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Bacterial Pyrogens: Beneficial Effects on Cancer Patients

Helen Coley Nauts

Epidemiological data assembled in the past 50 years indicate that in developed and developing countries the incidence of infection is decreasing at the same time that the incidence of cancer is increasing. Figure 1 shows the changing mortality rates for lung cancer and pulmonary infections 1930–1978.

It is the purpose of this report to review some detailed evidence we have assembled in the past 40 years illustrating the fact that acute bacterial infection in cancer patients favorably influences the outcome of the malignancy and the survival of the patient, and that the administration of bacterial vaccines also has a beneficial therapeutic effect.

Because fever appears to be an important component of the therapeutic action of bacterial vaccines and of infection, it seemed appropriate to bring our studies to this meeting and I am grateful to be asked to participate. The fact that the first studies on cancer and bacterial vaccines were done precisely 90 years ago, says a great deal for the pioneering spirit of the man who initiated them, William B. Coley, MD of New York. (Fig. 2)

Bacterial pyrogens were used for the first time in the treatment of cancer by Coley in 1891 [1–3]. After experimenting with living cultures derived from erysipelas patients [4], Coley used the mixed toxins of Streptococcus pyogenes and Serratia marcescens, then called Bacillus prodigiosus. His method became known as toxin therapy and his product is now referred to as mixed bacterial vaccines or MBV [5].

Just what *was* accomplished with MBV in these 90 years? We studied nearly 400 papers and monographs on the method published in this period of which nearly a third were by Coley [3,5]. Analysis of these and the unpublished histories we had assembled indicates that complete regression and 5-year survival occurred in 46% of the 523 inoperable cases and 51% of the 374 operable cases so treated. [5] (See Table I).

The highest percentage of success occurred in sarcoma of soft tissues, [6] lymphomas [5], including reticulum cell sarcoma of bone [7], and soft tissues. Complete or partial regressions also occurred in inoperable or metastatic carcinomas of the breast, colon, head and neck, uterus, ovary, renal, and testicular

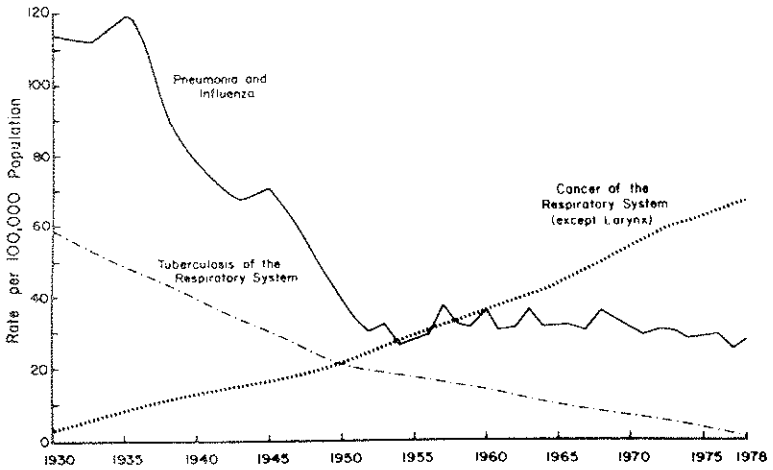

Fig. 1. Death rates among white males, U.S.A. 1930–1978.

cancers as well as in malignant melanomas, neuroblastoma, and various bone tumors [5]. Other beneficial effects included marked decrease or cessation of pain, improved appetite and weight gain (up to 50 pounds), reduction or disappearance of lymphedema, ascites or pleural effusion, and remarkable regeneration of bone [5]. Significant palliation (symptom free up to 5 years) and one apparently permanent result occurred in multiple myeloma [8].

Most of the 126 osteogenic sarcoma cases occurred in the long bones and received injections following surgery. It is significant that if injections were given for at least 4 months 85% remained well 4 to 40 years later, and those who died survived 4 to 13 years as compared to the average survival of 10 to 12 months following amputation alone in the period in which these cases were treated [9].

