Clinical Experience with Transfer and Direct Tumor-Specific Immunity in the Treatment of 24 Advanced Cancer Patients with Observations on "Post-Surgical" Immunoprophylaxis and Local Immunotherapy

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INTRODUCTION

UNTIL RECENTLY, concepts in the treatment of cancer in general have been centered on three major modalities, namely: Surgery, Irradiation, and Chemotherapy. Mathe'[1], however, has succintly emphasized that even the most witty combination of these time-tested approaches takes care only of approximately one-third of the total cancer cell population in the average tumor-stricken victim. There remains, therefore, even after a thorough treatment, the bigger, deceptive, and invisible enemy which must be handled and combatted continuously by the immune defenses of the host down to the "'last cell" in a guerrilla type of "cell-to-cell" contact through the relentless cell-mediated vigilance of a battered immunologic system which manytimes has been rendered incompetent in the latter stages of the warfare.

Because of repeated failures of these orthodox methods (mentioned above) to achieve acceptable cures and survivals, the pendulum of therapeutic posture in cancer has swung from one modality to the other, oftentimes with mixed feeling of confusion even among the sturdiest proponents of a particular modality. It should be emphasized that surgery, irradiation, and chemotherapy are by themselves immunosuppressive procedures and that although their initial effects are encouraging, the patient is frequently overwhelmed and overcome in the latter stages by unopposed and revitalized cancer cells. He, in effect, has become a vulnerable victim, for his defenses have been rendered immunologically impotent by the standard procedures.

During recent years, with some knowledge in human immunology, in a "last ditch" effort to salvage patient survival

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in cancer, Immunotherapy has become a beaconing light to some workers. In its incipient stage, the fascination is great, but there is apparently little to offer to the despondent cancer populace. There is a dearth of local experience in this field as it is abroad. However, it is conceded that the specialty of Cancer Immunology is gradually but steadily taking shape inspite of tremendous difficulties.

It was only during the last decade that we were afforded a clearer understanding of the Human Immune System relative to its behavior in the cancer victim as expounded by Gordon and Ford[2] and by Dmodchowski and Bowen[3]. This has brought us an articulate definition of what actually takes place in the host with respect to tumor-specific antigen recognition, processing, specific cell-mediated activation, and cytoeffector immune response to tumors recognized as non-self that we are provided a means not only for a more effective immunologic approach to the management of cancer but also to elucidate the basic question of how malignant cells manage to escape immunologic destruction.

Through a gradual accumulation of the most recent information on the subject as exemplified by the work of Hellstrom[4], we understand now the sluggish and often suppressed immune system of the advanced cancer patient in contrast to the heightened immunity among non-cancer and cancer-recovering patients. It is with this utter helplessness, impotence, and non-responsiveness of the immune defenses of the cancer victim, and the challenge brought about by the possibility of superactivation and utilization of the immune potentials of the non-cancer and cancer-recovering patients through specific and non-specific immunoactivation that this work was conceived. The allergory is akin to a drowning man who cannot swim. Utterly helpless and doomed to die, he needs a rescuer in the person of a competent swimmer.

In our country, the report of Villasor[5] on the immunopotential effects of BCG in advanced cancer in 1961 and 1965 was initially encouraging, but lasting results were not as dramatic. This however, was a giant step in cancer immunotherapy in our country. The trophoblastic hypothesis of Navarro[6] in the midsixties was challenging and probed into the possibility of further investigation into the "riddle of cancer" in an effort to develop new concepts, diagnostic procedures, as well as methods of treatment. In retrospect, the discovery of Alpha Fetoprotein (AFP) by Abelev in 1963[7] and of Carcinoembryonic Antigen (CEA) by Gold and Freedman in 1965[8] as immunodiagnostic procedures may have mirrored themselves from the human chorionic gonadotropin (HCG) test of Navarro. Gomez[9] in 1967 reported on the "immunosuppressive nature of cancer, "the significance of lymphocytic infiltration at the tumor-host interface, and the possibility of "cancer rejection" in man. Subsequently, in the same year, immunopotentiation techniques were initially employed by the same author[10]. Lately, Pineda[11] ingeniously elaborated on the employment of hemocellular transplant from a healthy syngeneic donor, alone ore combined with BCG administered to advanced cancer patients and reported some beneficial effects in at least two patients but with inconstant and unpredictable results in others.

It is the purpose of this treatise to present a non-heretofore described clinical study on Transfer and Direct Tumor-Specific Immunologic procedures in ad-

vanced human cancer with special attention to effects on tumor regression, survival time, and mortality, as well as observations on immunoprophylaxis. The author is not aware of any similar study undertaken in our country at this time of writing.

MATERIAL AND METHOD

Twenty-four patients with various types of malignant and potentially malignant tumors, most of them in the moderately or far-advanced state form the material of this report. There were 7 males and 17 females with ages ranging from 3 to 63 years.

Complete history, physical examination, pertinent X-rays, and blood counts, particularly the peripheral differential counts including atypical cells when present were routinely performed. Separate studies of leucocytic profiles on 53 cancer patients were also undertaken to determine the role of lymphocytes and other cytopathic effectors of cell-mediated immunity.

The patients were clinically grouped into three, namely: **Group 1** – Patients whose tumors were adequately removed with no recurrence or spread at the start of the treatment, **Group 2** — Patients whose tumors were adequately removed previously but had recurrence or spread at the start of treatment, **Group 3** — Patients whose tumors were not adequately removed and who had recurrence or spread at the start of the treatment.

Survival time was always calculated from the first visit or during the start of the immune treatment in all instances. Six patients were operated on between 1-2 years prior to immune treatment but survival times in these patients were counted not from the time of operation but from the immunotherapy.

IMMUNOLOGIC TECHNIQUES

Therapeutic manuevers depending upon the presenting need were as follows:

1. Administration BCG alone given directly to the cancer patient particularly after adequate tumor removal. In this sense, the therapy may be termed a "Post-Surgical" immunoprophylaxis. The BCG, given mainly as a recall antigen and non-specific immunopotentiator was given intracutaneously at the time of diagnosis at a dose of 0.5 to 1.5 cc similar to the technique of Villasor[5] once or twice depending upon the initial Delayed Hypersensitivity Reaction (DHR). When the first injection produced a violent or satisfactory reaction (3 to 5 cm of initial redness), no second dose was given. When the DHR was poor or timid, a second dose was given 10-20 days after the first. The scarification techniques as advocated by Mathe'[1] was not used in this series, although this author is contemplating its use on future patients.
2. Tumor — Specific Antigen (TSA) administered directly to the patient. This was either given alone or in combination with BCG. This maneuver was also given as a "post-surgical" immunoprophylaxis. The TSA was either allogeneic, syngeneic, or autologous in origin. No typing compatibility was required for allogeneic (nonrelated) TSA as long as the cancer cell type was similar.

Tumor-specific Antigens which are actually protein complexes were usually

given subcutaneously either fresh or treated with mitomycin as recommended by Mathe'[1]. In this series we prefer the former and sometimes use a little ether to reinforce antigen identification. Mitomycin inactivation was used only in 2 patients (cases 12 and 24). The TSAs were obtained by simple venipuncture in the following manner:

(a) As solubilized antigen (detached from the cell) taken from the serum of the same or another cancer patient (same blood type and tumor) as defined by Pilch and Golub[12] and demonstrated clinically by Griffiths[13].

(b) As cell-bound antigen either from the same or another patient with the same cancer cell type from coelomic cavity fluids which were positive histologically for cancer, or from resected tumors or involved nodes.

