Of Cavies and Men: The Propriety and Rationality of "Cancer Immunotherapy"

Immunotherapy of human cancer is at an early stage of development and its clinical applicability is controversial (1, 2). Results of animal studies (3, 4), however, suggest that immunotherapy can be applied ethically and optimistically to the treatment of some cancer patients. Cancer immunotherapy will be defined, its mode of action will be discussed, and suggestions, based on a cavian model and a naturally occurring bovine cancer, will be made about the types of cancer patients who might benefit from immunotherapy. The guinea pig model has permitted the development of immunotherapeutic methods that may be effective at a time when microscopic lymph node metastases are present. The naturally occurring disease, bovine "cancer eye," may provide a means of testing the results of model studies under field conditions. Clinical trials of cancer immunotherapy have been and probably will continue to be designed with little or no guidance from animal studies. Differences between animal models of malignant disease and human cancer justify the argument that protocols for the immunotherapy of human cancer based on clinical judgment alone are just as valid as those based on a combination of clinical judgment and the results of animal model studies. The main point of this article is the suggestion that clinical judgment alone may no longer provide sufficient justification for the establishment of appropriate trials of human cancer immunotherapy. Results of studies with naturally occurring animal cancers may guide the clinical practice of cancer immunotherapy onto paths that these studies predict will lead to success.

Regression of human neoplasms following deliberate treatments or accidental events that might be construed to be immunologic have been reported since the latter part of the 19th century. Reports of cancer regression following chance infections such as erysipelas inspired Coley (5) to treat cancer patients with bacterial toxins. His clinical studies spanned the years 1891-1936. Anecdotal records of his “toxin therapy” leave little doubt that occasionally striking and sometimes long-lasting regressions resulted from the treatment (6). Gross (7) in 1943 published the first unequivocal evidence that experimentally induced murine tumors possessed tumor-specific transplantation antigens. Since that time clinicians have provided clear demonstrations of regression, if not cure, of human tumors by immunologic maneuvers. Klein et al. (8) sensitized patients suffering from recurrent, multiple, planar basal cell carcinoma to allergens, such as dinitrochlorobenzene, and then applied the allergen directly to the tumors. Tumors regressed following the development of intratumoral inflammation, but no compelling evidence that tumor-specific host immunity contributed to beneficial results was found. Morton (9) and others (7) have reported regression of cutaneous lesions of recurrent malignant melanoma following intrallesional injection of BCG. In some patients, un.injected as well as injected lesions regressed. A few patients have remained tumor-free for several years. In most instances, however, regressions have been temporary, even though sometimes they appeared to be complete. No animal studies that have dealt adequately with recurrent cutaneous metastases have been reported.

Cancer immunotherapy is the promotion of physiologic resistance against carcinogenesis to: 1) prevent establishment of neoplastic disease, 2) limit its advancement and spread, and 3) eradicate malignant disease. The first of these goals has not yet been accomplished in humans and its achievement at present seems remote. The second goal is more likely to be reached than is the first, and the third has been achieved in a limited sense. Use of the term "cancer immunotherapy" is premature because this implies that we know "immunity" to be the means of cancer regressions that sometimes follow immunologic maneuvers. Claims that the "immune system" mediates cancer regression have come from in vitro studies or other investigations with no obvious relevance to established cancer. Even unequivocal demonstrations that tumor-specific immunity appears during immunologic cancer cures in animals have not provided incontrovertible evidence that the immune system is the mediator of such cures. For example, the development of tumor-specific delayed cutaneous hypersensitivity in guinea pigs was one concomitant of cancer cure by the intralesional injection of living Mycobacterium bovis (BCG) or a suitable nonliving mycobacterial preparation. Guinea pigs with tumors treated by

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BCG injections at sites remote from the dermal transplants also developed tumor-specific delayed cutaneous hypersensitivity, but they were not cured (10).

Studies with this guinea pig model have yielded information that may be applicable to the design of protocols for the treatment of some human carcinomas. The cavian model consists of a transplantable, syngeneic hepatocellular carcinoma that metastasizes to lymph nodes after intradermal implantation of an ascites form of the tumor. Untreated animals never survive once metastases are detectable. Most animals with these tumors growing in their skin can be cured by a single intratumoral injection of BCG cell walls incorporated into mineral oil drops in an aqueous emulsion, provided the treatment is given at or before the time that microscopically detectable regional lymph node metastases develop (11). Once lymph node metastasis detectable by palpation develops, the probability of cure by a single intratumoral injection of the mycobacterial vaccine approaches zero. The requirements for successful “immunotherapy” of guinea pigs with this tumor growing in their skin are: 1) treatment before the development of palpable metastasis and 2) injection of the BCG cell wall preparation directly into the skin tumor. Treatment of animals by administration of BCG at sites other than the lesion has not yielded consistent cures. Some success has been achieved by paraleosomal injection of the vaccine, followed by excision of the dermal tumor. 3) Treatment only once. Multiple treatments offer no apparent advantage with the guinea pig model. 4) Saturation of all visible parts of the tumor with the vaccine. 5) Injection of an adequate dose of vaccine. Achievement of cure rates of 80-100% required about 1 mg of cell walls. 6) Capability of animals to have an immunologic response to BCG antigens.

