

**A SCIENTIFIC ESSAY* REGARDING
A 25 YEAR EXPERIENCE IN
THE TREATMENT OF CANCER WITH
MULTIPLE IMMUNOTHERAPY MODALITIES**

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*Mandelbrot in his classic work, *The Fractal Geometry of Nature*, describes a scientific essay and casebook as follows. "A scientific essay is written from a personal point of view and without attempting completeness. It also tends to digressions and interruptions." Further, he describes a casebook as "a compilation concerning actual cases linked by a common theme." It is in this frame of reference that this essay is being written.⁽¹⁾

TABLE OF CONTENTS	PAGE
Introduction	3
Results	5
Discussion	6
Summary Table and Patient Synopses	9
Background Material and Methods of Preparation	26
Transfer Factor	27
BCG	28
Mixed Bacterial Vaccine and Coley's Toxin	29
Lymphoblastoid Lymphocytes (LBL)	31
Other Possibilities for Immunomodulation	32
References	33

INTRODUCTION

The endeavors to be presented here did not spring like Athena from the head of Zeus, fully clothed and armored. Rather, they grew out of the author's experience, as well as on a study of the medical literature for the past 40 years. In the format of a "scientific essay and casebook" as described by Mandelbrot, the results of treating 52 cases of cancer with adjunctive immunotherapy will be presented.⁽¹⁾ How the program in this clinic came to be started; the Bayesian statistical premises upon which it is based; the criteria for patient selection; and the results of therapy will be described.⁽²⁾ Since there are a number of excellent historical reviews in the literature regarding immunotherapy for cancer, only reports directly applicable to what has been done in this clinic are cited.^(3,4,5,6) The discussion centers upon opinions about which groups of patients adjunctive immunotherapy might be considered, about surrogate markers that can be considered in evaluation of therapy, about the current and future status of immunotherapy for cancer, and about criteria for reports that evaluate adjunctive immunotherapy.

Included in this paper, is a brief narrative of all 52 patients given immunotherapy in this clinic from 1991 to 1997. The 140 patients treated from 1973 to 1985 have been reported previously⁽⁷⁾ (records of patients treated between 1985 and 1990 were inadvertently destroyed.) In these reports are the reasons we evaluated the treatment of each patient as satisfactory, failure, equivocal or successful.

Also outlined, is the preparation of modalities produced in this clinic for administration to the patients. The methods of administering these modalities are also given. The medical literature that justifies the use of each modality is mentioned. In addition, other FDA approved modalities that seem reasonable to try on poor prognosis patients are briefly mentioned, along with literature citations that justify their use.

The immediate stimulus to start adjunctive immunotherapy in this clinic occurred when a physician colleague, a friend of the author, asked him if he could figure out a treatment program for a patient and friend of his who had generalized carcinoma of the breasts with skin, bone, liver and lung metastases. A search of the literature suggested it might be reasonable to administer a combination of bacillus Calmette-Guerin (BCG), transfer factor (TF) and immortalized lymphoblastoid lymphocytes (LBL).^(8,9,10,11,12) The use of combination therapy was suggested by the author's experience with antibiotics and others experiences using a combination of antineoplastic drugs.^(13,14) The use of mixed bacterial vaccines (MBV) suggested itself to the author because it seemed reasonable to stimulate general antibody production in patients with cancer. In addition, he had a mixed bacterial vaccine available that he had developed for burn patients.⁽¹⁵⁾ (The author was unaware of Coley's toxins at the time the program began). A conference was held with the cancer patient, her husband and the referring physician in which a theoretical basis for what was to be our "last ditch" attempt at treatment was outlined. Since maximum chemotherapy and radiation had already failed, all concerned opted for an attempt at immunotherapy. Two months after its initiation there was a decided improvement. The skin nodules regressed and no evidence of progression surfaced. Within six months, the patient had returned to full-time work and was asymptomatic. Two years later, she developed symptoms and signs of a central nervous system lesion that was rapidly progressing. It was decided that she had brain metastases and she was allowed to die without further intervention. Ironically, postmortem revealed that there was little sign of cancer, but

that she had died of central nervous system cryptococcosis. This case stimulated the beginning of our attempts at immunotherapy in cancer. (We have never seen a case as spectacular as this one was since).

The statistical rationale of this effort was based on Bayesian statistics as outlined by Thomas Bayes in 1761.⁽²⁾ The root of his method is that if something happens once it can be expected to happen again.⁽²⁾

By word of mouth and more recently because of the presentation of our results in 1986, over 200 patients have now presented themselves to the Waisbren Clinic for adjunctive immunotherapy.⁽⁷⁾ The patients surfaced either because they had heard of the program or because they were a patient in the author's office practice of internal medicine. Criteria for acceptance in the program are as follows: The patients must have had all accepted traditional methods of treatment that they could tolerate or that they would accept; the patient and their families are fully informed that no claims of efficacy are being made; the patients are informed regarding the total experience of the clinic up to the time of the treatment; the potential for untoward reactions; and the rationale for the use of each modality. Finally, they are made to understand that all treatments are to be given in the office, that the TF, MBV, Coley's toxin and LBL are all prepared in the office and that this is a treatment program rather than an experimental one. The latter point is because since all the modalities were to be given at once, the chance to prove efficacy of a particular modality is lost.

Suffice it to say, at this point in this report, each of these modalities had reasonable rationales for use in the treatment of cancer and each was well tolerated and caused no serious toxicity.⁽⁷⁾ Some of the patients have also taken by mouth, levamisole, cimetidine and isotretinoin. Medical literature that suggested the use of these agents is listed in section entitled, "Other Available Possibilities for Immunomodulation."

The criteria for evaluation of the results are as follows: The treatment is considered "satisfactory" in cases in which the patients are living and had also been given either chemotherapy or radiation, or in which the patient had cancer that had a fairly good prognosis without treatment. Immunotherapy was considered a "failure" if the patient died. Immunotherapy is considered a "success" if it appeared to the author that other clinicians would agree that the immunotherapy had helped the patient. The results are considered "equivocal" if the author felt there was a strong suspicion that the treatment might have helped, but that that the suspicion not strong enough to consider the treatment a success.

RESULTS

The table summarizes 52 cases. There were 22 failures, 16 satisfactory administrations, 4 successes, and 10 patients in whom the treatment was considered as a possible salutatory result (equivocal).

Details about the four patients who were regarded as successes are presented in the synopses, but they can be briefly summarized as follows: The first patient considered a success is a woman who presented in 1980 with a generalized Hodgkin's disease with huge cervical nodes (Case 4 in Synopses and Case 1 in Reference 7). She had failed on chemotherapy and had a white blood count of 1000. She made an apparent complete recovery with only immunotherapy and is alive and well today. The second success is a female who presented at age 16 with a grade 3 carcinoma of the ovary (Case 3 in Synopses and Case 5 in Reference 7). She received a modest dose of cisplatin and immunotherapy and is alive and well today, 17 years later. The third success is a 61-year-old male who presented in May of 1990 with a generalized hormone resistant carcinoma of the prostate (Case 22). His tumor regressed markedly on immunotherapy and accelerated when he stopped it. He is still struggling with his tumor. The fourth success is a man who had a carcinoma of his gastroesophageal junction that had metastasized into his mediastinum removed in 1993 (Case 47). He has received only immunotherapy and is alive and well today with no sign of tumor. One of the patients whom it seemed to the author that immunotherapy might have helped and who was considered equivocal was a woman with generalized carcinoma of the breasts whose skin lesion shrank and she returned to full employment after a year of immunotherapy (Case 16). There was almost entire regression of bone and lung lesions. She subsequently died of her disease.

At this point in this essay, many readers will be shouting "anecdote, anecdote", the buzzword that seems to this author to have caused many investigators not to believe what they see or hear. Perhaps these physicians should be reminded that digitalis and salicylates were discovered because of anecdotes and that anecdotes in literature (such as in the Bible and Shakespeare) have proven useful guides for many of us. It should be remembered also that these anecdotes are being presented in the context of the report that included all patients treated.

There were no instances of significant toxicity or morbidity among the 52 patients in this report. This is in counter-distinction to bone marrow suppression and other untoward results that limit chemotherapy and radiation in many of the patients. As detailed in the synopses, multiple surrogate markers of cancer activity were present in many of the patients. These included: CEA, PSA, CA-125, CA 19-9, CA 15-3, beta₂ microglobulin, and excessively high monocyte counts.

DISCUSSION

The dismal failure rate in the grade 3 patients is put into perspective somewhat by the fact that in each of these patients, chemotherapy or radiation or both have failed. Analysis of our dismal failure rate can be somewhat tempered by a report of "promising" results of using interleukin-2 treated T-cells to treat patients with grade 3 cancer of the kidney.⁽¹⁶⁾ In that study, only 2 of 48 patients could be considered as successes when one uses the criteria reported here, but it was concluded that the study confirmed antitumor activity.⁽¹⁶⁾

Furthermore, there are imponderables that must be accepted both by patients and physicians who participate in endeavors such as have been described. We will never know how many patients in whom the results were considered satisfactory might have been helped by these immunomodulation attempts. The same can be said for the attempts at immunomodulation in the patients in whom the results were considered equivocal. A scientific number also cannot be put on how much benefit some of the patients received by their receiving "hope" and by the satisfaction they and their families received by the knowledge that they were actively pursuing a rational course designed for their benefit, rather than a course that was designed for the purpose of getting scientific knowledge. The fact that no patients had any untoward reactions to immunotherapy stands in sharp contrast with general experiences with other modes of therapy. In this frame of reference it should be pointed out that nothing in this report suggests that other methods of treatment for cancer that have proven effectiveness should be denied patients so that immunotherapy can be evaluated. Thus at the present time, one indication for immunotherapy in cancer is that it can be tried when other methods have failed or have not been proven to be helpful. The 4 out of 52 patients in whom treatment apparently was successful tend to support Bayes who in 1761 concluded, "if something happens once it will probably happen again."⁽²⁾ If the premise that this can happen is accepted, studies designed to evaluate how combined immunotherapy may affect the elements that constitute cancer resistance should be done. The effect of immunotherapy on surrogate markers of cancer also should be determined. The few patients who do respond should be studied to determine in what manner or manners they are different from the nonresponders. The difficulties inherent in these kinds of studies are multiple. The analysis of changes induced by simultaneous administration of multiple agents is extremely difficult. Furthermore, getting funding for studies of this sort is equally difficult.