The antigens from resected tissues were minced in a sterile manner in the operating room, and ground before subcutaneous implantation through an incision separate from the main operative wound. Those obtained from body fluids and sera were injected similarly mixed with bacterial products or enzymes such as polyvalent bacterial vaccines, varidase, or BCG. Part of the resected tumors was submitted for biopsy and another part was stored in the freezer for future antigenic utilization.

3. Transfer Immune Factors in form of serum and white blood cells or whole blood administered to the cancer patient subcutaneously from a sensitized human donor preferrably but not necessarily syngeneic (related) and of the same blood type as the patient. Sensitization consisted of the donor having received either TSA as described above, or TSA-BCG combination, or BCG alone when TSA was not available. Transfer Immune Factors were given periodically, at first 2 times a week for 2-3 weeks, then weekly for 1 month then once every 15 to 30 days there-after when signs of clinical remission appeared. This was sustained for a total average of 15 to 18 transfers.

In this set-up, Transfer Immunity consisted of the following possible constituents, namely:

(a) Transfer Factor (TF) as originally demonstrated by Lawrence in 1955[14].

(b) Immune RNA is also a possibility as demonstrated by Mannick and Egdahl[15] and confirmed by Sabadini and Sehon[16]. This factor, however, is mainly obtained from animals (rodents, sheeps, monkeys) rather than humans and is easily inactivated by tissue ribonuclease.

(c) Serum Factors —

(1) Unblocking Serum Factor (USF) — described by Hellstrom, et al[17] which abrogates the "blocking" of cell-mediated tumor immunity among cancer patients also earlier reported by the same workers[4].

(2) Antibody — Dependent Cellular Cytotoxic factor (ADDC) also called the "arming" antibody, lym-

phocytedependent antibody, and "Synergistic" cytotoxicity as recently investigated by MacLennan[18] and Perlmann[19]

4. Local Immunotherapy in cases of cutaneous and subcutaneous cancers either as a local recurrence or metastatic spread to he subcutaneous tissues. In this series an ointment consisting of a combination of fibrinolysin and desoxyribonuclease was applied locally on the cutaneous and subcutaneous tumors daily as abvocated by Kelin[20]

In cases of metastasis, or when adequate solid tumor removal was impossible because of extensive growth or spread, inductive chemotherapy usually with cyclophosphamide with or without steroids was initially utilized to reduce tumor burden to at least 10^5 cells (Mathe'[1]), or to shrink the lesions to not greater than 1 cm. per cluster even when multiple as advocated by Southam[21] to render these residual cells vulnerable to eventual immunologic maneuvers.

When initial chemotherapeutic induction has been achieved, or when peripheral lymphocytic population has significantly been reduced to levels below 5,000, the drug was promptly withdrawn and transfer or direct immunity was administered and periodically given until host resistance has been overhelmingly potentiated. As soon as immunotherapy was started, chemotherapy was absolutely omitted so as not to offset positive immune responses.

Radiotherapy was utilized only in three instances: one for ovarian suppression in a breast cancer, one for recurrent epidernoid skin cancer, and the other, for a neck mass in reticulum cell sarcoma. Chemotherapy and radiotherapy, therefore, were only adjunctive and inductive modalities and were not necessary in the treatment.

High dosages of amino-acids and inosine were given during the whole period of the treatment to potentiate immune cell regeneration and immunoglobulin synthesis as part of a multimodality concept of treatment in cancer.

For Transfer Immunity, only healthy donors were selected having the same blood type and preferrably but not necessarily related (syngeneic) with the patient. The donors usually received TSA with BCG combined, or BCG alone. Full knowledge of the procedure was required and consents were signed by both donor and patient. The cases in this series reflected only those whose families or friends fully consented to the procedure since great difficulty was encountered in the process.

A separate group of 33 patients with various types of advanced cancer who had either surgery or chemotherapy but without immunotherapy as described herein was used as control.

RESULTS

Of the 24 patients, 21 were operated on but only 14 had adequate removal of their tumors, one of whom was a huge recurrent breast tumor which was treated like a primary lesion. Eight of these patients had no demonstrable spread or recurrence at the time of immunotherapy while six showed either recurrence or systemic spread. Five patients had

only exploration and biopsy, while two had primary surgery leaving distant metastases unaltered. Three patients were diagnosed mainly by unequivocal radiologic signs (see table 1).

The diagnoses of the different tumors are listed in table 2. These were obtained prior to immunologic treatment. Nine patients had ductal infiltrating carcinomas of the breast, two had choriocarcinoma, and two had reticulum-cell sarcoma. The remaining eleven had one diagnosis each, namely: primary neurogenic cancer of the right lung (neurilemmoma), adamantinoma, bronchiolar carcinoma, lung carcinoma (radiologic), tongue carcinoma (epidermoid), mediastinal cancer (radiologic), adenocarcinoma of the pancreas, ovarian carcinoma, esophageal carcinoma (radiologic), giant cell tumor of the humerus with fracture, and epidermoid skin carcinoma, interorbital area. For detailed information of the clinical materials see Plate 1.

TUMOR EFFECTS

Specific cytopathic effects on tumor of patients whose malignancies were adequately removed are seen on table 3 and demonstrated the following:

(1) Dramatic dissolution of pulmonary, subcutaneous, cutaneous, nodal metastasis or recurrences and effusions with stabilization of bone lesions in 3 patients: 2 with breast carcinnoma, 1 with choriocarcinoma (see figures 1, 2, and 3).

(2) Intermittent or partial dissolution and growth slowing of recurrent cutaneous and pectoral incisional lesions in 1 patient with recurrent breast cancer one year after radical mastectomy, and a recurrent ovarian carcinoma removed 1 1/2 years previously.

(3) Absence of recurrence in seven patients with adequate removal of: breast cancer in four, adamantinoma in one, giant cell tumor in one, and tongue cancer in one. One of the breast cancers in this group was huge local recurrence 24 months after a pervious radical procedure. There was no recurrence 9 months after a second operation with subsequent immunotherapy.

(4) Marked slowing of bronchiolar cancer adequately removed 24 months previously, and an epidermoid skin cancer removed one year previously.

Tumor effects on patients whose malignancies were either inadequately removed or not removed at all were noted as follows:

(1) Moderate to marked slowing of: a massive neurogenic pulmonary growth, an esophageal cancer with temporary remission and restored ability to swallow, and two breast cancers, one of whom is still alive after 72 months.

(2) Progression of tumor growth was observed in: one lung cancer with mediastinal extension, one pancreatic cancer, one choriocarcinoma, two reticulum-cell sarcomas, and one mediastinal cancer.

SURVIVAL TIME

Survival times calculated from the first visit or at the start of immunotherapy are seen in table 4. Group 1 consisting of 8 patients had a survival time range of 9-96 months with a mean of 35.87 months. As of this moment seven of eight patients (87.5%) as still alive.

Group 2 consisted of 6 patients with a survival time range of 6-60 months and a mean of 27.16 months. Five of six patients are still alive (83.33%).

Group 3 had only two patients: One survived 30 months, the other only two months, a mean survival time of 16 months. Both patients have died.

Group 4 consisted of 8 patients with a survival time range of 1 to 72 months with a mean of 12.25 months. All have died except one (12.5%). Of the total 24 patients, 13 are alive (54.1%) at the time of writing. The overall mean survival time was 24.16 months.

The Control Group consisting of 33 patients with their respective organ cancer listed in table 5 had an age range of 4 to 78 years. 17 were males and 16 were females. The mean survival time were 2.7 months (range 1-18 months). One female patient with a sluggishly growing ductal breast cancer survived 18 months. All patients died at the end of the follow-up.

