantation of human cancer cell lines also produces an immune state as evidenced by accelerated rejection of repeat implants (175). To date there is no convincing evidence of circulating antibodies in the recipients of such homotransplants. No attempt has ever been recorded of use of serum from recipients of homotransplants as a therapeutic procedure for human cancer, and failure to detect circulating antibodies in the above experiments offers no incentive to attempt such studies.

Of greatest importance from the standpoint of possible therapeutic applications of immunology to cancer are the studies with isologous systems. Gorer has recently reviewed studies of this type (59). In a truly isologous system those normal antigens which are present in cancer cells are not foreign to the host, and thus any antibody response would be the result of antigens which are unique to the cancer cells; and the isologous tumor is in the identical immunological situation with relation to its host as is a spontaneous tumor and hence should respond to antiserum treatment in the same way as a spontaneous tumor (ignoring such factors as tumor site and vascularization). Thus, any therapeutic response to antiserum treatment which might be demonstrated in a truly isologous system would have implications for clinical cancer therapy, because such a response would indicate that even if the antiserum did cross-react with normal cells, an acceptable therapeutic ratio between toxic and therapeutic effects had been achieved. Many studies (6, 40, 57, 68, 111, 116, 124, 146) have demonstrated antitumor immune reactions in presumably isologous systems, but others have failed to do so (10, 107); the painstaking genetic studies of histocompatibility genetics by Snell (169) and by Amos and Gorer (5) and their co-workers throw doubt on the genetic uniformity of tumor and host in the earlier studies. Recently, Amos and Day (4) were unable to demonstrate antibody formation against EL4 and EL5 leukemia in histocompatible C57BL mice, and Foley (50) could not produce immunity to early passage mammary cancer in C3H mice. On the other hand, Foley (51) was able to produce immunity in C3H mice against a methylcholanthrene-induced sarcoma, only one passage removed from its original host, and Hirsch et al. (79) induced a weakly protective active immunity against an early passage mammary tumor in BALB mice. Thus, there is still no agreement, and no completely convincing evidence, concerning a specific immune reaction against a tumor in a truly isologous system; but the possibility still remains that at least some tumors show sufficient antigenic differences from their host of origin to excite some degree of specific immune response. Also in support of this possibility are the observations of Gorer and Amos (60), who were able to produce antibodies against the EL4 leukemia by inoculation into the homologous mice and to separate from this antiserum an antibody which reacts with the tumor cells but not with normal tissue cells of the C57BL line. Amos and Day (4) extended this type of study to three additional in-line tumors with similar results.

Since a specific immune response necessitates a recognizably foreign antigenic stimulus, it would seem axiomatic that no normal tissue could be antigenic to the individual of which it is a part, unless some change has occurred within a tissue which alters its antigenic status with respect to the host. Such changes might theoretically occur through changes in anatomical relationships, through mutation, or through the acquisition of an extrinsic component such as a haptenic chemical or a virus. An impressive amount of data is accumulating to support the thesis that certain diseases of man are due to auto-immunization. Studies of Hashimoto's struma have demonstrated circulating antibodies capable of reacting with thyroglobulin in vitro (155) and with thyroid tissue...
as demonstrated by the fluorescein-labeled antibody technic (206). It may be postulated that in this disease some extrinsic pathogen such as a virus invades thyroid tissue and initiates cell destruction with release of thyroglobulin which is antigenic and thus produces antibodies only coincidentally. An alternative hypothesis, however, is that the antibodies against thyroglobulin, having been produced, then have the capacity to destroy those cells which are rich in thyroglobulin, thus causing the thyroiditis. Although neither possibility bears immediately upon the cancer problem, both are of interest, because the former would illustrate that antigens specific for a single type of human cell do exist and under some conditions might excite an antibody response, while the second would suggest that antibodies could damage cells through reaction with intracellular antigens. Strong evidence is also accumulating that diseases of the rheumatoid group, nephritis, nephrosis, and periarteritis in man are of autoimmune etiology (101, 119).

In experimental therapeutic studies in cancer patients attempts have been made to utilize active and passive immune mechanisms. Kelloch (87) in 1922 autotransplanted irradiated cancer tissue in an attempt to stimulate immunity in cancer patients. Stone and co-workers (186) made similar studies using cancer tissue killed by freezing. Graham (65, 66) auto-inoculated killed cancer tissues prepared with Freund's adjuvants and reported a slight antineoplastic effect. The cytologic criteria used for evaluation are, however, not generally accepted and in any case fall short of a therapeutic effect. Finney attempted immunization using cancer tissue in Freund's adjuvant and reported the formation of serum antibodies detectable by the tanned erythrocyte technic, and which after concentration caused regression of skin metastases on direct inoculation.