In view of the above, questions that surface in regard to immunotherapy are as follows: Does it help anybody? Who should be given this type of therapy? Should modalities be given in combination? Who should administer immunomodulation therapy? There are no definitive answers to these questions but we will share our opinion in these regards. First, does immunotherapy help anyone? Not only our experience but the mountains of scientific literature in this regard suggests that it does help some patients (see all references). An intangible benefit that is rarely mentioned but that we have found to be real is that at least it gives some people hope. Regarding the question of who should get immunomodulation therapy, there is more difficulty. It is our opinion the prime candidates for immunotherapy are those whose cancer has been surgically removed and who have been given other accepted treatments but who still have a good chance of recurrence. All of the patients reported here had received traditional therapy but some in addition had accepted immunotherapy on the basis that it might reduce the chance of their having a recurrence.^(17,18) The largest group of patients in whom immunotherapy would be indicated, in my

opinion, is a group of women with cancer of the breast with node involvement who have received usual therapy but who still have a 10 to 20% chance of recurrence within five years.⁽¹⁷⁾ It would not be feasible to give a high enough research priority to prove this. However, to this observer it seems a reasonable thing to do with the proviso that the unproven assumption can be accepted by all concerned that because immunomodulation helped grade 3 cases, it might also prevent recurrence in grade 1 and 2 cases. If immunotherapy is to be used, it is also reasonable to suggest the modalities should be used in combination. We know that the immune system is a complex multifactorial system that has few functions mediated by a simple lymphokine or substance. Thus, it seems reasonable in the case of immunotherapy to follow the leads demonstrated in chemotherapy of both AIDS and cancer, and to use combinations of immunotherapeutic agents. These can be expected to be more effective than the use of any single lymphokine. Who should administer immunotherapy? It seems that economic factors will force individual small groups to get involved. If they do not, a large share of their patients will end up either in foreign countries or in medical centers in the United States, where only experimental methods are being used. All the modalities mentioned here can be prepared and legally given as long as they are administered in the personal physician's office. This does not violate federal law. It should be pointed out that for the cost of treating two patients with intensive chemotherapy and autologous bone marrow transplant, a physician's office or small clinic could prepare the material mentioned in this report and administer it to 20 patients. In the short term, programs such as presented here, should not harm institutions that do engage in large-scale obviously important experimental studies. This is because there are not enough clinics or physicians prepared to enter the endeavor of immunotherapy to compromise the programs of academic centers. In the long term, time will have to determine the upshot of the general use of immunomodulation in this country. Commercialization of modalities such as active T cells, transfer factor and mixed bacterial vaccines seems far off because they are in public domain and it probably would not be commercially worthwhile to develop them for mass sales. On the other hand, immunomodulation modalities such as the interferons, interleukins, isotretinoin, cimetidine, BCG and levamisole are all readily available and can be used by any physician who becomes convinced it is reasonable to administer any of them to their patients. If it becomes generally accepted that the immunomodulation produced by multiple agents has a place in cancer treatment, a two-track system of cancer therapy will probably develop. On the one track will be patients who feel comfortable with participating in the experiments designed to prove the efficacy of a particular entity or entities and on another track will be physicians and patients who feel that all reasonable albeit unproven modalities for cancer should be used in poor prognosis cancer patients. In this group, surrogate markers such as have been used to evaluate AIDS treatment will have to come into play. The limited laboratory studies done on the patients in this report suggest that markers such as CEA, PSA, CA 15-3, CA 19-9, CA 125 absolute monocyte counts, and T-cell counts might be helpful in this regard. Direct observation in the scanning electron microscope of tumor cell mononuclear cell interactions of the type we described in 1978, might also be helpful.⁽¹⁹⁾

Who should pay for multiple immunotherapy agents for poor prognosis patients with cancer? One could argue that the same payees who financed the failed chemotherapy and radiation therapy in grade 3 patients with brain and pancreatic cancer should be candidates for this role. The answer to this question seems out of the purview of a medical practitioner such as the author, but in a country that is able to send a man to the moon and a computer to Mars, an answer should be able to be found.

Finally, it is our hope that this report will be helpful to physicians and patients who are investigating adjunctive cancer treatments. We have tried to answer the following questions: (1) What is the scientific rationale of the treatment? (2) How many patients have been treated by the methods proposed? (3) Exactly what is being used and how is it prepared? (4) How many untoward results have resulted from the treatment? (5) Will involvement in a treatment program of this type prevent a physician from using simultaneously other modalities that might help? (6) How successful has the treatment program been? It would seem the answers to these questions should be the minimum required by physicians and patients who are considering adjunctive or any type of additive cancer therapy.

SUMMARY TABLE AND PATIENT SYNOPSES

Summary table and inclusive synopses of 52 patients treated with immunomodulation between 1991 and 1997. In each case, there is a subjective evaluation of the treatment. The grading system that was used for the purpose of this paper is as follows:

Grade 1 - Localized (entirely confined to organ of origin).

Grade 2 - Direct extension and/or nodal involvement.

Grade 3 - Distant metastasis (spread to tissue or organs remote from origin).

SUMMARY TABLE REGARDING 52 PATIENTS WITH CANCER TREATED WITH IMMUNOTHERAPY 1991-1997

Synopsis Case Number in Text	Type of Cancer	Grade at Diagnosis*	Grade when seen	TF rec'd	BCG rec'd	MBV & Coley's rec'd	LBL rec'd	Date Diagnose d	Months between Immuno & 07/97	Months between Immuno & Death	Radiation	Chemo	Effectiveness
2	Breast	1	1	15	15	15	0	02/77	245	--	No	No	Satisfactory
5		2	2	141	134	145	0	12/80	199	--	Yes	Yes	Equivocal
9		2	2	39	39	39	14	07/88	108	--	No	Yes	Satisfactory
10		2	2	33	34	33	5	07/86	132	--	No	Yes	Satisfactory
11		Unknown	Unknown	73	72	73	0	07/86	132	--	No	Yes	Satisfactory
16		2	3	16	17	16	8	07/88	--	13	Yes	Yes	Equivocal
18		1	3	4	4	4	0	09/88	14	--	Yes	Yes	Satisfactory
24		3	3	12	12	12	11	07/90	--	63	Yes	Unknown	Failure
25		2	3	5	4	5	4	12/90	--	2	Yes	Yes	Failure
39		2	3	6	6	6	3	11/93	--	7	No	Yes	Failure
40		Unknown	Unknown	4	4	4	4	06/93	Unknown	Unknown	Unknown	Unknown	Failure
41		1	1	41	41	42	0	03/93	52	--	No	No	Satisfactory
50	1	1	26	26	26	0	01/95	26	--	Yes	No	Satisfactory	
4	Lymphoma	3	3	24	19	18	5	06/77	222	--	Yes	Yes	Success
7		3	3	3	3	3	3	08/85	--	3	No	Yes	Failure
12		3	3	82	82	82	20	02/87	125	--	No	Yes	Satisfactory
19		2	2	33	31	33	15	02/89	101	--	No	Yes	Satisfactory
27		3	3	35	34	36	20	05/91	--	31	No	Yes	Equivocal
33		3	3	4	4	4	4	01/92	31	--	Yes	Yes	Satisfactory
38		1	1	42	41	39	20	12/92	--	45	No	No	Failure
42	Unknown	Unknown	6	6	6	1	07/93	9	--	No	Yes	Failure	
15	Prostate	1	3	6	6	6	6	01/88	20	--	Yes	Yes	Satisfactory
22		3	3	43	42	43	19	03/90	86	--	Yes	Yes	Success
36		1	3	11	11	11	11	10/89	--	12	Yes	Yes	Failure
45		1	3	2	2	2	0	07/93	--	1	Yes	Yes	Failure
52		3	3	29	29	29	16	06/95	25	--	Yes	Yes	Equivocal
6	Colon	1	1	78	78	77	0	07/84	156	--	No	No	Satisfactory
21		1	1	62	62	61	20	09/89	94	--	No	No	Satisfactory
26		3	3	3	2	3	2	01/91	--	1	No	No	Failure
44		3	3	3	2	3	3	02/93	--	2	No	Yes	Failure
28	Lung	3	3	2	2	2	2	07/91	--	4	Yes	No	Failure
29		3	3	8	8	8	8	08/91	--	5	Yes	No	Failure
46		1	1	43	43	40	25	09/93	--	46	No	No	Equivocal
49		3	3	1	1	1	0	01/95	--	7 days	Yes	No	Failure
51		3	3	2	2	3	2	05/96	--	1	Yes	No	Failure

Grade 1 = Localized (entirely confined to organ of origin).

Grade 2 = Direct extension and/or nodal involvement.

Grade 3 = Distant metastasis (spread to tissue or organs remote from origin).