RESULTS OF IMMUNOLOGIC PROCEDURE —

The result of the immunologic procedures employed are seen in table 6. BCG was used alone on cases 2, 3, and 4 of Group 1. Only one had eventual recurrence and died (66.6%). TSA alone was used on cases 1,6,7,8,12,13,15 and 24. Six of eight patients (75%) are still alive, four from Group 1, one from Group 2, and one from Group 4.

Transfer Immunity utilizing only BCG which alone was available at each particular instance was used on cases 9,11,16,-17,18,19,21 and 23. Only 2 of 8 patients (25%) are alive, all from Group 2.

Transfer Immunity utilizing BCG and TSA to sensitize the donor plus direct employment of TSA and BCG on the patient was used on cases 5,10,14, 20, and 22. Three of the five patients (60%) are alive, one from Group 1, and 2 from Group 2.

POST-SURGICAL "IMMUNOPROPHYLAXIS"

This was done on 8 patients in Group 1, on one patient in Group 2, on one patient in Group 3, and on three patients in Group 4. Only 7 patients (7 of 8 patients or 87.5%) all in Group 1, are alive, giving an overall survival rate of 53.84% for all groups. TSA was used in 6 patients, TF was used in 4, and BCG in 3. The results are seen in table 7. Interestingly, two cases (1 and 7) with low malignancy (adamantinoma and giant cell tumor) had no recurrence 30 and 47 months after therapy, respectively.

Lymphocytic Profiles

Of the 53 patients separately studied for peripheral lymphocyte profiles, 36 were terminal cases while 17 were in the process of clinical remission. Of the terminal subjects, 13 had lymphos below 10%, 8 with lymphos between 10-15%, 8 had between 16-20%, 5 had 21-30%, while only 2 had over 30%. Of the remitting cases, no patient had below 10% count, 10-15% count, or 16-20% count. Eleven had counts between 21-30% while 6 patients had over 30%. The results can be viewed in table 8. Atypical lymphos as an expression of blastogenic responses were observed on two patients. In one of these, a significant eosinophilia was observed (35%). The same patient had a dramatic dissolution of metastatic lesions. Examples of unfavorable and favorable lymphocyte responses are seen in table 9.

This author was able to observe significant lymphocytic increases with inosine and essential amino-acids in conjunction with immunotherapy. In one remitting patient (case 14) for instance, an initial count of 25% on 8-2-75 increased to 37% on 8-16-75 without significant change in the total WBC. A similar observation was seen in cases 9, 10, 17, and 23 who were maintained on these adjuvants throughout the length of their treatment.

Local Immunotherapy

Local Immunotherapy with combined fibrinolysin and desoxyribonuclease was uwsed in the cutaneous and subcutaneous lesion on cases 9, 10, and 14. Case 9 had intermittent flattening while cases 10 and 14 had dramatic disappearance reflecting also probably not only local but also systemic immune responses resulting from TSA and TF.

DISCUSSION

The study of cancer has often fascinated surgeons, pathologists, radiologists, and biologists alike. Surgeons often capitalize on the excisional approach and have been able to prolong survival times in cases of purely localized malignancy. When the extent of the lesion is precarious, the long term results are poor and it becomes the duty of the chemotherapist and radiotherapist to render adjuvant aid at a stage when host resistance has obviously waned. Frequently, the latter two modalities enhance rather than check tumor growth particularly when doses are inadequate because of their inherent capacity to further immunosuppress biologic defenses in the same manner that surgery does to the patient, the difference being that surgery produces a rebound immunologic response probably because of tumor burden reduction as hypothesized by Simmons[22].

It is now known that the above mentioned modalities can only cure about one-third of the cancer patients when treating perceptible disease[1]. This leaves a considerable amount of imperceptible tumor cells which comprises the residual, insiduous, and upredictable enemy. This is that particular state of affairs that brings recurrence and eventual demise of the immunobiologically helpless cancer patient. Many-times, one would only hope that the left-over cell burden would not exceed the capacity that can be handled by the existing immune defense in a particular patient. It is in this concept that a multimodality approach to cancer treatment has been advocated by Haskel[23].

The role of immunotherapy in the treatment of cancer although slow in its development, has lately gained momentum with a better understanding of "biologic immunodynamics". The finding by this author in 1967[10] of the immunosuppressive behavior of cancer as revealed by absence or scanty lymphocytic infiltration at the tumor-host interface has given insight into the need of some maneuver that would bring about a potentiation of the host resistance. Experience has shown that most patients with advanced cancer and, therefore, with considerable tumor burden have an almost absolute refractory immunosuppression not responsive to ordinary nonspecific immunostimulants such as BCG or other bacterial vaccines as advocated by Villasor[5], or to non-sensitized hemocellular transplant as reported by Pineda[11], hence, the unpredictability of these immunologic procedures.

In advanced cancer patients with severe immunosuppression, intracutaneous

BCG did not produce a reaction (7 patients) even after repeated inoculations, showing obvious anergic status. In some patients with minimal immunosuppression, however, hemocellular transplant itself could be beneficial probably because of Hellstrom's USF. This is one of the components (serum factors) this author relied on during transfer immunization.

Physiology of the Immune System

There are unequivocal evidences to show that immunity of tumors are exercised by the Cellular or Lymphocytoid Division rather than by the Plasmacytoid Division of the Immune System as amply described by Gordon and Ford[24]. The schema of the Physiology of the Immune System is seen in figure 4. The sensitized T-lymphocyte which has matured through the thymus and, therefore, thymus oriented is the obvious cytopathic effector, However, if the T-lymphocyte is not tumor-specifically sensitized, then the USF is non-effectual since the unopposed cytopathic effector mechanism has no specific direction or target cell. For this reason, non-specific hemotransplant is of no physiologic value. **The most ideal and rational approach is tumor-specific sensitization and/or transfer immunity from a healthy, syngeneic, specifically sensitized donor.**

The Plasmacytoid or Humoral Division which is represented by the B-cell or bursa oriented cell, so called because in the chicken these cells are derived from the hindgut bursa of Fabricius, is in man derived from the lymphoid follicles of the Peyer's Patches and probably the appendix. These plasmacytes elaborate immunoglobulins or serum antibodies which are mainly responsible for immune responses in bacterial infections, foreign body and allergic reactions. They seldom take part in tumor immunity. Moreover, by creating antigen-antibody complexes with tumor receptor sites, they may actually enhance tumor growth producing the so-called "Serum Blocking Factor" SBF) earlier reported by Hellstrom[4] (see figure 5). This is the more plausible explanation of cancer patients who inspite of high titres of tumor antibodies are unable to "reject" their own tumor lending credence to the hypothesis of the immunosuppressive behavior of cancer in its autonomous stage[10].

Tumor-Specific Antigen

One of the various new properties which characterize cancer cells is the acquisition of protein complexes which have not been present or defined in the cell prior to malignant change. The existence of these TSA in both animal and human tumors has been recognized for years[3]. The malignant cell may carry a variety of antigens, either intracellular or at the cell surface. These antigens may be recognized as "foreign" or "non-self" by the host's immune system, and an immune response may be mounted specifically against the antigens and against the tumor cells that bear them. The immune response is usually believed to be cell-mediated (Lymphocytoid Division) and the mechanics is similar to a transplantation rejection process. It is to be emphasized here that the cancer cell is distinct from the antigen itself. It is therefore, with practical importance that we distinguished our approach in securing the TSA into the so called "solubilized" or cell-free, and the "cell-bound" antigens, the former obtained by simple venipuncture, the latter by surgical excision, aspiration of coelomic fluids, or biopsy.