Additional results with the guinea pig model indicated that tumor immunity was unable to cope with “minimal residual disease” remaining after radical surgery (12). Guinea pigs with a growing, transplanted, intradermal carcinoma, palpable draining lymph node metastases, and microscopic (nonpalpable) metastases in the next lymph nodes of the chain were treated by intratumoral injection of BCG into the dermal transplant. A week after BCG inoculation, the injected tumor and the draining lymph nodes were excised, leaving minimal residual disease in the form of microscopic metastases in the next lymph nodes of the chain. Eventually, these animals died with large, palpable lymph node metastases at several sites throughout the body. Excision of growing primary transplants, draining lymph nodes, and the next group of lymph nodes in the chain without administration of BCG cured some animals with or without palpable metastases in the draining lymph nodes. Tumor immunity developed in animals cured by radical surgery performed at a time when the draining lymph nodes were palpable but did not develop in animals treated surgically at an earlier stage in the disease when no palpable metastases were detected. In these experiments, tumor immunity was assessed by the ability of animals to reject an intratumoral transplant of tumor at a site remote from the original challenge site (contralateral challenge). A single intratumoral injection of BCG without surgery was effective therapy only when no metastases existed or when spread was limited to microscopic (nonpalpable) draining lymph node metastases. Animals cured by intratumoral BCG developed the ability to reject a contralateral challenge. Not only was intratumorally administered BCG ineffective against palpable metastases, but also it had no influence on the results of subsequent radical surgery.

Even the demonstration that animals with growing transplants and microscopic regional metastases could be cured by the passive transfer (adoptive immunization) of lymphoid cells from healthy donors that were hyperimmunized with a mixture of BCG and tumor cells (13) did not prove that “sensitized” lymphoid cells mediated cures in animals treated by intratumoral BCG.

Active specific immunotherapy in the form of intratumoral inoculations of living tumor cells admixed with BCG was effective therapy only if given well before the development of microscopic metastasis (14). Experiments are in progress to determine whether active, specific immunotherapy will be effective against minimal residual disease. Should specific immunotherapy be effective under that condition, support for some clinical trials will be provided.

The guinea pig model, like all models, is limited in its applicability to human cancer. Recently, however, the guinea pig model was used in the design of studies of naturally occurring, metastatic, bovine ocular squamous cell carcinoma (15, 16). In those studies, 70% of cattle with primary cancer and without palpable metastases treated by intratumoral injection of BCG cell wall vaccine have had either regression or arrest of disease. Some of these animals have been free of visible tumors for more than 2 years. All untreated animals have progressive malignant disease.

That tumor regression can be induced by apparently immunologic methods is remarkable, because immunotherapy or vaccine therapy for infectious diseases is effective prophylactically but rarely after disease symptoms appear. The hope that the treatment of minimal residual malignant disease would be tantamount to immunoprophylaxis received support neither from our guinea pig studies nor from relevant clinical trials that had been in progress long enough to draw valid conclusions (2). Logically then, patients with untreated primary stage 1 disease are the prime, perhaps at present the only, candidates for immunotherapy.

Results of studies with guinea pigs and cattle lead me to make the following suggestions for future clinical trials of immunotherapy: 1) Use BCG cell walls at a concentration of 1 mg per ml incorporated into mineral oil droplets emulsified in salt solution (11). The mineral oil accounts for only 3% or less of the emulsion. Nonliving BCG is recommended to avoid the potential of disseminated mycobacterial infection. 2) Treat patients with previously untreated primary cancer and with at most microscopic metastases in the draining lymph nodes. 3) Administer the BCG cell wall vaccine intratumorally. 4) Treat only once and in such a way as to
saturate all visible tumor with the aqueous emulsion of mineral oil containing BCG cell walls. 5) Perform only those additional cancer therapies that are ethically required but not until at least 2 weeks after inoculation of BCG cell wall vaccine. 6) Be prepared to deal with possible untoward side effects. 7) Determine the “immunologic status” of patients before, during, and after treatment.

These suggestions impose severe but surmountable barriers to the initiation of clinical trials of cancer immunotherapy based on relevant animal studies. The following cancers seem particularly suited to immunotherapy trials: 1) stage I inoperable bronchogenic cancer occurring at or near the carina. 2) stage I squamous cell cancer of the penis in patients who refuse resection. 3) stage I inoperable cancer of the anus. 4) stage I cancer of the head in which surgery would cause unacceptable mutilation. 5) stage I, Clark’s level 4, malignant melanoma. A trial of this disease is in progress at the National Cancer Institute, but living BCG is being used rather than cell wall vaccine. 6) Any other stage I malignancy in which the best clinical judgment predicts lack of success by or contraindicates the use of currently accepted treatments.

Success with any or all of these cancers ultimately might permit application of immunotherapy to patients with cancer curable by currently accepted treatments.

Robert Burns, in his poem To a Mouse, opened our minds with the line “The best-laid schemes o’ mice an’ men Gang aft agley.” The best planned clinical protocols of cancer immunotherapy may also go awry unless the plans are based on animal studies that are as close to clinical reality as possible.

REFERENCES
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