Synopsis Case Number in text	Type of Cancer	Grade at Diagnosis	Grade when seen	TF rec'd	BCG rec'd	MBV & Coley's rec'd	LBL rec'd	Date Diagnosed	Months between Immuno & 07/97	Months between Immuno & Death	Radiation	Chemo	Effectiveness
13 35	Endometrium	2 1	2 3	38 2	38 2	38 2	0 2	04/87 04/92	123 --	-- 4	Yes No	No Yes	Satisfactory Failure
3 23	Ovary	3 3	3 3	38 31	37 30	37 31	0 29	08/79 05/90	215 85	-- --	No No	Yes Yes	Success Equivocal
31 47	Esophageal Junction	2 3	3 3	1 38	1 38	1 36	0 24	12/91 11/93	-- 43	1 --	Yes No	Yes No	Failure Success
20	Osteogenic Sarcoma	1	3	2	1	2	2	01/90	18	--	Yes	Yes	Satisfactory
1 30	Mouth	1 1	2 1	45 53	46 52	46 51	25 8	11/79 01/92	-- 65	77 --	Yes Yes	No No	Equivocal Equivocal
43	Stomach	1	3	4	4	4	4	09/93	--	3	No	Yes	Failure
37	Pancreas	2	3	5	5	5	5	08/92	--	2	Yes	Yes	Failure
34	Melanoma	1	1	20	20	19	17	10/92	--	18	No	Yes	Failure
14	Parotid Gland	2	3	20	19	19	10	01/91	23	--	Yes	No	Equivocal
8	Penis	1	1	63	63	63	17	11/86	Unknown	Unknown	No	No	Equivocal
17	Cervix	2	3	6	6	6	6	08/88	--	5	Yes	No	Failure
48	Bladder	1	1	9	9	9	0	08/94	35	--	No	No	Satisfactory
32	Leukemia	N/A	N/A	8	8	8	5	01/92	--	7	Yes	Yes	Failure

Case 1: This man at age 59 was found to have a grade 1 squamous cell carcinoma of his mouth which was treated with excision and drainage. He was a long time patient of this clinic and he decided to forego immunotherapy. At age 69, the tumor recurred and he again had excision and radiation and then decided on immunotherapy. He received BCG (46), TF (45), MBV (46) and LBL (25). After 51 months he elected to stop immunotherapy. The tumor then recurred and he opted for local excision and radiation without resuming immunotherapy. A metastatic tumor appeared in his neck six months later and he decided to let nature take its course. He died at age 75 with tumors throughout his neck and pharynx. An argument could be made that the five years of tumor free existence, and the recurrence shortly after immunotherapy was discontinued might have been related to the effects of the immunotherapy. Accordingly, we will classify this patient as equivocal.

Case 2: This patient was 31 years old when in 1977, she was found to have an intraductal carcinoma *in situ* of her breast. Several years before she had a shallow malignant melanoma and has a strong family history of cancer so she elected to have preventive immunomodulation therapy. She had BCG(15), TF (15) and MBV (15) over a period of 15 years. She then moved to the West Coast. She appeared for a checkup in 1993 and there was no evidence of recurrence of either the melanoma or breast cancer. She opted to take one injection of BCG, MBV and Coley's toxin in 1993. She was contacted (7/97) and she remains well. This case is considered satisfactory.

Case 3: This patient was 16 years old when a grade 3 carcinoma of the left ovary was removed in 08/79. (Case number 5, previous communication).⁽⁷⁾ Malignant cells were found in abdominal ascites. Her local oncologist gave her a very poor prognosis so she presented herself for treatment at this clinic. Immunotherapy was begun and she was given, at monthly intervals, cisplatin in modest dosage. She was also given BCG (37), MBV (37) and TF (38) at increasing intervals for 46 months. She had a large hydatidiform cyst removed from her remaining ovary in 1988 and has had two uneventful pregnancies since that time. This case in our opinion best fits in the success category since we feel that a grade 3 carcinoma in the ovary of a 16-year-old would not have been expected to respond to a modest dose of cisplatin.

Case 4: This woman was 39 years old when she was diagnosed with generalized Hodgkin's in 06/77. (Case number 1, previous communication).⁽⁷⁾ Huge cervical nodes were present and growing in spite of her having received chemotherapy and radiation therapy at two medical centers. Her white blood count was under 2000 as a result of high dose methotrexate therapy she had received six months before. She was started on immunotherapy in 01/79 and over the next six months the nodes disappeared. She was first seen monthly, then at six-month intervals and then at yearly intervals at this clinic and has received BCG (19), MBV (18), TF (24) and LBL (5). She was last seen in 08/91 and at that time was well and healthy. A follow-up call on 11/97 revealed that she was alive and well. We consider this case as a successful response.

Case 5: This woman was 38 years old when an infiltrating carcinoma of the breast was discovered. Two of 10 axillary nodes tested positive for metastatic disease. She had very

poor veins and several attempts to get IV ingress for chemotherapy failed. (Two shunts clotted and present methods of IV ingress had not been developed). She had two injections of Cytosan, which caused a generalized febrile reaction and a severe rash. She stopped an attempt at radiation therapy after two treatments because she felt it caused severe nausea and diarrhea. She then opted for immunotherapy, which was continued for 12 1/2 years when she stopped. She received BCG (134), TF (141) and MBV (145). This case is considered equivocal, although it certainly gives a strong suspicion that a patient with grade 2 adenocarcinoma of the breast would not have had this survival without any treatment at all.

Case 6: This woman who had a strong family history of colon cancer had a malignant polyp removed from her colon on 07/84 when she was 62 years old. As a long time patient of this clinic she opted for immunotherapy. Since the diagnosis she received BCG (78), TF (78), MBV (77) and she continued to receive treatments for 13 years. Colonoscopies have revealed benign polyps on several occasions over the years of treatment. We considered this a satisfactory result. Whether or not this program may have been preventive of other colon cancers due to the familial nature of this disease, will never be known.

Case 7: This man was 38 years old when he developed a small cleaved and large cell lymphoma in 08/85. He retired from his job and spent the next 10 years of his life seeking a cure. He received five courses of M-BACOD and five courses of CHOP after which he still had malignant cells in his bone marrow. In 1990, he received seven courses of DHAP. In 1992, he received additional chemotherapy with cladribine and CEPP. In 1994, there were still malignant cells in bone marrow. At this time, his bone marrow was markedly depressed. He had also received monoclonal antibody treatments. He began twice weekly therapy with urine extract obtained at the Brudzinski Clinic in Houston, Texas. He continued this for about a year. He presented himself for therapy at the Waisbren Clinic in 12/94. He was markedly anemic and had generalized lymphadenopathy. Over the next four weeks he received TF (3), MBV (3), BCG (3) and LDL (3). He did not return. Follow up revealed that he died in 03/95. This must be considered a treatment failure. His persistence in obtaining chemotherapy in multiple centers around the country may have prolonged his life.

Case 8: This male was 45 years old when a squamous cell carcinoma of the penis was found during a circumcision operation in 11/86. He underwent a partial penectomy with urethroplasty and a left inguinal node dissection. Regional lymph nodes were negative for spread. Consultants did not suggest radiation and chemotherapy so it was decided to give immunotherapy. He was given this monthly until 10/09/89 when the treatments were spaced to every two months. In 11/90 lymph nodes appeared in his inguinal area and a biopsy showed it to be a metastatic squamous cell carcinoma. A complete bilateral node dissection was done. He was restarted on immunotherapy and this was continued until 10/93. In all he was given BCG (63), TF (63), MBV (63) and LBL (17) over an 83-month period. He was lost to follow up. This case is considered equivocal in that, at the least, an 83-month survival after a carcinoma of the penis that had spread is unusual.⁽²¹⁾

Case 9: This woman was 52 years of age when an adenocarcinoma of the breast grade 2 with involvement of 7 to 14 nodes was diagnosed in 07/88. She was treated for six months with Cytosan, methotrexate, 5-FU and prednisone. She was a long time internal medicine patient at this clinic and opted for adjunctive immunotherapy. She was given TF (39), BCG (39), MBV (39) and LBL (14) over a period of 38 months. She is well with no symptoms or signs of carcinoma 108 months after diagnosis. We have classified this result as satisfactory with full knowledge that she might have done just as well with the chemotherapy that had been used. However, she is representative of the type of patient that we feel should be given immunomodulation therapy because even with chemotherapy, there is a high rate of recurrence (10 to 20%).⁽¹⁷⁾

Case 10: This woman had a 2.5 cm mass removed from her breast in 07/86 when she was 66 years old. Five of 17 axillary nodes, which were examined, contained metastatic adenocarcinoma cells. No other spread was found. She was given a six month course of Cytosan, 5-FU, Adriamycin and methotrexate, she also opted for immunotherapy and she received BCG (34), TF (33), MBV (33) and LBL (5) over a period of 7 1/2 years. She was living and well in 12/97. This case is considered satisfactory because the result could have been achieved by chemotherapy alone.

Case 11: This woman was 46 years old when a centrally located adenocarcinoma of the breast was removed in 07/86. Due to the location of the tumor and the fact that the area was drained by central lymph nodes, she was given a six-month course of chemotherapy and then started on tamoxifen 10 mg a day by mouth. During the ensuing 11 years she was given BCG (72), TF (73) and MBV (73). This case is classified as satisfactory since the chemotherapy might have been all that was necessary. As a long time patient of this clinic, the patient had enough confidence to accept our suggestion that she should receive immunotherapy on occasion to perhaps reduce her 10 to 20% chance of recurrence.⁽¹⁷⁾

Case 12: This male was 63 years of age when on 02/87 a large nonresectable and non-Hodgkin's lymphoma with multiple lymph node involvement was found during an abdominal operation to correct the bowel obstruction that had been caused by this lesion. He was put on a monthly cycle of ifosfamide, vincristine, doxorubicin and prednisone regimen for six months. He elected to have adjunctive immunotherapy, which he has continued to the present. He has received BCG (82), TF (82), MBV (82) and LBL (20) at intervals that have decreased to every two months. An exploratory laparotomy during an abdominal hernia repair in 1993 revealed no evidence of lymphoma and he has remained well and active. Due to the chemotherapy regimen used, we will never know whether the adjunctive program played a role in his salutary response, but he has noted the course of other patients who had chemotherapy at the time he did and has elected to continue sporadic immunotherapy.

Case 13: This woman at 67 had an endometrial cancer removed in 04/87. She was given a course of radiation. She was a long time patient at this clinic and opted for immunotherapy. She continued this therapy with increasing intervals between treatments until 12/93. She received BCG (38), TF (38) and MBV (38). There has never been any

sign of spread and she was alive and active in 12/97. Since she might have done as well just with surgery and radiation, we can only evaluate this case as satisfactory.