Griffiths[13] has shown that cancer cells

abound in the blood in 42 of 70 patients (60%) even among silent, localized colonic cancers. It is obvious, therefore, that the score could be up to 90% when it comes to cell-bound antigens in cases of full-blown metastatic cancer. This author, moreover, predicts an almost 100% availability in the peripheral blood in cases of solubilized antigens. In the future, it will be an expedient plan to set up a bank of fresh frozen cancer tissues of various types as a vaccine pool similar to the one described by Mathe'[1] at the Institute of Cancer and Immunogenetics in France.

In this report, the author has introduced specific immunization by way of immunoprophylaxis, cancer suppression, and transfer immunity with the end in view of a well-directed specific immune response. From the data presented, there was no recurrence of the tumor 30, 21, 18, 9, 42, 47, and 96 months, respectively, in Group 1, all patients being presently alive (100%). One patient aged 30 (case 6) suffered no recurrence and is alive 42 months after initial surgery and immunization inspite of one pregnancy during the follow-up period. There was only one patient (case 2) whose growth slowed (24 months) but developed metastases and died. There were two patients in group 2 with TSA immunization. One had a dramatic dissolution of pulmonary metastases and is alive today 60 months after initial immunization (see figure 2). The other patient had growth slowing of an epidermoid carcinoma of the interorbital skin but latter died of cerebral spread 24 months after immunotherapy. One patient in Group 3 and one in Group 4 had marked slowing of growth, but eventually, of the 8 patients with direct TSA administration in all groups, six (75%) are alive between 24 to 96 months after immunotherapy. Deaths in Groups 2 and 3 merely reflect the factor of tumor burden which runs pare' pasu' with tumor-induced immunosuppression and is oftentimes a decisive element in determining immunologic victory or defeat.

It has been conceded by cancer immunologists that tumors with sizes over 1 cm. are difficult to disintegrate immunologically. The experience in this series, however, have shown that metastasis as big as 1 inch even when in multiple clusters all over the body dissolved dramatically as early as one to two months time as exemplified by cases 10, 11, 12, and 14 (see figures 1, 2, and 3). Some big solid tumors may pose as impenetrable barriers, although a "second set" type of homograft-like rejection may occur similar to the "Gell's perivascular islands" of Jones[25] which can cause an acute ischemia, necrosis, and dissolution regardless of tumor size.

The specificity of tumor antigens to induce corresponding specific reaction is exemplified by the work of Hellstrom and associates[26] who observed inhibition of various tumor cultures by autogenous or allogeneic leukocytes from patients with the same type of tumor in 88 to 91% as against 3 to 7% of normal cell cultures. Most interestingly, leukocytes from cancer patients caused destruction of allogeneic tumor cells of the same type but not tumors of other histologic types. The recent clinical trial by Marcove, et al[27] of autogenous vaccines in the treatment of osteogenic sarcoma merits attention.

Southam[24], in his experiments in mice observed that tumor-takes of transplanted methylcholanthrene-induced sarcoma were only 50% less in immunized than non-immunized animals. Experience in

man although not well controlled, showed that reduction of takes was not more than 50% of control values, and to get approximately to that degree, it takes a ratio of 1,000 leucocytes to 1 tumor cell for an effective cell-to-cell contact.

The preparation of the tumor-specific antigen itself deserves mention. According to Southam[21], the most effective form of tumor vaccine is the intact tumor cell, either viable, or metabolically alive but treated with chemicals, bacterial products or irradiation to prevent cell propagation but retains as well as reinforces its antigenicity as suggested by Rios and Simmons[38]. This author suspects that in big solid tumors antigenicity is nil if the host-tumor interface remains as a thick barrier leaving no means of "immunologic exchange" between the tumor and the host, thereby perpetuating unchecked tumor growth. When the tumor eventually finds its way to the blood stream, immunosuppression has gone too far for the host to take care. Thick TSA tissues when not comminuted adequately and attenuated as described prior to subcutaneous implantation may produce a "take" which occurred in one patient in earlier experiments. The lesson was learned and subsequently corrected.

When severe immunosuppression has prevailed, TSA alone may be too weak to evoke a response. The use of TSA in combination with BCG becomes an alternative. This is a simpler method devoid of moral and donor problems when compared with Transfer Immunity. Recent reports by Powles[28] showed dramatic results among patients with acute myelogenous leukemia using stored viable tumor cells plus BCG. Fefer, quoted by Simmons[22] described 12 patients who received subcutaneously their own leukemic cells, lethally irradiated in vitro with 10,000 rads plus intravenous infusions of peripheral lymphocytes from a normal identical twin. Complete remissions occured in 87% of cases with six patients having complete remission at 11 to 44 months without chemotherapy. The cultured cell-BCG immunization technique of Sokal and Aungust[29] is merely a variation.

Recently, Rosato[30], et al used Vibrio cholera neuraminidase as an adjunctive treatment with monthly injections of autochthonous tumor cells to 25 patients with various types of cancer. Six who received the full course of 6 injections are all alive without clinical evidence of progression more than 8 months after the start of treatment. It is clear, therefore, that the TSA may need some sort of immunopotentiation in the more advance ype of cancer with severe immunodepression. The adjunctive treatment apparently reinforces the TSA by causing a DHR through the following mechanisms, namely: 2) production of a less rigid cell surface structure allowing easier membrane deformation and phagocytosis of the TSA by macrophages, b) unmasking of antigens allowing greater recognition, and (c) facilitation and accessibility of antibodies to antigenic receptor sites on the surface of the cancer cell. Employing cytotoxicity assays in vitro using autologous target cells grown in tissue culture, Rosato[30] observed cytolysis without tumor enhancement or "blocking" effect in 4 of 5 patients in whom this was measured, In this series, TSA combined with BCG was not used alone but in conjunction with Transfer Immunity by reason of exigency. Of 5 patients where this was used (case 5, 10, 14, 20, and 22), 3 or 60% are alive. The non-response of patients in group 4 (cases 20 and 22) was

due to overwhelming tumor load and immunodepression.

Transfer Immunity

Lawrence[14] in 1955 was the first to report on the rtansfer of delayed hypersensitivity responses to tuberculin and other antigens in man with dialyzable extracts of human peripheral lymphocytes. This was termed the "Transfer Factor" (TF). In 1960, specific accelerated rejection of skin homografts in man were found to be mediated by this factor by the same authors[31]. Although its use has been confirmed in non-cancer immune deficiency diseases such as Wiscott-Aldrich syndrome, its more dramatic role in recent years has been focused on malignancy. It is similar but distinct from Immune RNA of Pilch and Golub[12], the difference being on the fact that the former is obtainable from the lymphocytes of man while the latter mostly from that of animals and is, moreover, inactivated by tissue ribonuclease while the TF is not. Ribonuclease, however, can be inactivated in turn by low molecular weight dextran.

Southam[21] refers to Lawren's TF as "Instructional Immunotherapy" for although it does not contain the antigen to which immunity is conferred, nor is antigenic of itself, it somehow transmits information which "instructs" the recipient's immune system to respond to the same antigen which sensitized the donor. The appeal then for such non-antigenic material for immunotherapy is obvious based on the assumption that healthy donors who have built up immune resistance to a wide variety of cancer cells could offer their leucocytes to the cancer recipient who is unable to defend himself against the malignancy. This was precisely the concept utilized by this author in this treatise. With the administration BCG to the donor, he acquires a heightened, non-specific immunity, but with the addition of TSA, he develops, in effect, a specific, hightened immunity when transferred "instructively" to the cancer patient and confers not only a recall DHR but also a specific cytotoxic instigator to a remarkable degree.