By using MBV therapy as an adjuvant to conservative surgery, Coley was the first to avoid amputation in patients with sarcoma or giant cell tumor of the extremities. A few other surgeons followed his lead. Of the 128 cases in which amputation was avoided, 57% remained well, as compared to 32% of the 166 cases in which amputation was performed.

The highest percentage of successes with conservative surgery occurred in giant cell tumor of bone (96%) [10] and in operable sarcoma of soft tissues (80%) [6]. The poorest occurred in Ewing's sarcoma as most of these children had received excessive radiation prior to MBV [11].

Fig. 2. William B. Coley, MD.

If MBV was begun prior to radiation, the response of the tumor was enhanced while protection of normal tissues was observed. Recent studies indicate that the response to chemotherapy is also enhanced by bacterial vaccines and hyperthermia [12,13].

Huth was one of the first to report that acute concurrent infections may increase the survival of leukemia patients [14,15]. Clarkson et al noted that patients with acute leukemia receiving Pseudomonas aeruginosa vaccine maintained drug-induced remissions considerably longer than controls treated only by chemotherapy [16].

Several thoracic surgeons have reported a much higher 5-year survival in lung cancer patients who developed empyema postoperatively [4, 44–51]. Several oncologists have shown that cancer patients respond best to microbial products

TABLE I. Five-Year Survival of 896 Patients With Various Types of Tumors Treated With Coley Toxins (Mixed Bacterial Vaccines)

Type of tumor	Total No. of cases	5-Year Survival			
		Inoperable		Operable	
		(No.)	(%)	(No.)	(%)
Bone tumors					
Ewing's sarcoma	114	11/52	21	18.62	29
Osteogenic sarcoma	162	3/23	13	43/139	31
Retic. cell sarcoma	72	9/49	18	13/23	57
Multiple myeloma	12	4/8	50	2/4	50
Giant cell tumor	57	15/19	79	33/38	87
Soft tissue sarcomas					
Lymphosarcoma	86	42/86	49	—	—
Hodgkin's disease	15	10/15	67	—	—
Other soft tissue sarcomas	188	78/138	57	36/50	73
Gynecological tumors					
Breast cancer	33	13/20	65	13/13	100
Ovarian cancer	16	10/15	67	1/1	(100)
Cervical carcinoma	3	2/3	67	—	—
Uterine sarcoma	11	8/11	73	—	—
Other tumors					
Testicular cancer[a]	64	14/43	34	15/21	71
Malignant melanoma	31	10/17	60	10/14	71
Colorectal cancer	13	5/11	46	2/2	(100)
Renal cancer (adult)	8	3/7	43	1/1	(100)
Renal cancer (Wilms' tumor)	3	—	—	1/3	33
Neuroblastoma	9	1/6	17	2/3	67
Total	896	238/523	46	190/374	51

[a]Including 16 terminal cases.

to which they have been previously exposed. Staphylococcus and Pseudomonas aeruginosa are now the two most frequently isolated organisms. Using these and others Waisbren has been administering a mixed bacterial vaccine to his cancer patients for over 6 years. He originally used this vaccine to prevent septicemia in critically burned patients in a large regional burn unit. It was highly successful, and isolation and antibiotics were no longer required. He then began treating his cancer patients with most encouraging results [17].

The first randomized trial of a modern preparation of MBV (Coley's original formula) is being carried out at Memorial Sloan-Kettering Cancer Center in New York in nodular nonHodgkin's lymphoma patients. Of a total of 37 patients in the trial, half received chemotherapy alone, the other half chemotherapy plus MBV. At the end of over 4 years, it was found that nearly 30% of the patients on chemotherapy alone had died, whereas none of those receiving MBV as well as chemotherapy had died [18]. Kempin et al reported that "the improvement in complete remission rate and remission duration in the MBV-treated group is being further assessed as our study continues, but the current data strongly suggest a potential role for MBV therapy in the management of nonHodgkin's lymphoma" [18].

WHAT ELEMENTS IN THE PROTOCOLS ADOPTED HAVE BEEN SHOWN TO DETERMINE SUCCESS OR FAILURE?