Case 14: In 1988, this man was 48 years old when a tumor of the parotid was removed and called benign. In 1991, the tumor recurred and invaded the maxillary sinus. This was malignant. He was given 7400 cGy of radiation at a cancer center. In 07/95, there was recurrence and when the region was explored the tumor was considered to be inoperable. He was turned down for further surgery and radiation at two cancer centers. He presented in severe pain in 08/95. Having heard of the surgical approach to tumors of this type by Dr. John Lore' in Buffalo, New York, we asked him to see Dr. Lore'. Dr. Lore' did resect the remaining parotid gland. He did a radical neck dissection and restructured the mandible in 10/95. Immunotherapy was started concomitantly. In 07/96, recurrence of a mucoepidermoid carcinoma was found in the foramen spinosum and radiation therapy was given. By CT scan this resolved in 05/97. In 06/97, the patient developed what seemed like a tic douloureux. A brain lesion was found and brain surgery was performed in 10/97. He has received BCG (19), TF (20), MBV (19) and LBL (10) over a period of 22 months. Since he is still living in 07/98 with a tumor that was thought to be inevitably fatal two years before, this case might be considered equivocal. Of course, the brilliant surgery of Dr. Lore' should be given most of the credit.

Case 15: This man was found in 01/88 to have a grade 1 carcinoma of the prostate at age 62. A suprapubic prostatectomy was done and he was started on Lupron. In 1991, bony lesions were found in his pelvis and he received maximum radiation to that area. The bony lesion then became stable by bone scan. On 11/95, a follow-up PSA test revealed the level to be 124. He then had a CT scan of his abdomen and chest and a repeat bone scan and no evidence of active lesion was found. He then presented himself to this clinic for immunotherapy. As is the practice of this clinic, we suggested to him that he have a MRI of his brain since no focus that had caused a rise in the PSA had been found. This MRI showed that he did have cerebral metastases. This was removed by surgery and was found to be a metastatic cancer of the prostate. While the diagnostic studies were being done, he received BCG (6), TF (6), MBV (6) and LBL (6). Within two weeks after his brain surgery, his PSA normalized. He did not return to this clinic (home base was Florida) and he has remained living and well in 12/97. This case was labeled as satisfactory, but there is a strong probability that removal of the solitary metastases was responsible for the gratifying outcome.

Case 16: This woman at age 31 was found in 07/88 to have an adenocarcinoma of the breast with three positive axillary nodes. She was given a six-month course of Cytoxan, methotrexate and 5-FU. In 07/91, she was found to have extensive pulmonary and bone metastases at her chest wall and she was given radiation therapy to the lung. Her CA 15-3 was 192 and her CEA titer was 25. She had a marked depression of her bone marrow when she presented herself to this clinic in 10/91. She had some symptomatic relief from radiation of her chest wall metastases and she refused further chemotherapy that had been offered to her. She was started on a full immunomodulation program including levamisole and isotretinoin by mouth. In 12/91 the chest pain increased. At that time, she had a pleural effusion, which was tapped. In 01/92 she rather abruptly began to feel

better and the lung lesion showed definite improvement. The CEA titer lowered to 18. Clinical improvement continued and in 05/92 her CA 15-3 had decreased to 57 and all of her bone and lung lesions appeared to have stabilized. She returned to full-time work. A bone scan in 06/92 showed improvement of the diffuse osteoblastic metastases particularly in the lumbar spine. In 07/92 her CEA titer was 5.5 and she was still working full-time with no pain. In 08/92 her CEA titer still was low, but her CA 15-3 had risen to 71. She was asymptomatic and still working full-time at this time. A CT scan of her chest in 09/92 showed a reduction in pleural effusion with moderate residual and concomitant improvement of the consolidation in the right lung field. There were still presumed stable nodular metastases in the posterior basilar segment of her left lung. In 10/92 her CA 15-3 rose to 135 and her CEA titer rose. Her cough had returned and a hard node had appeared on her neck. At that time, she developed a compression fracture of her thoracic vertebra. Her pleural effusion returned and yielded adenocarcinoma cells. A bone scan revealed numerous new lesions. She decided against any further therapy and died at home in 11/92. The patient had received BCG (17), (TF) 16, MBV (16) and LBL (8) and took by mouth levamisole and isotretinoin over the period that she was being treated. Although patient died there seems to be rather unequivocal evidence that the immunomodulation therapy led to some extra good quality of life in this patient. The cessation of pain for 12 months, the fall in her CEA-titer and CA 15-3, the improvement on the CT scan and her return to work all lend credence to this conclusion. Of particular interest is the demonstration that the CEA titer and CA 15-3 may well be valuable surrogate markers for the response to immunotherapy. We classify this patient as equivocal, since she died of her disease but she was reminiscent of the patient mentioned in the introduction whose response led to the endeavor being presented here.

Case 17: This woman was 35 years old when cancer of the cervix was found in 08/88. When the uterus was removed, nodes were found to be involved. She then received eight weeks of radiation therapy. In 01/91 her laparoscopy revealed liver involvement and metastatic nodules throughout the abdomen. She presented herself at this clinic in 05/91 having decided to forego chemotherapy. During the next two months she received MBV (6), TF (6), LBL (6) and BCG (6). The treatments were tolerated well. She died in 10/91 so the case has been classified as failure.

Case 18: This woman in 09/88 had a grade 1 carcinoma of the breast removed at age 36. In spite of there being no nodes, she was given six months of chemotherapy. In 01/92 multiple metastases were found throughout her spine. At various clinics, she was given megestrol acetate, goserelin, aminoglutethimide and radiation therapy. She had rather stable bone pain when she presented at this clinic in 05/96 and a bone scan showed multiple spine lesions. She was given BCG (4), TF (4) and MBV (4) over a period of two months. She became discouraged when during this time her CA 15-3 rose from 90 to 140, so she decided to manage herself on a program we worked out with her. It included: levamisole 50 mg a day, isotretinoin 20 mg and cimetidine 400 mg a day orally. She was to take twice a week, interleukin-2 7 million units subcutaneously and alpha-interferon 4 million units. We have no way of knowing how compliant this strong-minded woman was with this program. However, when contacted in 07/97, she stated that she was active

and holding her own and that she would call us when she felt she needed to. All that can be said about this treatment is that it was satisfactory.

Case 19: This man was 55 years old when a grade 2 Hodgkin's disease was found by an inguinal lymph node biopsy. His bone marrow was clear. He was given a six-month course of nitrogen mustard, vincristine, procarbazine and prednisone. In addition, he was given BCG (31), TF (33), MBV (33) and LBL (15) over a period of 33 months. The inguinal nodes normalized and he opted to stop therapy and as of 12/97 was well and active. This is considered a satisfactory result with the realization that the chemotherapy may have been the sole factor responsible for end result.

Case 20: This man was age 16 when his tibia was removed on 01/90 because it contained an osteogenic sarcoma. He received chemotherapy, which included cisplatin, Adriamycin, ifosfamide and VP-16 on two occasions. There was "poor toleration and severe bone marrow depression." From 1991-1995, multiple pulmonary metastases were found. Some nodules were removed, but new ones appeared. During the 18 months before he presented at the Waisbren Clinic he had received some sort of vaccine treatment in Mexico. When seen in 01/96 he appeared chronically ill. He was given a program of levamisole, isotretinoin, and cimetidine to be taken by mouth and interleukin-2 and interferon to be self-injected subcutaneously. He elected to continue copper sulfate and mushroom extract. He was given BCG (1), TF (2), MBV (2) and LBL (2) over a period of one week, he never returned. When contacted on 07/09/97 his mother said that he was still very ill, but that he was alive. We have no way of knowing whether or not he complied with this program nor what the result was. However, there was no toxicity, so we would consider this as a satisfactory result even though the patient's preferences supervened over our feeling that more vigorous immunotherapy would be appropriate.

Case 21: This woman was 65 years old when she presented at this clinic with blood in her stool in 09/89. A grade 1 carcinoma of the colon was removed and a colostomy was done. She was a long time patient of this clinic and she opted for immunotherapy. She received BCG (62), TF (62), MBV (61) and LBL (20). The CEA titer prior to the surgery was 24. It normalized two weeks after surgery and has been normal since. Yearly evaluations have failed to reveal any evidence of recurrence or spread of the tumor and she is leading an active life. This is considered only a satisfactory result since it might have occurred without immunotherapy. A point of interest is that at diagnosis, her monocyte count was 24%. The unpublished studies in our laboratories had shown this to be an ominous prognostic sign which, fortunately in this case, did not turn out that way.

Case 22: This man was found in 03/90 to have a grade 3 carcinoma of the prostate with bone metastases at age 53. There were numerous metastases throughout his pelvis and he was in constant pain. He had received flutamide and LHRH agonist without response and he been advised that further treatment would be futile. He elected to try immunotherapy and decided to forego the LHRH and flutamide. His PSA in 04/90 was greater than 100. By 06/90 his PSA was normal. This may have been an effect of previous therapy. He started on levamisole 50 mg a day in addition to immunotherapy. His bone scans showed multiple lesions in his pelvis. By 08/90 he stated that his bone

pain had completely gone away, although the lesions on the bone scan were still clearly visible in 10/90. He began to take ketoconazole and isotretinoin by mouth. Ketoconazole was started because his testosterone level was 31. The level went to zero, but he discontinued it and in 02/92 it had crept back to 184. In 11/90 he had recurrence of bone pain, so he was given radiation therapy to his pelvis. By 01/91 his pain was under good control and working full-time. A bone scan in 04/92 showed definite improvement in the lesions previously described as blastic metastases. At that time the patient decided to space out his immunotherapy to every two months and in 10/92 he discontinued therapy. In 10/93 his PSA was found to be 8.1 and he continued to feel well. In 04/94 his PSA had risen to 19.6. He continued to feel well and opted to forego therapy. In 04/95 a new lesion was found in his cervical vertebra. This was treated with radiation in 06/95 (4000 cGy). In 05/96 there was an increase in multiple bone lesions by bone scan and at that point he decided to resume immunotherapy because metastases to his humerus was causing severe pain. At that time, his PSA was 1819 and it fell to 249 by 06/96. By 11/96 the PSA had again risen to 540. At that time, we began to inject Coley's vaccine intravenously in order to get the theoretical benefit of hyperthermia. In 12/96 he developed weakness in his left leg due to a metastatic lesion at T8. This was treated successfully with local radiation and he regained complete function. Immunotherapy was continued but his PSA was 554 in 05/97. Symptomatic improvement continued over the summer of 1997 and he went back to full-time work. He received in 08/97 another 3500 cGy of radiation to his shoulder. Symptomatic improvement has continued and he spent one-month duck hunting in 10/97. Over the years that he has received immunotherapy, he has received BCG (42), TF (43), MBV (43) and LBL (19). We have labeled this case a success with an assist from judicious local radiotherapy. Whether he might not have had the recurrence if he had continued immunotherapy on a monthly basis is a matter of conjecture.