When using transfer elements including serum instead of just only leukocytes as originally used by Lawrence[14], this author also availed of two serum factors aside from the possible availability of Immune RNA. The serum factors, previously mentioned are: (1) USF of Hellstrom, and (2) ADCC factor of MacLennan and Perlmann.

Two patients, in Group 2 where transfer BCG was used are both alive (cases 9 and 11) 41 and 12 months, respectively. The rest of the patients who received transfer BCG all died, one belonging to Group 3 and five from Group 4. One of the above survivors (Case 11) had dramatic dissolution of abdominal spread and ascites. The over-all effectivity for all groups with transfer BCG was a poor 25% reflecting severe refractory immunosuppression. In comparison, the effectivity of 50% for combined Transfer and Direct Immunity utilizing TSA plus BCG for both approaches seems encouraging and should be used more often in advanced cases. It is observed however that transfer BCG was used more often than transfer TSA. The reason is reluctance on the part of the donor in accepting the procedure for fear of cancer propagation. However, the argument itself is not valid, first, because the TSA is initially deactivated by pre-treatment as previously described, and second, because of the concept of Immunologic

Surveillance in healthy individuals as advanced by Burnet[32].

Survival Time and Mortality

The mean survival time in this series of 35.8 months in Group 1 and 29.2 months in Group 2 is indeed encouraging. For example, in Group 1 we had a superextended survival of 96 months in one patient and over 40 months in two, and the rest between 9-30 months with only one death. The mean survival among patients given autologous tumor cells treated with Vibrio cholera neuraminidase after surgery by Takita, et al, as quoted by Simmons[22] was only 17.4 months.

Although the mean survival time in Group 2 was only 29.2 months, the longest survivals for this group were 60 and 41 months, respectively. The rest had between 12 to 24 months with only one death at the end of the follow-up. Group 3 and 4 did not fair well (16 and 12.2 months mean, respectively), although one patient who is still alive has a 72-month survival time. These results speak cogently for themselves when compared with the 33 control patients without immunotherapy who had a mean survival time of 2.7 months, all of whom have died.

Comparison with the BCG group of Villasor[5] (see table 10) which had 7 survivors out of 43 patients (16.2%) at 24 months, the survival in this series were 10 out 24 patients alive 24 to 96 months (41.6%), while the actual number of living patients is 13 (54.1%) which is highly significant. The results in Group 1 and 2 are inspiring and should invite more attention and study as well as employment of bigger and adequately controlled series. It is, moreover, obvious from this data that tumor burden is a critical factor if immunotherapy is to succeed. The poor results in Groups 3 and 4 are witness to this fact.

Lymphocytic Responses

The study of peripheral lymphocytes in this series deserves mention since they are the principal agents of immunity against tumor cells. As early as 1922 MacCarty[33] has already mentioned the significance of lymphocytic infiltration around breast cancers as a determinant in host rejection of the tumor and a favorable prognostic sign relative to sur vival. It is unfortunate that this observation was discredited for half a century before eventually gaining some support.

Evidences have shown that lymphocytes become significantly reduced in a good number of patients whose progress is dismal. As a matter of fact, the decrease or increase of the lymphocyte population is of prognostic significance which will presage whether the patient is going to succumb to the disease or get well in the not too distant future. In the authors' personal unlisted experience, the forst and most accurate prognosis were on those patients whose lymphocyte counts slumped below 10% pare' pasu" with very high total WBC counts beyond 15,000.

The appearance of atypical cells in two patients (cases 10 and 18) was suggestive of blastogenic repsonse which according to Pilch and Golub[12] is indicative of prior sensitization of lymphocytes to tumor antigens. This may, therefore, be interpreted to represent detection or recognition of TSA by the host.

The appearance of significant eosinophilia in one patient (also with atypical lymphos) with dramatic tumor dissolution indicated either the presence of a

foreign agent, an allergic reaction, or an antigen-antibody repsonse. By elimination, the latter may be the most likely mechanism to explain this occurrence. This antigen-antibody phenomenon has been amply expounded by Wetherley-Mein[34] who claimed that eosinophils are involved in the initiation of antibody synthesis. It appears that antigen-antibody complexes could be phagocytosed by eosinophiles. Defense against pathogenic effects of immune complexes by eosiphiles is significant in the light of Hellstrom's SBF[4]. Other functions of the eosinophiles are fibrinolytic activity and histamine inactivation whose relationship to cancer is still unknown.

"Post-Surgical" Immunoprophylaxis

Cancer Immunoprophylaxis in the strict sense of the word refers to immunoprocedures performed on the non-cancer patient to prevent a future occurrence of the actual cancer. In this study the term immunophylaxis was used rather loosely and was preceded by the word "post-surgical" to qualify succinctly what this author had in mind. The word was used only with respect to those patients who had actual removal of the tumor and were given either BCG, TSA, both, or with TF.

From the figures in this study, immunoprophylaxis was effective only when the tumor was adequately removed. The figure of 87.5% effectivity (7 of 8 patients) clearly justifies the procedure, although a bigger series would be more convincing. Moreover, immunoprophylaxis may be effective even with tumors of low malignancies as seen in two patients. To date, only two other human experiments had been done aside from this present series. One was by Bjorklund[35] who inoculated small groups of elderly men with a vaccine containing a mixture of human tumor cell in the hope that the resulting homograft immunity would inhibit the development of future cancers. Up to the present, however, no follow-up reports had been published. The flaw in this experiment, however, is that the prophylaxis was made late in life, although it can be opined that this is the age when tumors occur more frequently and, therefore, demands prevention. The other study was a collaboration between the group from Sloan-Kettering Institute, and that from Ohio State University Medical School[36] with the primary objective of studying homograft rejection phenomena and TSA. In that experiment, nearly 300 volunteers in the Ohio Penitentiary received living tissue culture cell homografts of various human cancer cell lines. Long-lasting homograft immunity directed toward TSAs was demonstrated in these men. The follow-up was between 14 to 20 years, and although it was difficult to trace every body because of frequent change of abode, those who were accounted for ten years or more from the time of inoculation (about one-third of the original number) showed only two known cases of cancer (2%). Although no conclusion was possible, immunoporphylaxis, either post-surgical or the true preventive measure is a fascinating procedure which will do doubt find its place in our future conduct with cancer-prone patients.

Local Immunotherapy

The subject of local immunotherapy for superficial lesions merits attention. Klein, et al[20], in his experiences with basal-cell and breast cancer (recurrent) as well as mycosis fungoides using locally applied dinitrochlorbenzene (DNCB), streptokinase-dornase, and PPD showed eradica-

tion of skin cancers in 95% in a group of 90 patients. The mechanism is brought about by DHR to haptens of relatively small molecular weight producing selective antitumor effects against malignant and premalignant epidermal lesions and lead to their eradication. Of three patients where local immunotherapy was used in this series, all responded with either flattening or complete disappearance of cutaneous and subcutaneous lesion (100%).

The Donors

The donors selected for transfer immunity were preferrably of the same blood type and related to the patient. This is merely to avoid the usual problem with histocompatibility antigens encountered with non-syngeneic donors during subsequent transfers. The experience here, however, has shown that non-related isotyped donors did just as well with excellent results even after over 12 transfers (cases 10 and 14). A history of hepatitis not only in the prospective donor but also in the patient is an absolute contraindication to transfer immunity. TSA in this case is the logical recourse.