Grace (62) demonstrated cytolysis of tumor cells in lymphoma cutis after direct infiltration with an antiserum prepared in rabbits. The passive immunity approach has also been attempted in the experimental treatment of human cancer. The most recent studies are by Murray (126) and by Buinauskas et al. (29), who used antisera prepared in horses and sheep respectively against human tumor tissues. Murray reported subjective improvement and his clinical impression that life was prolonged, but no convincing data to support a conclusion of specific anticancer effect. Buinauskas et al. reported partial and transient shrinkage of nodes in two of the three patients treated. The lack of convincing therapeutic responses and the theoretical objections discussed above certainly discourage continued trials of crude antisera but do not constitute evidence against the theoretical possibility that this approach might yet be developed to the point of practical application through improved technics of antigen preparation or antibody extraction.

The studies of the past and present decade on reticulo-cytotoxic serum (24, 167) and on krebiozen (1) bear a superficial resemblance to this approach, but since these are prepared from serum of animals injected with human spleen tissue and Actinomyces bovis, respectively, there is no basis for considering these materials as anticancer sera. The possibility that they contain nonspecific humoral defense factors is admissible, but the lack of convincing antineoplastic effects has removed them from clinical or experimental interest. It should be recognized that the production of a specific immune response, active or passive, to tissue antigens does not automatically guarantee that the immune reaction so produced will act detrimentally to the antigenic tissue. Specifically, the assumption that antitumor antibodies will necessarily inhibit tumor growth is not justified by the available experimental data. Specific immune tolerance (18, 19, 118) is a phenomenon in which an active immune reaction results in the unopposed acceptance rather than the rejection of a foreign antigen. Under certain circumstances, the passive administration of antitumor serum will stimulate rather than inhibit tumor growth. This phenomenon has been studied by Casey, by Kaliss, and by Snell and their co-workers (31, 59, 84), but the reason for these opposite responses is still unexplained. The possibility that it represents a cross-reaction of the antiserum with normal host tissues which is detrimental to their participation in the rejection reaction deserves consideration. Martinez et al. (116) have reported that in mice which were immune according to the criterion of accelerated transplant rejection, metastases from the primary tumor transplant continued to grow. Numerous other studies, however, testify that the more frequent result of antibody administration is inhibition of tumor growth, although such inhibition may be evident only if treatment was started in the very early period after tumor transplantation.

Experiments with virus-induced tumors (like other virus infections) have shown only prophylactic rather than therapeutic effects from active or passive immunization. In such studies a unique carcinogen which is presumably also an antigen (i.e., the oncogenic virus) is known to be present. Unless this agent is either nonantigenic or has antigenic identity with the host tissues, or unless
through some phenomenon such as induced toler-
ance the host fails to recognize this antigen as for-
gien, it would reasonably be presumed that specific
immune mechanisms would be capable of acting
against the oncogenic virus. The fact that such
mechanisms are not commonly effective in com-
bating the resultant tumor fits the hypothesis that
circulating antibody does not affect an intracellu-
lar pathogen or the cell in which it resides.

When a transplanted cell is foreign to the re-
cipient, it follows that the host is likewise foreign
to the grafted cell. This scholastic nicety has
achieved scientific and potential clinical impor-
tance with the use of grafts of bone marrow or
lymphoid tissues for the repair of complete reticu-
lo-epithelial system destruction after a high dose
of total-body irradiation for the eradication of
leukemia. In this situation, a successful graft may
react against its host with a resulting syndrome
designated as "homologous disease" (199).

To summarize this discussion of the place
of specific immune reactions in the management
of human cancer: (a) The very possibility of anti-
neoplastic effects rests on the existence of antigens
which are unique to neoplastic tissue, and against
which specific antibodies can be produced which
will inhibit cancer cell growth. (b) Recent studies
with mouse leukemia and with established lines of
human cancer cells raise our hopes that such
unique antigens might exist but as yet give no in-
dication of how widely a given cancer antigen may
be distributed among various spontaneous tumors,
or whether cross-reactions with normal tissues
might be encountered. (c) If these antigenic re-
quirements are fulfilled, prophylaxis by active im-
munization would theoretically be possible, but as
yet there are no experimental data to confirm or
refute this possibility. (d) The possibility of thera-
peutic usefulness further demands that methods
be devised to correct the immunologic inadequacy
of the patient who has already failed to defend
himself against cancer. Of all experimental studies,
only those of Gorer and Amos and co-workers ap-
ppear to fulfill the requirements of antitumor spec-
ificity and limited therapeutic effect. None of the
clinical experimentation with active or passive
immunization is adequate in quantity or in quality
to conclude that a specific antitumor effect has
been produced. However, neither this fact nor the
naiveté and even quackery which have character-
ized some of the uses of sera in cancer patients
refute the theoretical possibility that therapeutic
effects might eventually be achieved through
specific immune mechanisms.

2. By nonspecific immunologic mechanisms.—
Little is known of the factors, the mechanisms, or
the importance of nonspecific immunity. This area
is of considerable interest, however, since it is rela-

tively unexplored, because the multitudinous
problems of specific immune reactions do not ap-

ply and because of the clear evidence that pro-
dures which repress nonspecific defense mecha-
nisms also diminish host resistance to transplanted
cancer.