Case 23: This woman was age 36 when adenocarcinoma of the ovary with multiple omentum metastases was found in 05/90. She was given a course of Cytoxan and carbo-platinum monthly for six months and opted to try immunotherapy as well. She refused further chemotherapy after five months of the Cytoxan and carbo-platinum. She felt well when the chemotherapy was stopped and she returned to full-time employment. In 05/91 she developed a mass on her operative incision which on biopsy showed metastatic ovarian carcinoma. A CT scan of the liver showed metastatic lesions. In 08/91 levamisole, cimetidine and isotretinoin were added to her immunotherapy program. A laparoscopy in 09/91 showed metastases from serous adenocarcinoma of the ovary. A consultation was sought from a new oncologist who administered alpha interferon and intraperitoneal monoclonal antibody. In 03/92 he re-evaluated the patient and concluded the treatment had not been effective. In 07/93 a nodule was removed from her abdomen that was positive for carcinoma. She stopped immunotherapy at that time. She received BCG (30), TF (31), MBV (31) and LBL (29) over 33 months. Her husband reported her living and well in 10/97. It seems likely that she received Taxol in some form or another after 07/93 but information in that regard was not volunteered. This case is classified as equivocal since a survival for seven years after a grade 3 carcinoma of the ovary is very unusual.

Case 24: This 61-year-old woman in 07/90 was found to have bilateral adenocarcinoma of the breasts with bone metastases to the ribs, clavicles and hips. Her skin had started to break down over both breasts. The consensus of three oncology consultants was that she should have bilateral mastectomies, radiation to the bone lesions and long term tamoxifen. This was done and she also opted for immunomodulation therapy. She received BCG (12), TF (12), MBV (12) and LBL (11) over a period of 11 months. She took by mouth levamisole, isotretinoin and tamoxifen. In 05/91 a bone scan showed progression of bony lesions and during that month she suffered a collapsed vertebra due to the metastases. She moved from this area and we understood at that time that she was to try further chemotherapy. We talked to her husband in 05/96 and he stated that she had died in 11/95. This case must be considered a failure of immunomodulation therapy although a case could be made for it having prolonged her life.

Case 25: This woman was 39 years old when in 12/90 she developed inflammatory carcinoma of the breast with node metastases. When seen at this clinic 15 months after diagnosis, she had had two courses of chemotherapy and a course of intensive radiation with the help of autogenous bone marrow transplant. In spite of these treatments, she had numerous subcutaneous masses and bone and lung metastases. Her CEA titer was 19. She was given BCG (4), TF (5), MBV (5) and LBL (4) over a period of one month. At that time brain metastases were found and after several radiation treatments to her brain, she decided to forego further treatment and died 17 months after diagnosis. This case was a failure. Her CA 15-3 was 221 when she was first seen and rose to 345 just before she died.

Case 26: This male was 43 years old when an adenocarcinoma of the colon that had metastasized to his liver was found on 01/91. He refused any attempt at chemotherapy and presented himself for an attempt at immunomodulation therapy at this clinic in 05/92. He had ascites and a large liver and felt very weak. He was jaundice and had an ammonia level of 450. He was given BCG (2), TF (3), MBV (3) and LBL (2) over a period of 12 days. He then returned to his home which was out of state. Two weeks later, he returned for treatment. At that time, he was moribund and was hospitalized for comfort care. He died in 06/92. This was considered a failure.

Case 27: This man presented in 05/91 with a large inguinal node that proved to be due to a large cell lymphoma. He received a six-month course of chemotherapy and immunotherapy was begun after one month. During the next 29 months, he received BCG (34), MBV (35), TF (35) and LBL (20). Two years after therapy was begun, large nodes appeared in his neck, axilla and mediastinum for which he received radiation therapy. After which, the patient declined further therapy and died 31 months after diagnosis. Whether the fact that after a year of monthly treatments the patient requested that his treatment be spaced out to six weeks and then eight weeks was a factor in the recurrence will never be known. The 31 months' survival in a large cell Hodgkin's lymphoma leads us to consider this an equivocal result.

Case 28: This woman was 37 years old when in 05/76 an adenocarcinoma of the breast was treated with a mastectomy. There were 18 lymph nodes, which were positive for

cancer. She was treated with 5-FU, methotrexate and Cytosan and immunotherapy was begun. She was also given a course of radiation. Immunotherapy was continued until 10 years had passed. At that time she was in good health with no complaints. In 1990, the wound of her 1976 operation broke down. When I saw her in 05/91, a CEA titer of 41 was noted and her CA 15-3 was 37. In 07/91 a pleural biopsy was done which showed a metastatic squamous cell carcinoma to the ribs and pleura. It was felt that the primary tumor was in the lung in an area that had been thought to have been scarred due to radiation therapy. The patient was in severe pain due to axillary involvement. The patient and her family requested another try at immunotherapy and began in 07/91. A course of radiation was given to the axilla, but the rib pain continued so immunotherapy was discontinued. She received only BCG (2), TF (2), MBV (2) and LBL (2) during this course of treatment. She was admitted to a hospice where she died in 11/91. This case was considered a failure in the treatment of a generalized squamous cell carcinoma of the lung. The successful treatment of her breast cancer was recorded in our previous report.⁽⁷⁾

Case 29: This man was 57 years old when in 08/91 a grade 3 inoperable squamous cell carcinoma was found in the lung. There was a spread throughout his mediastinum. He was started on radiation and immunomodulation therapy. He received BCG (8), TF (8), MBV (8) and LBL (8). He died suddenly at home five months after combined therapy was started. A specific cause of death was not ascertained since an autopsy was not performed. He did have an artificial valve due to a previous bacterial endocarditis suffered when he was severely burned. This case was considered a failure.

Case 30: This man was 69 years old when a squamous cell carcinoma of the mouth was discovered in 01/92. It was surgically removed and no further treatment was suggested. He opted for immunotherapy and it began on a monthly basis. After 18 months, treatments began to be spread out to six-week intervals. In 08/95, a carcinoma of the left ventral tongue and an *in situ* carcinoma of the floor of the mouth were found. No evidence of other spread was found but there was a palpable submental node. The patient refused radical surgery and opted for radiation and intensification of immunotherapy. He then received 7000-cGy radiation. Immunotherapy began at two-week intervals and to the present has been given monthly. He was alive and well on 12/97 with no evidence of recurrence. He has received BCG (52), TF (53), MBV (51) and LBL (8). This probable response was consistent with our previous experience in regard to this type of tumor. It recurred when immunotherapy was spaced out and seemed quiescent when he was given more frequent treatments. We consider this result equivocal. In 02/98 an adenocarcinoma of his stomach was removed, and he is now receiving intensified immunotherapy since oncology and radiation therapy physicians who were consulted in this regard turned him down for chemotherapy and radiation therapy.

Case 31: The patient was 52 years old when a large, inoperable carcinoma of the cardioesophageal junction was found in 12/91. He was given extensive radiation therapy in 01/92 and 02/92. This was followed by three months of chemotherapy. Prior to his examination at the Waisbren Clinic in 10/92 a bypass between his vena cava and his right auricle had treated a superior mediastinal syndrome. His radiologist and oncologist felt

that treatment options had been used up. He was given a single immunotherapy BCG, MBV, TF and LBL in 10/92. He did not return for further treatment and died at home in 11/92. This patient is included to meet our strict criteria of all inclusiveness and he is being classified as a treatment failure even though it was apparent that a fair trial of immunotherapy was not achieved.

Case 32: This man at age 49 was diagnosed in 01/92 as having chronic B-cell lymphocytic leukemia. Before he was seen at this clinic he had 18 months of chemotherapy given at a major center immediately after diagnosis. In mid-1995, he had extensive radiation therapy to his neck, groin and axilla in an unsuccessful attempt to shrink large lymph nodes. At that time, he also had six cycles of 2CDA. After this he developed thrombocytopenia which persisted in spite of prednisone. He had been turned down for bone marrow transplant by several medical centers. His long time oncologist suggested he stop attempts at treatment and accept the inevitable. He was unwilling to accept this advice and in 02/96 he presented himself for immunotherapy treatment. An immunotherapy program was worked out and in addition, he was to take subcutaneous interleukin-2 and alpha interferon. Coley's vaccine was to be given intravenously to cause hyperthermia. His platelets were to be kept at 15,000 units by platelet transfusion given at his home hospital at regular intervals. During the five months of this program, his white blood count varied from 59 to 200,000 and the white count in 05/96 was 80. A definite decrease in his generalized lymphadenopathy was noted. He received BCG (8), TF (8), MBV (8), LBL (5) and four intravenous injections of Coley's vaccine. He received a brisk hyperthermia reaction with the Coley's vaccine and this caused him to decide to stop treatment at this clinic after five months. It was subsequently learned that he had developed AIDS before he died in 09/96. The probability seems to be that his AIDS was caused by repeated platelet transfusions. This case was classified as a failure, although a definite decrease in the lymphadenopathy was noted after immunotherapy was begun.

Case 33: This man was 46 years old when in 01/92 he was diagnosed as having a large cell lymphoma. He received eight courses of chemotherapy with M-BACOD and extensive radiation with only partial response. These were given at several medical centers. In 1993 he began treatment with the IV administration of a material extracted from urine which was supplied by a clinic in Houston and was self-administered. He presented himself at this clinic in 12/94. He had lesions in his bone marrow, pelvis and soft tissue masses. Over the next two months he received BCG (4), TF (4), MBV (4) and LBL (4) by injection. He took by mouth levamisole, cimetidine and isotretinoin and then discontinued these treatments. When contacted in 10/97, he stated that he was holding his own and still running an active business. He did not reveal what other treatments he had received between 01/95 and the present. We will never know what might have helped this patient, but he exemplifies the type of patient who has the motivation and finances to explore all avenues. It appears that he has succeeded in prolonging his life and we classify this result as satisfactory.