Adjunctive Therapy

The discussion of immunotherapy will not be complete without certain factors which may be responsible for adequate lymphocyte production. Protein is one of the most vital raw material which can accelerate cell production. Preferrably, this should be in essential amino-acid form when assimilated by the patient in order to facilitate prompt synthesis without undergoing too much digestive work when introduced orally. Interestingly, amino-acids in contrast to the usual natural complex protein, passes through the gut into the portal system to the liver readily without much ado and there undergo rapid protein synthesis. It is even more effective when administered intravenously.

Hypoproteinemia is a common observation among advanced cancer patient probably because of nausea, inanition, poor absorption, and deficient protein synthesis. This results in poor body resistance and immunodepression. Patients given amino-acids, however, regain their serum protein values and, consequently also, their lymphocyte and antibody capacities, and frequently experience some kind of remission.

The role of Inosine in reversing lymphopenia either after chemotherapy, radiotherapy, or because of cancer immunosuppression itself has been firmly established by Kondo and Aoyama[37] in 1965. Lymphocyte regeneration is probably by way of the Inosine-Ribosephosphate-AMP-ADP-ATP pathway facilitating nucleotide and protein synthesis even under conditions of hypoxia. In this series at least 20% of the cancer patients were brought to satisfactory lymphocytic levels either after inductive chemotherapy or during the immediate cost-surgical period. This phenomenon cannot be explained solely by the effect of immunotherapy alone.

SUMMARY

Twenty-four patients with various types of cancer were given transfer and Direct-Specific Immunizations which at times were reinforced with BCG under conditions of exigency. The patients were grouped as follows: **Group 1**— Tumors adequately removed, no metastasis or spread, **Group 2** — Tumors adequately removed previously but with existing spread or metastasis at time of immunotherapy, **Group 3** — Tumors not ade-

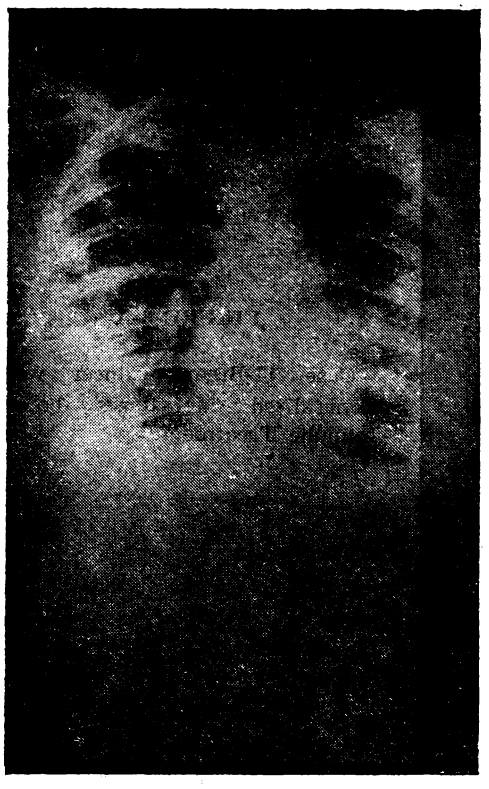

FIGURE 2-A

Case 12-Choriocarcinoma with Pulmonary Metastases before Immune Treatment.

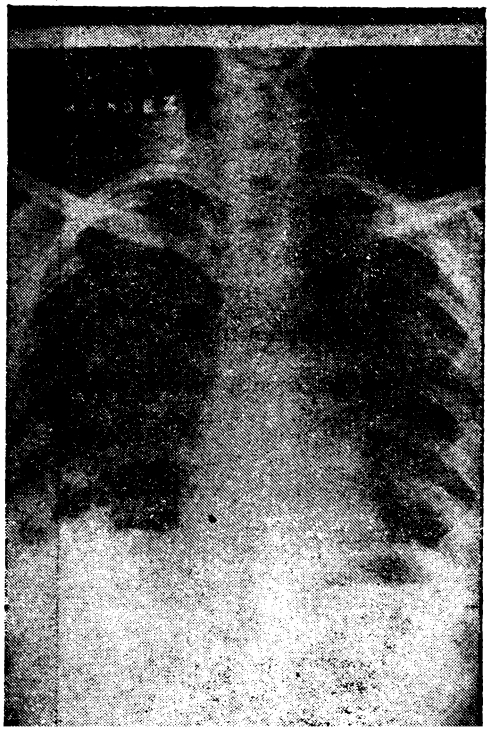

FIGURE 2-B

Case 12-Two months after Immunotherapy.

Sept.-Oct., 1976
J. P. M. A.

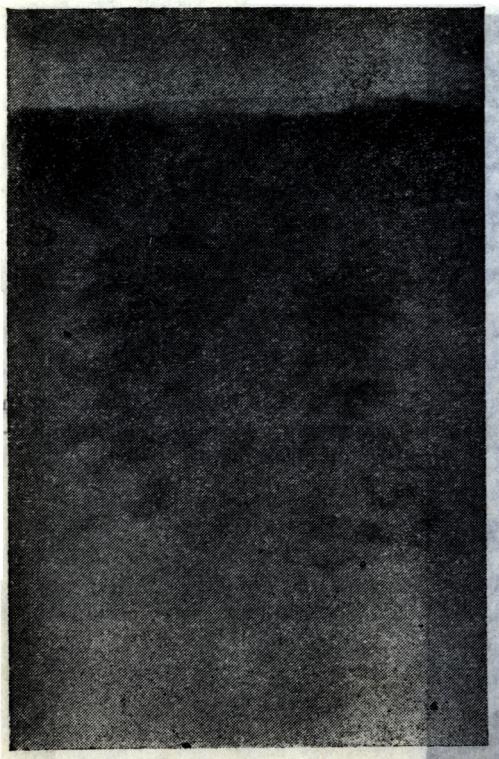

FIGURE 3-A

Case 14-Breast Cancer with Generalized Metastases before Immune Treatment.

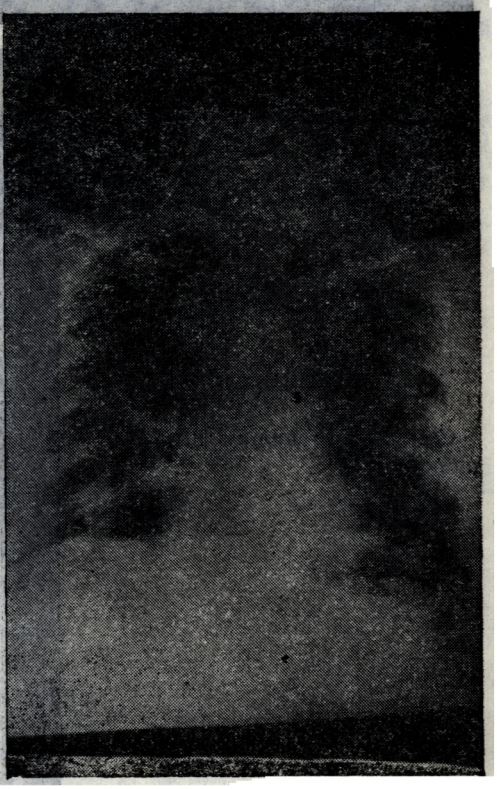

FIGURE 3-B

Case 14-One month after Immune Treatment.