Deficiencies of total complement activity (158,
172) or of complement components 1, 2, 3, and 4
have not been detected in cancer patients.

Serum properdin level is correlated with tumor
growth. This is illustrated by the progressive drop
in serum properdin titers in mice bearing Sarcoma
180 (92) or Gardner lymphosarcoma (73, 76), and
in rabbits with Brown-Pearce carcinoma (138). It
is also apparent from the increased rejection rates
of Sarcoma 180 in mice (97), of a benzpyrene-in-
duced sarcoma in rats (125), and of the human
sarcoma H.S. #1 in conditioned rats when proper-
din is elevated following administration of small
doses of polysaccharide; and, conversely, by the
impaired rejection of these same tumors and of
the human tumors H.Ep. #3 (135) and H.R. 132
(74) in conditioned rats when properdin levels are
depressed by massive doses of polysaccharide. In

man, too, properdin levels are generally low in
patients with advanced cancer (44, 47, 157, 159,
178). Occasionally properdin inhibitors are de-
monstrable in serum (46). The rejection of homo-

transplanted cancer cells is strikingly impaired in
those cancer patients with no detectable serum
properdin (178). It is evident, however, that the
correlation between properdin and growth of spon-

taneous or transplanted cancer is not necessarily a
causal relationship. It might be merely the result
of a simultaneous but unrelated fluctuation in tu-
mor growth and properdin level; or the properdin
titers might merely reflect abnormalities of some
as yet unrecognized defense factors which are
causally operative in the rejection of tumors. The
fact that properdin has no cytotoxic effect on hu-

man cancer cells in tissue culture (179) is consist-
ent with this suggestion. The recent report by
Ross (156) that mice are protected against bac-
erial infection by administration of properdin
which had been denatured by boiling strongly sug-

gests that the protective factor is not properdin
itself, but other factors which vary in concert with
properdin levels. It must also be emphasized that,
with the exception of the serum levels in cancer
patients, all the observed relationships of proper-
din to cancer concern transplanted tumors, and,
even if it be found that properdin is active in the rejection of transplanted tumors, it cannot be assumed that the same mechanisms are operative against spontaneous human cancer.

Elevation of properdin levels by the administration of small doses of polysaccharides has been accomplished in experimental animals (98) and normal man (41, 164). In cancer patients, limited trials by Grimm7 and by Southam (171) had no striking or sustained effect on properdin levels. This apparent failure to increase properdin levels is not surprising in view of the great deficit of properdin observed by Southam and coworkers in some cancer patients. Grimm has reported7 suggestive therapeutic effects from repeated small doses of the bacterial polysaccharide “pyrexal,” but even if such effects are confirmed it does not necessarily follow that they are an effect of properdin. Polysaccharides have been used clinically for the treatment of neoplastic disease in the form of Coley’s mixed toxins and Shear’s polysaccharides for many years and unquestionably do produce occasional clinical remissions. The possibility that these materials work through stimulation of nonspecific defense factors deserves consideration.

The administration of properdin to correct the properdin deficit of patients with advanced neoplastic disease is the most obvious and direct approach to determine whether or not this material has any activity against cancer. Preliminary trials sufficient to demonstrate that human properdin is nontoxic and to demonstrate its rate of disappearance have been carried out, but therapeutic trials have not yet been accomplished.1

The possibility of administering nonspecific humoral factors for the treatment of neoplastic disease has no apparent theoretical objections but does propose numerous practical problems. The production of such agents from human blood requires tremendous quantities of blood but could probably be accomplished without loss of the presently used serum fractions. A human tissue source such as placentas might also be used. Such substances might also be obtained from animal sources, but this possibility carries with it the probability of more rapid destruction of the heterologous protein and the danger of foreign protein reactions. The known or postulated actions of other nonspecific cellular and humoral factors have been mentioned above. As yet the study of such factors has rarely been extended to man, and they are still so poorly understood that not even speculation seems possible.1

VI. CONCLUSION

In conclusion, lest the tone of this review seem too pessimistic concerning the possibility of clinically useful application of immunologic methods in combating cancer, we should recall that there already exists a fairly impressive array of antineoplastic chemicals which act directly on the cancer cell. It is no exaggeration to say that some of these agents are as effective against certain neoplasms as are most of the bacteriostatic agents which are so dramatically effective against infectious diseases. The difference between infectious and neoplastic diseases in responsiveness to chemotherapy might well be due to the inadequacy of host defenses in the latter. If this be true, even a slight improvement in host immune mechanisms might contribute significantly to the efficacy of chemotherapy. This would seem to be a type of combination therapy which merits further study.

Since Humpty Dumpty was evoked as an opening gambit, it seems appropriate to close by comparing the present situation of the cancer immunologist to Humpty Dumpty—with respect to the wall which we are straddling between two great disciplines of medical science, our extreme vulnerability in assuming that position, the jabberwocky quality of this and other discussions of this subject, and the unsatisfying note on which both stories end.

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Relationships of Immunology to Cancer: A Review

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