Case 34: This woman was 41 years old when she presented with a deep malignant melanoma on her shoulder. This occurred while she had been on monthly

immunotherapy for multiple sclerosis for 10 years.⁽²¹⁾ The melanoma rapidly progressed in spite of a course of cisplatin, DTIC and interleukin-2 and BCG (20), TF (20), MBV (19) and LBL (17) which was given over a period of 14 months. She died 18 months after onset with fungating lesions throughout her body. This treatment was a failure. Of interest is the fact that she developed malignant melanoma while she was receiving immunotherapy for multiple sclerosis.⁽²¹⁾ We did note regression of specific lesions when they were injected with a mixture of BCG and Coley's vaccine. This case was considered a failure.

Case 35: This woman at age 42 had an endometrial cancer removed in 04/92. She had a hysterectomy and no further treatment. In 03/94 there was a recurrence of a tumor in the vaginal vault and eight inguinal nodes. She had the nodes removed and received eight weeks of radiation. In 09/94 liver metastases was found. During seven months of chemotherapy the liver metastases almost disappeared only to start growing again in 08/95. She went to Mexico for "hydroperoxide chelation." When seen in this clinic in 01/96 her CA-125 level was 1048 and she had severe lymphopenia. A recent liver scan showed multiple liver lesions. Even though the probable futility of treatment was thoroughly explained to her she opted to try immunotherapy. She was given BCG (2), TF (2), MBV (2) and LBL (2) for one month. To achieve hyperthermia, she was given 0.5 ml of Coley's toxin IV and this did achieve a brisk temperature rise to 104° F. By 02/96 she reported herself too sick to come from out of state for therapy and stated that Paxil be tried. She died in 05/96. This case is classified as a failure.

Case 36: This man was 64 years old when a carcinoma of the prostate was discovered in 10/89. A total prostatectomy was done. In 1992 he had an orchiectomy and radiation therapy. In 05/95 generalized bone metastases was found and his PSA was 142. He was started on flutamide. He presented here in 08/95 with extreme generalized bone pain and a PSA of 257.5. He was given BCG (11), TF (11), MBV (11) and LBL (11). He also took interleukin-2 4 million units subcutaneously weekly and interferon alpha 4 million units subcutaneously weekly. By mouth, he took levamisole, cimetidine and isotretinoin. After eight months of treatment, which did not seem to be helping his pain, he decided to stop all therapy and he died in a hospice in 08/96. This was a definite failure in counter distinction to cases 15 and 22.

Case 37: This man was 64 years of age when in 08/92 he was found to have an infiltrating ductal carcinoma of the pancreas. Five of eight regional lymph nodes were found to show tumor involvement. He received both chemotherapy and radiation therapy during the ensuing six months. He presented himself at this clinic in 03/93 with generalized complaints of weakness and abdominal pain. A CT scan found that he had multiple liver metastases. He opted to try immunomodulation therapy even after being informed of his dire prognosis. He received BCG (5), MBV (5), TF (5) and LBL (5). He discontinued therapy in 04/93 because of intractable pain. He died several weeks later. This case is classified as a failure.

Case 38: This man was 81 years old when in 12/92 during a right carotid endarterectomy a node was found which showed changes of "diffuse intermediately differentiated lymphocytic type lymphoma of a B-cell phenotype." The oncologist at the medical center where the endarterectomy was done did not feel any treatment was indicated at that time. As a long time patient at this clinic, he decided on immunotherapy and began treatment in 02/93. In 02/95 a pulmonary nodule in the perihilar region was found on a chest x-ray. This was first interpreted as being due to recurrent lymphoma. In 08/96, he had an episode of hemoptysis and the hilar mass, which had been quiescent for 18 months, had greatly increased in size. A biopsy of the cervical lymph node revealed adenocarcinoma. It was felt that this was from a primary adenocarcinoma in the lung. Well-differentiated lymphoma cells were also seen. At the request of the patient and his family, radiation therapy was begun. He died in 09/96. He received BCG (41), TF (42), MBV (39) and LBL (20). This case is considered a failure because lymphoma and adenocarcinoma were present after three years of immunotherapy. Whether the three years of immunotherapy prolonged his life is too conjectural for him to be placed in the equivocal category.

Case 39: This woman at age 50 had adenocarcinoma of the right breast, which responded to chemotherapy, radiation and a mastectomy. At age 68, a new adenocarcinoma was discovered in the left breast with "positive lymph nodes." After surgery, chemotherapy was begun, but was discontinued after several months because of bone marrow toxicity. She presented herself at this clinic at age 69. She was jaundiced from liver metastases and cachectic. Between 09/94 and 12/94 she received BCG (6), MBV (6), TF (6) and Coley's vaccine IV (3). By mouth, she took isotretinoin and levamisole. Bilateral pleural effusions developed in 01/95 and she died in 04/95. Her CEA titer rose from 20 in 09/94 to 31 in 12/94. This case was considered a failure.

Case 40: This woman was 53 years old when in 04/93 she consented to have a baseball sized mass in her breast subjected to a needle biopsy. This revealed an inflammatory carcinoma of the breast. She had strong feelings against radiology and chemotherapy for treatment of cancer and I had strong feelings about treating a mass of this size with just immunomodulation. The compromise was that I would start her on immunomodulation if she would consent to a consultation with an excellent oncologist in her home state. She was given BCG (4), MBV (4), TF (4) and LBL (4) for one month and then was lost to follow up. Without a follow up, we cannot be sure what happened to this lady, but I would assume that she died of her tumor and was a failure.

Case 41: This woman was 89 years old when a small adenocarcinoma of her left breast was discovered. She had a simple mastectomy and was started on tamoxifen. She refused chemotherapy and opted for immunotherapy. Seven months later she had a local recurrence. This was removed under local anesthesia and monthly immunotherapy was continued. At present, she receives immunotherapy every two months. She is active and lives a full life. She and her family have requested that we continue therapy. In all, she has had BCG (41), TF (41) and MBV (42). Treatment was considered satisfactory.

Case 42: This woman was 41 years old when she was diagnosed as having a large cell lymphoma in 07/93. She was given CHOP with modest shrinkage with generalized lymphadenopathy occurring. After a second course of CHOP, she was given an autologous bone marrow transplant after intensive chemotherapy. In 07/94 she was given anti-B cell antibodies with again modest shrinkage of the lymph nodes. In 01/96, she developed viral myocarditis with heart and renal failure. In 04/96, the lymph nodes again enlarged. She presented herself to this clinic for a trial of immunotherapy in 10/96. At that time, her oncologist had declined to give her further therapy. She was given BCG (6), MBV (6), TF (6) and LBL (1). During the four months of treatment, she self-administered at home subcutaneous interleukin-2 7 million units biweekly and alpha-interferon 4 million units biweekly. There seemed to be shrinkage of the nodes in her axilla, but at the end of four months a gallium scan suggested further nodal involvement so it was mutually decided to suspend therapy. She was contacted in 10/97 and was alive and functioning. She received some additional chemotherapy between 02/97 and 09/97. This case is classified as a failure, although, the fact that she is still alive is of some interest.

Case 43: This man was 61 years old when he was found to have adenocarcinoma of the stomach in 09/93. In 05/94 metastases to the liver was found and cisplatin, Adriamycin and 5-FU were given. An elevated CEA titer was said to have normalized. In 01/95 liver metastases was again noted and in 05/95 he developed a firm mass in the sternum. In 06/95 he presented with a desire to intensify chemotherapy with his original oncologist and to augment it with immunotherapy. His CEA titer was 28 and his CA 19-9 was 96. He was given BCG (4), MBV (4), TF (4) and LBL (4) for two months. We were informed that he died in 09/95 while he was receiving additional chemotherapy. This case is considered a failure.

Case 44: This man at age 57 was found to have an adenocarcinoma of the colon with lymph node involvement in 02/93. After a hemicolectomy he was started on 5-FU. He received an apparent initial response. In 01/94 his CEA titer, which had normalized, rose to 205 and multiple liver metastases had grown. He presented at this clinic in 04/94. His CEA titer was 1079 and his CA 19-9 was 13,888. He was given BCG (2), MBV (3), TF (3), LBL (3) and alpha-interferon. After a month of this treatment, his CEA titer was 1607. He died in 06/94. This treatment was a failure.

Case 45: This man was 71 years old when he was found to have a prostate carcinoma in 07/93. He received hormonal and radiation therapy. At age 75, he had developed generalized metastases to his bone, liver and lungs, and he was in heart failure. We were prevailed on by his family to try "last ditch" therapy and he received BCG (2), TF (2) and MBV (2). In two weeks it became apparent that he could not survive so treatment was stopped. He died five weeks after first being seen at this clinic. Retrospectively, we should have not been convinced by his family to start treatment. He is classified as a failure by our strict criteria in that regard.