PHYSIOLOGY OF THE IMMUNE SYSTEM

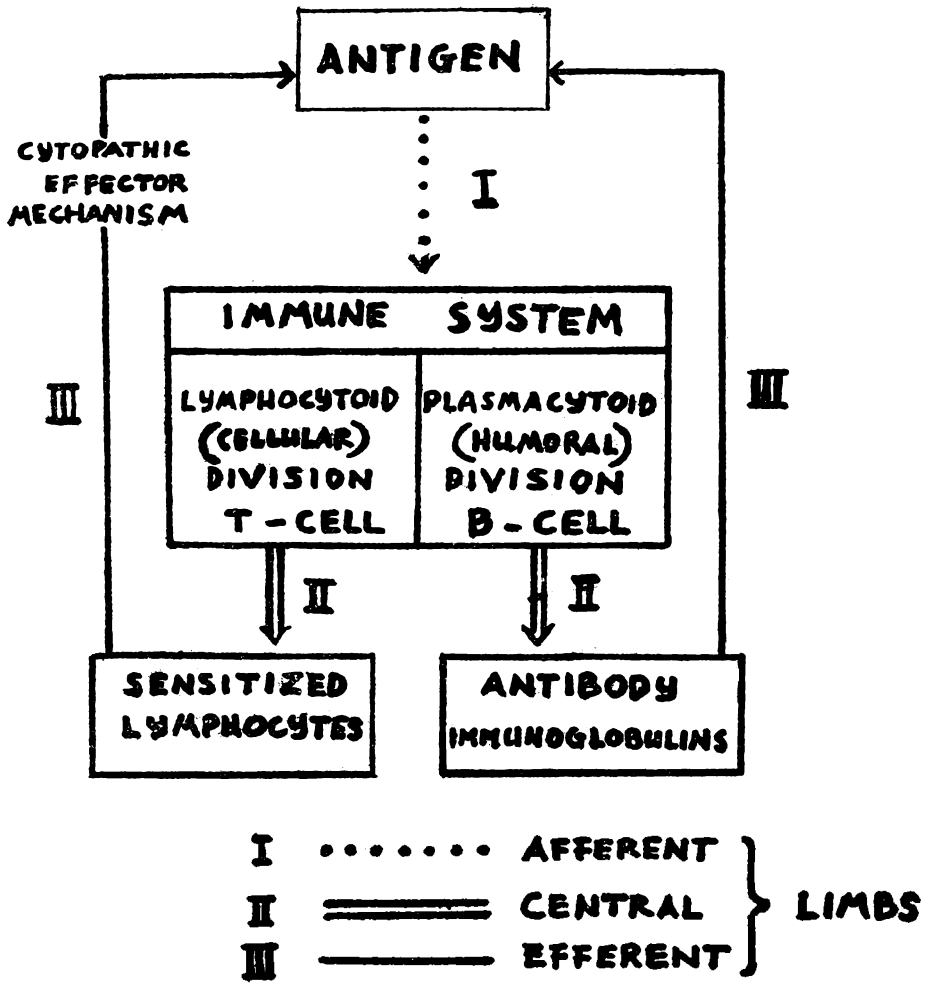

FIGURE 4

quately removed, with local or systemic spread, Group 4 — Tumors not removed, with local or systemic spread.

In group 1, all are alive except one (7/8 or 87.5%) between 9 to 96 months (mean 35.8 mo.) with recurrence of tumor only in one patient. In Group 2 (6 patients), four had dramatic dissolution of the spread and recurrence, two had growth slowing and all are alive except one (5/6 or 83.3%) 6 to 60 months (mean 27.1 mo.). In Group 3 (2 patients), all died with a mean survival time of 16 months. In Group 4 (8 patients), only one is alive (12.5%) after 72 months, with a mean survival time of 12.2 months. Control studies in 33 advanced cancer patients without Immunotherapy revealed a mean survival time of 2.7 months, with no living patient after that period. Survival time was calculated from the first visit or in-

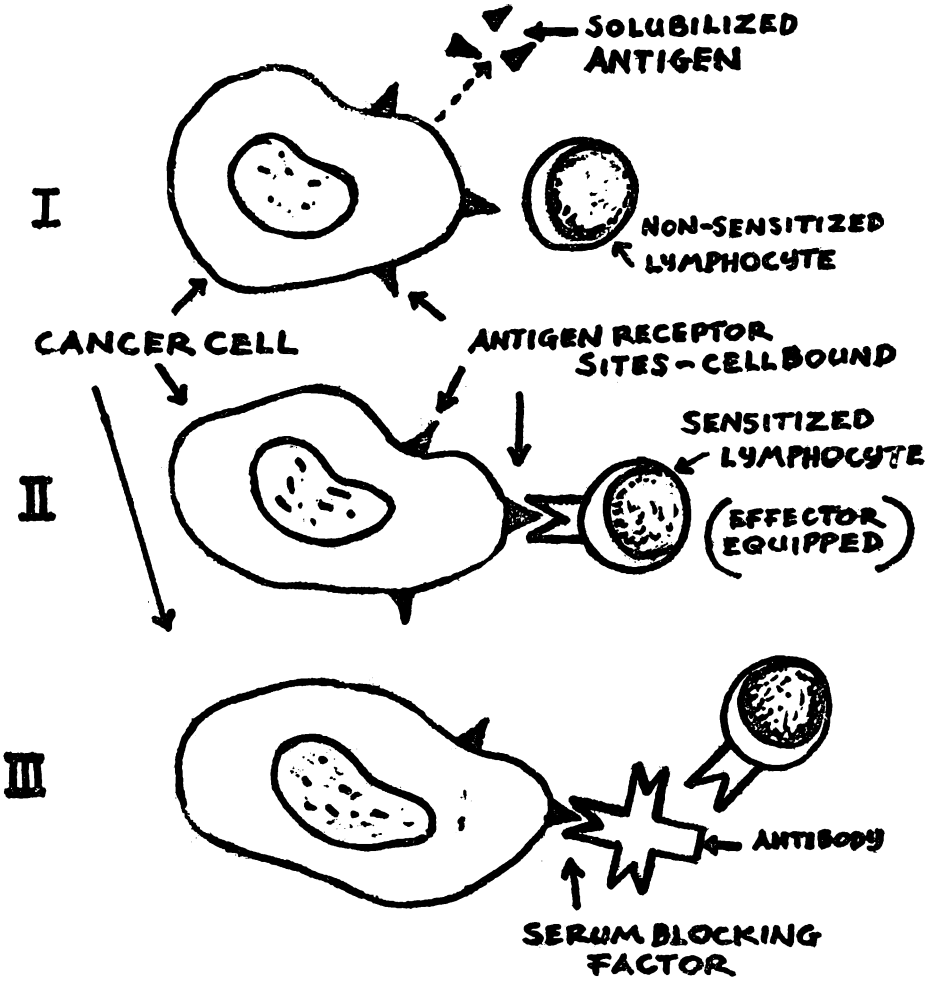

FIGURE 5

stitution of immunotherapy and not from the previous operation. Comparison with Villasor's series was discussed. Included in this study was an experience with local immunotherapy for cutaneous lesions.

Tumor burden was a critical factor as shown in Groups 3 and 4. The results in Groups 1 and 2 were encouraging and invite more attention, study and employment of bigger series.

"Post--Surgical" Immunoprophylaxis was discussed relative to its effectivity (7/8 or 87.5%) in Group 1 and an overall survial rate of 53.8% for all groups. The role of lymphocytes as cytopathic effectors of cell-mediated immunity as well as the prognostic significance of its peripheral population has been emphasized. The presence of atypical cells and significant eosinophilia in some patients and their relationship to antigenic recognition and tumor antigen-antibody interaction was mentioned. Finally, the regenerative potential of Amino-acids combined with Inosine in conjunction with Immunotherapy was revealed by improvement in lymphocyte levels which cannot to explained solely by immunotherapy alone.