Case 46: This man, at age 62, had revealed at surgery an adenocarcinoma in the right upper lobe and a mucous adenocarcinoma in his right lower lobe of his lungs. The latter

lesion was found during the surgery. There was no evidence of spread of either lesion so the oncologist at the medical center in which the surgery was done advised against chemotherapy or radiation. He was a long time patient of this clinic and opted for immunotherapy. He received BCG (43), TF (43), MBV (40) and LBL (25) between 10/93 and 12/96. A new lesion appeared in his right upper lobe in 10/96. A needle biopsy revealed to be an adenocarcinoma. When this was found to be progressing, he refused radiation and chemotherapy and opted to try to participate in an interleukin-2 treated tumor associated lymphocyte program at a medical center. He was given this treatment, but he continued to deteriorate and died while under hospice care in 07/97. This case will be considered equivocal although it is consistent with our previous finding that a longer than expected survival with carcinoma of the lung in patients can be expected when a patient receives immunomodulation therapy.⁽⁷⁾

Case 47: This man at age 64 had a large carcinoma of his cardioesophageal junction, which had invaded his esophagus and his mediastinum. The carcinoma was removed in 11/93. There was nodal involvement in the regional greater curvature. The oncologist at the medical center where the surgery was done recommended no further treatment. He was a long time patient at this clinic and opted for immunotherapy. Since 12/93 he has been given BCG (38), MBV (36), (TF) 38 and LBL (24). There has been no evidence of further cancer spread and he has been well and active. He takes by mouth levamisole and cimetidine. We consider a 44-month survival of a grade 2 carcinoma of the cardioesophageal junction without any other therapy, a success of immunotherapy.⁽¹⁸⁾

Case 48: This man was 78 years old when a grade 3 recurrent transitional cell carcinoma of the bladder was diagnosed in 08/94. He was given intravascular BCG monthly for six months and a six-month course of immunotherapy. He was given BCG (9), TF (9) and MBV (9). He had recurrent tumors while under treatment with intravascular BCG and immunotherapy. However, twenty-seven months after diagnosis no further evidence of tumor was found. He had a fatal stroke in 12/97. This is considered only a satisfactory result because the result might have been obtained from the intravascular BCG that was given.

Case 49: This woman was 61 years of age when in 01/95 a biopsy of the cervical mass revealed a squamous cell carcinoma which was felt to have its origin in the lung. There was evidence of multiple mediastinal nodes. Palliative radiation to prevent a superior mediastinal syndrome was given followed by a course of cisplatin and Navelbine given at a university medical center in 04/95. She presented at this clinic in 06/95 and she was given BCG (1), MBV (1) and TF (1). She returned to her home, which was out of state and died one week after initial therapy. She was on constant oxygen when seen and suffering from radiation pneumonitis. This case was considered a failure. It is included due to our rigid, all-inclusive criteria for this report.

Case 50: This woman was 46 years of age when a grade 1 carcinoma of the breast was removed by a lumpectomy. Axillary node dissection showed 12 nodes to be devoid of cancer. Radiation therapy began, but she developed a x-ray burn and cellulitis of the breast after three weeks of treatment that necessitated antibiotic treatment. She refused

further radiation. She opted for immunotherapy. Since 05/95 she has received BCG (26), MBV (26), TF (26) and she is alive and well in 12/97. The case is classified as satisfactory.

Case 51: This man was found at age 62 to have an adenocarcinoma of the lung with widespread metastases in 05/96. In spite of radiation therapy the initial metastases were enlarging in the mediastinum and bones. He received BCG (2), MBV (3), TF (2) and LBL (2). He exhibited a brisk febrile response to the IV LBL. His CEA titer was 160 when therapy started and 168 just before his death. During the last six weeks of his life he received weekly subcutaneous interleukin-2 7 million units twice a week and interferon alpha 4 million units twice a week. He took by mouth daily levamisole 50 mg. He died two and one half months after diagnosis. This case is considered a failure.

Case 52: This patient was 69 years old when he presented in 06/95 with an enlarged prostate and a PSA of 40. A CT scan showed an enlarged prostate gland and enlargement of iliac and pelvic lymph nodes. A bone scan showed activity in the left side of the sacrum and right ischial tuberosity. A fine needle aspiration of a pelvic lymph node showed "metastatic" carcinoma probably from the prostate. Immunoperoxidase studies of the sections confirmed the diagnosis of metastatic carcinoma of the prostate. Immunotherapy with BCG, MBV, TF and LBL began while he explored other treatment options at medical centers. He opted for castration. Following the castration, his PSA went down to 1.1. Levamisole and isotretinoin were being taken orally at this time, as was ketoconazole. A repeat CT scan in 12/95 showed shrinkage of the pelvic lesions and patient felt well. He was started on bicalutamide at that time at the suggestion of a urologic oncologist. In 02/96 his PSA was 7. His testosterone level in 03/96 was 25. A CT scan in 05/96 showed further improvement in the pelvic node pathology. A bone scan in 12/96 showed improvement in the pelvic metastatic lesions.

In 03/97 the PSA had risen to 8.7 and symptoms of prostatitis had appeared. At that time, a CT scan showed progression of pelvic lymphadenopathy. The bone lesions by scan were if anything, better. At that time interleukin-2 4 million units subcutaneously every week and interferon 4 million units subcutaneously every week began. He did not tolerate these medications well and they were discontinued after a month. In 05/97 the PSA was 35 and the serum testosterone 15, and his bicalutamide was discontinued. A CT scan in 05/97 showed further progression of his pelvic lesions and a transurethral prostatic resection was done to relieve symptoms. He then was given 5200 cGy of radiation to the pelvic area at a medical center with considerable relief of his pelvic pain. In 11/97 his PSA was 40. He was feeling weak and he attributed this to radiation. In all he received TF (29), BCG (29), MBV (29) and LBL (16). He was relatively asymptomatic in 03/98 and by CT scan the pelvic lesions had improved. This case is considered equivocal although the patient (who is a physician) and I have a strong suspicion that he has been helped by immunotherapy.

BACKGROUND MATERIAL AND METHODS OF PREPARATION

In this section, the background material regarding immunomodulation agents used in this clinic will be reviewed. In addition, brief directions regarding the production of the agents used will be presented. Directions as to how these agents can be administered are also included. The interested reader has only to run a MEDLINE* query matching up each agent with "cancer" to obtain printouts listing the numerous articles about each modality that are now in the medical literature. Accordingly, only selective references will be included here.

The details of the methods used in this clinic are not "set in stone." Interested parties with the proper background should be able to produce the modalities mentioned without undue difficulty. They may wish to contact Dr. David Armstrong of Sloan Kettering Cancer Institute or Dr. C. O. Starnes of Amgen Corp. in California for suggestions regarding the preparation of Coley's vaccines, and Dr. H. H. Fudenberg, a pioneer in transfer factor and its use, in regard to his thoughts regarding transfer factor preparation.

The use of mononuclear cell therapy is in its infancy and laboratories that are already engaged in using interleukin-2 treated T-cells should have no difficulty in exploring the production and use of other theoretically active mononuclear cells.

Obviously, the author cannot take responsibility for production of or use of vaccines, cells or transfer factor not produced in his own office laboratory.

*Medical Literature Analysis and Retrieval System

TRANSFER FACTOR (TF)

One stimulus to use transfer factor was that it was common knowledge that TF was considered for treatment of a famous politician's son for sarcoma of the femur in the early 1970s.⁽¹²⁾ The second stimulus was the report of Oettgen et al that two of seven cases of intractable inflammatory carcinoma of the breast had responded to treatment with TF.^(10,12) Furthermore, delayed hypersensitivity which is stimulated by TF is well documented as a factor in the resistance to cancer.⁽²²⁾ Subsequent to our beginning to use TF in cancer, numerous reports have appeared that suggest that TF might have a place in the treatment of cases of sarcoma, mycosis fungoides, lung, head and neck cancer and prostate cancer.⁽²³⁻³¹⁾

TF is a mixture of substances obtained from the dialysate of human lymphoid cells. The source of the cells has varied in our hands from cells leukophoresed from relatives of patients who are to receive the cells to lymphoblastoid cells immortalized through contact with Epstein-Barr virus.⁽³²⁾ TF obtained from immortalized lymphoblastoid lymphocytes has been shown to have similar traits to that obtained from buffy coats. At present, we use TF obtained from immortalized lymphoblastoid lymphocytes due to concerns about transmission of infection from donors to patients. A unit of TF is arbitrarily set as the lyophilized dialysate obtained from 5×10^8 lymphoid cells.⁽²²⁾

Our present method of preparing TF is as follows: Immortalized lymphoblastoid cells are grown in RPM media and centrifuged cells are pooled until enough are obtained to make at least a hundred doses of TF. These cells are kept at -70 degrees centigrade until adequate numbers are obtained. These cells are then thawed and frozen three times to disrupt the cell membranes. They are then placed in sterile dialysis tubing (molecular weight cut off at 10,000). The preparation in the tubing is then dialyzed against sterile injectable water for 48 hours at 5 degrees centigrade. Dialysates are aseptically transferred to sterile freeze drying containers after preliminary freezing and freeze dried for approximately 24 hours. The samples are reconstituted with sterile injectable distilled water so that one-milliliter (ml) contains the dialysate of 5×10^8 cells. The reconstituted TF is then passed through a 0.22 microgram Millipore filter. Sterility tests are done on representative samples. The reconstituted TF is then put in sterile syringes in 1 ml aliquots. These are stored at -70 degrees C. until use. Representative aliquots of TF have been tested for potency by the migration inhibition test of Wilson with not entirely satisfactory results.⁽³³⁾

BACILLUS CALMETTE-GUERIN (BCG)

Rosenthal and his associates deserve credit for suggesting that BCG which is an attenuated form of tubercle bacilli, might be helpful in the treatment of cancer.⁽³⁴⁾ Initial studies were in mice and showed that BCG did improve the resistance of mice to cancer.⁽³⁴⁾ Davignon et al noted that childhood leukemia incidence fell in Europe with the advent of BCG vaccination.⁽³⁵⁾ Mathe' then used this observation to treat a group of children with acute leukemia and reported that there were some encouraging results.⁽³⁶⁾ We began BCG use based on the work of Rosenthal and Mathe'.^(34,35,36) Dr. Rosenthal's laboratory at the University of Illinois was kind enough to provide us with our BCG material which is a subculture of the original BCG developed by the Pasteur Institute. At present BCG is commercially available.