Plate 1. TRANSFER AND DIRECT TUMOR-SPECIFIC IMMUNITY. SPECIFIC TUMOR EFFECTS AND SURVIVAL

Group	Case	Age	Sex	Cancer	Tumor Effects	Survival Time in Months	Present Status
1 —	1	50	F	Jaw	NR	30	A
	2	51	F	Lung	MS	24	D
	3	50	F	Breast	NR	21	A
	4	53	F	Breast	NR	18	A
	*5	54	F	Breast	NR	9	A
	6	38	F	Breast	NR	42	A
	7	3	M	Bone	NR	47	A
	8	63	M	Tongue	NR	96	A
	*second operation for local recurrence						
Group 2 —	9	55	F	Breast	PD	41	A
	10	36	F	Breast	DD	20	A
	11	52	F	Ovaries	PD	12	A
	12	22	F	Trophoblast	DD	60	A
	13	48	F	Skin	MS	24	D
	14	47	F	Breast	DD	6	A
Group 3 —	15	54	F	Breast	MS	30	D
	16	52	F	Trophoblast	PG	2	D
Group 4 —	17	50	F	Lungs	MS	10	D
	18	58	M	Lungs	PG	2	D
	19	7	M	RES	PG	5	D
	20	58	M	Pancreas	PG	3	D
	21	62	M	Esoph.	PD	3	D
	22	61	F	RES	PG	2	D
	23	60	M	Mediast.	PG	1	D
	24	55	F	Breast	MS	72	A

Legend: NR— No recurrence, MS — Marked slowing of growth, PD— Partial dissolution, DD — Dramatic dissolution. PG— Progression of growth, RES — Reticulo-endothelial system D — Dead, A — Alive

Plate 1. CLINICAL MATERIAL

Classification			No. of Patients
A. With Surgery			(21)
1. Adequate Tumor Removal		14	
a) no spread		8	
b) with spread		6	
2. Inadequate Tumor Removal		2	
3. Exploration or biopsy only		5	
B. Radiologic Diagnosis Only			(3)
Total			24)

Table 2. DIAGNOSES OF MATERIALS

Tumor	No. of Patients
Duct Carcinoma, Breast	9
Choriocarcinoma	2
Reticulum-Cell Sarcoma	2
Esophageal Carcinoma (radiologic)	1
Neurogenic Sarcoma, Lung	1
Giant Cell Tumor, humerus with fracture	1
Adamantinoma	1
Epidermoid Skin Cancer	1
Bronchiolar Carcinoma, Lung	1
Lung Carcinoma (radiologic)	1
Tongue Epidermoid Cancer	1
Mediastinal Cancer (radiologic)	1
Adenocarcinoma, pancreas	1
Ovarian Carcinoma	1
TOTAL	24

Table 3. SPECIFIC TUMOR EFFECTS WITH TRANSFER AND DIRECT TUMOR-SPECIFIC IMMUNITY

Classification		No. of Patients
A. Tumors Adequately Removed		(14)
1. Dramatic dissolution	3	
2. Intermittent or partial dissolution	2	
3. Absence of recurrence	7	
4. Marked slowing of growth	2	
B. Tumors Inadequately or Not Removed		(10)
1. Moderate to marked growth slowing	4	
2. Progression of tumor growth	6	
TOTAL		24

Table 4. SURVIVAL TIME AND EFFECTIVITY RATE

Group	No. of patients	Range-mo.	Mean-mo.	Survival Ratio	% Alive.
1	8	9—96	35.87	7/8	87.50
2	6	6—60	27.16	5/6	83.33
3	2	2—30	16.0	0/2	0.00
4	8	1—72	12.25	1/8	12.50
All Groups	24	1—96	24.16	13/24	54.10
Control	33	1—18	2.7	0/33	0.00

Table 5. ORGAN CANCERS IN 33 CONTROL PATIENTS —

Organ Site	No. of Patients
Lungs	9
Breast	7
Liver	4
Skin and Subcutaneous Tissue	3
Colon, Rectum	2
Cervix	1
Pancreas	1
Esophagus	1
Intestines	1
Bone Marrow	1
Muscle	1
Bone	1
Pleura	1
TOTAL	33

Table 6. IMMUNOLOGIC PROCEDURES

Agents Used	Case	Group	Tumor Effects	Result	% Alive
A) BCG Alone	2	1	MS	Dead	
	3	1	NR	Alive	2/3 (66.6%)
	4	1	NR	Alive	
B) TSA Alone	1	1	NR	Alive	
	6	1	NR	Alive	
	7	1	NR	Alive	
	8	1	NR	Alive	6/8 (75%)
	12	2	DD	Alive	
	13	2	MS	Dead	
	15	3	MS	Dead	
	24	4	MS	Alive	
C) TFusing BCG	9	2	MS	Alive	
	11	2	DD	Alive	
	16	3	PG	Dead	
	17	4	MS	Dead	2/8 (25%)
	18	4	PG	Dead	
	19	4	PG	Dead	
	21	4	MS	Dead	
	23	4	PG	Dead	
D) TF Using TSA +BCG	5	1	NR	Alive	
	10	2	DD	Alive	3/5 (60%)
	14	2	DD	Alive	
	20	4	PG	Dead	
	22	4	PG	Dead	

Legend: DD-Dramatic dissolution, NR-No recurrence, MS-Marked Slowing, PG— Progression of Growth.

Table 7. IMMUNOPROPHYLAXIS

Group	No. of Patients	Alive %	Dead
1	8	7(87.5%)	1
2	1	0 (0%)	1
3	1	0 (0%)	1
4	3 (biopsy only)	0 (0%)	3
Total	13	7(53.84%)	6

Table 8. LYMPHOCYTE PROFILES IN 53 CANCER PATIENTS

A. Terminal Patients		(36 Patients)
Lymphocyte Count:		
Below 10%	13	
10—15%	8	
16—20%	8	
21—30%	5	
over 30%	2	
B. Remitting Patients		(17 Patients)
Lymphocyte Count:		
Below 10%	0	
10—15%	0	
16—20%	0	
21—30%	11	
over 30%	6	

Table 9. UNFAVORABLE AND FAVORABLE RESPONSES RELATIVE TO LYMPHOCYTIC PROFILES AMONG CANCER PATIENTS

(a) **Unfavorable** — (untreated)

(1) Patient E.T., 33 yrs., F — Breast Cancer
Initial Counth — WBC — 17,000 **lymphos**—14 Eost-2
Su'bseq. Count — WBC — 19,000 **lymphos**— 7 Eos-0
Result: died

(2) Patient R.T., 40 yrs., M — Lung Cancer
Feb. 3, 1967 — WBC — 13,500 **lymphos** — 19 Eos-1
Feb. 14, 1967 — WBC — 25,000 **lymphos** — 9 Eos-1
Result: died

(b) **Favorable** — (With Immunotherapy)
Patient L.S., 36 yrs, F (Case 10) — Breast Cancer
Jan. 19, 1974 — WBC — 17,000 **lymphos** — 3 Eos-11
March 29, 1974— WBC — 17,000 **lymphos** — 25 Eos-35
atypical
(lymphos seen)

Result:
Dramatic Tumor
Dissolution, Alive

Table 10. COMPARISON BETWEEN SPECIFIC AND NON-SPECIFIC IMMUNOTHERAPY

Workers	No. of Patients	Survival Time	Survivors	%
Villasor	43	at 24 months	7	16.2
This Author	24	24—96 months	10	41.6
(do)	(do)	6—96 months (present survivors)	13	54.1

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