Since 1972, there have been numerous reports that suggest the possible utility of BCG for the treatment of cancer.⁽³⁷⁻⁴⁴⁾ It is used for the treatment of superficial bladder cancer and this use was approved by the United States Food and Drug Administration.⁽⁴¹⁾ Relatively recent reports that suggest that BCG has a place in cancer therapy are those in which it seemed to help cancer of the lung, malignant melanoma and gastric cancer.^(42,43,44) The most convincing of these articles is by Popiela, et al⁽⁴⁴⁾ In the study of these investigators, 325 patients with cancer of the stomach were randomly put in groups set up to determine if BCG added to 5-FU would increase time of survival.⁽⁴⁴⁾ It did.⁽⁴⁴⁾ Concomitant with reports of clinical results that have been reported, there have been many reports of laboratory studies that suggest BCG has a salutary effect on elements of the immune system that have been shown to be important in cancer chemotherapy.⁽⁴⁵⁻⁴⁹⁾ BCG has been shown to stimulate macrophage activity; to activate killer cells, both lymphocytic and monocytic; to sensitize cancer cells to T cell activity, and to increase tumor necrosis factor.⁽⁴⁵⁻⁴⁹⁾

Along with articles reporting clinical and *in vitro* activities of BCG have been a wide variety of reports of untoward reaction.⁽⁵⁰⁻⁵⁸⁾ Statistically, these are not too worrisome in view of the literally millions of individuals who have received this live vaccine worldwide. There have been many reports of the development of miliary disease, generalized lymphadenopathy, local vertebral osteomyelitis, pulmonary infection, fatal sepsis, abscesses, osteomyelitis and meningitis.⁽⁵⁰⁻⁵⁸⁾ At present, we discuss these reports with patients pointing out their rarity and let the patient decide whether their cancer risk outweighs their chance of having an untoward reaction to BCG. In the many patients we have treated with BCG, we have never observed an untoward reaction.

Our present use of BCG is as follows: It comes in an ampoule, which contains $1-8 \times 10^8$ colony forming units of BCG. To each ampoule we add 2 ml of preservative free saline. 0.4 ml of this mixture is dripped on the skin of the thigh or buttocks and spread onto an approximately 4 x 4 inch area. A tine (multiple puncture device) is placed on a magnet and pressed just hard enough to break the skin (nine times) and then this area is covered by a sterile 4 x 4 gauze and taped securely, so that it can be kept dry for 48 hours. If sensitivity is obtained, the area reddens and even festers 48 hours after

treatment. If the tine device cannot be found, a scarification method will accomplish the same intradermal penetration.

The articles regarding the effectiveness *In Vitro and In Vivo* of BCG might well indicate its use in all cases of cancer that might recur in spite of traditional therapy.⁽⁵⁰⁻⁵⁸⁾

MIXED BACTERIAL VACCINE (MBV) AND COLEY'S TOXIN

Our rationale for beginning the use of mixed bacterial vaccines in the treatment of cancer was a general feeling that since cancer antigens have been shown to exist, that a general stimulus of antibody production, such as one would receive with a MBV might be worthwhile.⁽⁵⁹⁾ Our second reason for using MBV was that we had an available supply which was prepared for use to prevent infections in patients with severe burns.⁽¹⁵⁾ I had not been aware of Dr. Coley's vaccine therapy for cancer until four years after we started to use MBV. At that time, an article appeared by Helen Coley-Nauts*, Dr. Coley's daughter, in which she summarized his work.^(60,61) Dr. Coley had noted in 1893 that patients who developed erysipelas after surgery for sarcoma seemed to have increased survival.^(60,61) Accordingly, he developed a vaccine that consisted of the remains of both beta hemolytic streptococci and *Serratia marcescens*. Mrs. Coley-Nauts has collected over 500 anecdotal articles that attest to the possible efficacy of what has come to be known as Coley's toxins.

Because of Coley's work and the numerous references to its efficacy that had been collected by Helen Coley Nauts, we made and added Coley's vaccine to our program. We have used both our MBV and Coley's vaccines simultaneously since 1976.

The mechanism or mechanisms by which MBV might influence immunity to cancer is unknown. In my opinion the active principles probably are muramyl peptides which are universal components of bacterial cell walls and which are well known as adjuvants to immunologic activity. Endotoxin may be the other active principle. This has been shown to stimulate antibody production perhaps by the presence of the blood group A substance within it.^(63,64) Weinman and Starnes discussed the effect of Coley's vaccines on tumor necrosis factor which may be one of its important activities.⁽⁶⁾

Proof of efficacy of Coley's vaccine and other bacterial vaccines that meets modern standards is hard to come by. Suffice it to say there are literally hundreds of articles attesting to its value, particularly for sarcoma. These articles, plus its safety, seem to make it worthwhile to try in problem cancer patients. One might remember when considering the use of bacterial vaccines that the anecdotes in their regard probably equal those that stimulated Whithering to use the fox glove extract for heart failure.

Over the years the bacterial species used in our MBV have changed.⁽¹⁵⁾ The microorganisms that we now suggest are as follow: *Escherichia coli*, *Aerobacter aergenes*, coagulase positive *Staphylococcus aureus*, *Proteus vulgaris*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and Group A beta hemolytic streptococci (all of these organisms are readily available at any active clinical laboratory).

*This listing of references is available by request to the Cancer Research Institute, 1225 Park Avenue, New York, New York 10128. Mrs. Nauts also has written a book that details her father's work which is coming out as this is being written and it can be

obtained from the same address. (William B. Coley, M.D., His Life, His Mission, His Legacy-In Press).

The MBV is mixed as follows: One milliliter of the above mentioned cultures which are kept in frozen milk is placed in 10 ml of appropriate synthetic media and incubated overnight at 37 degrees C. The resulting cultures are then placed in a one-liter flask of the same media and grown for 24 hours. The streptococcal cultures are grown for 48 hours. Experience in bacterial counting suggests that this growth time will yield approximately 5×10^8 organisms per ml. Organisms are then heat killed. After they are heat killed and this is confirmed by sterility testing, they are centrifuged at 1100 rpm for one hour and the supernatant decanted. Sterile PBS is then added to the resulting button and again the mixture is centrifuged at 1100 rpm for 30 minutes and decanted. Ten milliliters of PBS is then added to each bacterial button, and the mixtures are combined. The resulting MBV is fixed to a final concentration of approximately 1×10^9 organisms per ml by figuring the total estimated number of bacteria that had grown. The vaccine is studied for sterility both before and after it is placed in vials.

Coley's toxins, which more properly should be called Coley's vaccine, are prepared in the manner detailed above. However, only the two species of bacteria suggested by Coley are used, i.e., Group A beta hemolytic streptococci and *Serratia marcescens*.

The usual dose of each vaccine is 1 ml given subcutaneously.

In conversation with Helen Nauts, who has spent 40 years studying the results of her father's work, we have gathered that she feels the best results have been obtained when Coley's vaccine is given three times a week by alternating a subcutaneous, interdermal and intravenous routes. For financial and geographic reasons, we have been unable to follow these recommendations and have given this vaccine at less frequent intervals.

LYMPHOBLASTOID LYMPHOCYTES (LBL)

The importance of lymphocytes in immunity has been well-known since the mid-1960s.⁽⁶⁵⁾ Even before that, in 1951 Bierman presented evidence that cross transfusion of leukemic cells between patients with intractable lymphomas were tolerated and even may have been beneficial.⁽⁶⁶⁾ Moore, in 1971, gave lymphoblastoid lymphocytes that had been immortalized by Epstein-Barr virus to cancer patients with encouraging results.⁽¹⁰⁾ In 1980, Waisbren and Hurley showed in the electronic microscope that mononuclear cells attack cancer cells both by affixing themselves to them and by hurling substances we now call propulsions into the tumor cell cytoplasm.⁽⁶⁷⁾

Our laboratory had Epstein-Barr lymphocytes on hand in 1970 because they had appeared in the blood of a patient with fever of unknown origin that was being cultured for virus growth. Accordingly, on the basis of their availability and Moore and Gerner's report, we gave some of these cells to our initial patient.⁽¹¹⁾ Since then we have given immortalized lymphoblastoid cells to patients with poor prognosis cancer. Our usual dose is approximately 2×10^7 given intravenously in 2 ml of saline.

The dosage of LBL that we have used (2×10^7) is minuscule compared to that used by Rosenberg and his colleagues in later years.⁽⁶⁸⁾ In addition, we use B-cells, whereas he and his colleagues are using T_8 cells that have been activated by interleukin-2.⁽⁶⁸⁾ These cells can be identified in the peripheral blood by Wright stain for 24 hours after infusion.

The LBL that we use are well tolerated and usually evoke a febrile response between 101° F and 104° F. This fever in itself may be beneficial.⁽⁶⁹⁾ Patients are informed that the Epstein-Barr virus that has immortalized the B-cells has been associated with cancer.⁽⁷⁰⁾ However, in view of the patient's desperate situation, our patients with poor prognosis carcinoma have accepted the theoretical risk that this fact may entail. To date we have never had an untoward result using these cells.

There are two hypothetical explanations as to why a relatively small number of unmatched B-cells might help patients: 1. They may evoke a host versus graft reaction that might reject nonhost tumor cells. 2. Since the B-cells are known to process antigen, they might combine tumor antigen with patients HLA.⁽⁷¹⁾ A satisfactory junction between tumor antigen and HLA of recipients has been shown to be a requirement of getting T-cells to act immunologically.

Epstein-Barr virus can immortalize lymphocytes by a standard procedure⁽⁷⁰⁾. They also can be obtained by culturing the buffy coat of the blood of patients which infectious mononucleosis.

**OTHER POSSIBILITIES FOR IMMUNOMODULATION THAT ARE AVAILABLE
FOR POOR PROGNOSIS CANCER PATIENTS**

Other readily available, approved by the FDA, immunomodulation modalities can be considered for use in poor prognosis grade 3 cancer patients or in patients at high risk of recurrence. These modalities can be used under the guidance of their personal physicians. These medications include cimetidine, levamisole, isotretinoin, subcutaneous and intranasal interleukin-2, and interferon A.⁽⁷²⁻⁷⁹⁾ Typhoid vaccine can be substituted for MBV and it can be injected subcutaneously and intravenously. This is because typhoid vaccine, which is made from whole cells, should contain muramyl peptides, which may well be the active principle of MBV.^(80,81)

The references in regard to all of the above modalities clearly suggest that they may act as immunomodulators, that they are relatively safe, and that each has apparently helped some patients.⁽⁷²⁻⁸¹⁾

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