Analysis of nearly 900 detailed histories of microscopically proven cases of cancer treated with MBV indicate that the main factors affecting efficacy of the treatment were: (1) stage of disease and/or magnitude of tumor burden; (2) immune competence of patient; (3) potency of vaccine used; (4) dosage, frequency, and duration of injections; (5) contact with tumor cells, ie, site of injection; and (6) timing of toxin therapy in relation to surgery, radiation, and chemotherapy.

Few physicians seem to have recognized the importance of technique of administration, especially the need to produce *adequate febrile reactions* consistently. These could best be obtained by injections given in or near the tumor area or intravenously, or in larger doses intramuscularly. Three times as many inoperable sarcomas (See Fig. 3) had complete and permanent regressions if reactions averaged 38.5–40.5°C, as occurred in cases in whom little or no fever was induced [6, Fig. 4, p 23]. *Duration* of treatment was of even greater importance (Fig. 4). This was evident not only in the MBV cases but also in the infection cases. While a larger number of complete regressions occurred following erysipelas, these transient infections did not produce as many permanent results as occurred following more prolonged mixed pyogenic infections with fever, especially staphylococcus, occurring in or near the tumor [4]. Recent end-result studies have shown that if injections were continued from 4 to 12 months, 80% 5-year survivals were obtained in a number of different neoplasms. Optimum *frequency* appeared to be three to five injections weekly at first, gradually decreasing to injections administered monthly if given more than 4 months [5,6]. Advanced disease and previous extensive radiation or chemotherapy have been found to decrease the potential effect of MBV [5–8,10].

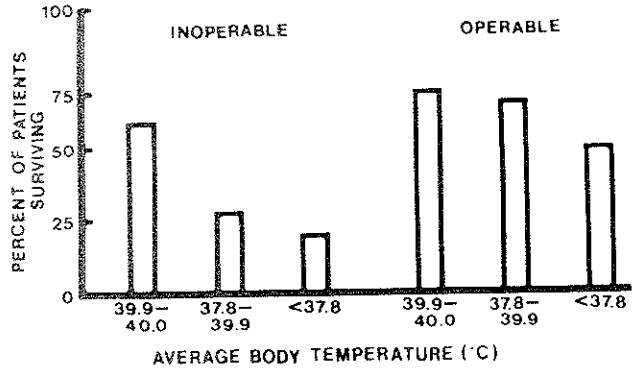

Fig. 3. Correlation between fever and 5-year survival of patients with cancer.

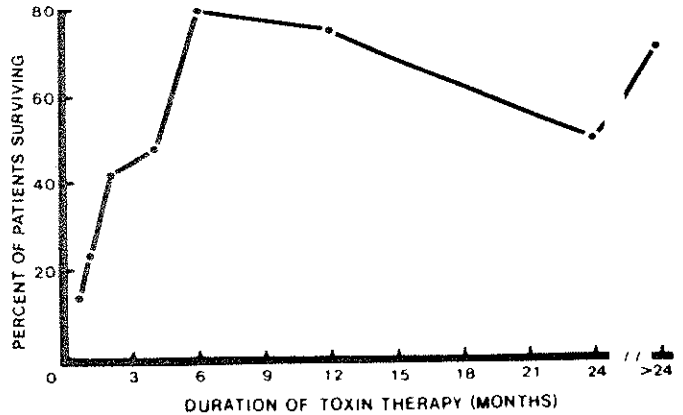

Fig. 4. Correlation between duration of toxin therapy and 5-year survival of patients with inoperable cancer.

MECHANISM OF ACTION OF BACTERIAL PYROGENS

No one using MBV empirically during Coley's lifetime knew that in addition to producing fever, bacterial vaccines can stimulate the reticuloendothelial system, activate macrophages, increase hematopoiesis, and increase production of endorphins and endogenous interferon. We now recognize that these profound

effects were responsible not only for the regression of extensive tumors but also for pain relief, improved blood picture, rapid wound healing, and regeneration of bone, as well as increased appetite and weight gain seen in these patients.

More recently, the *role of iron* has been recognized in the balance of host–parasite relations, and some strains of virulent bacteria are known to acquire the capacity to sequester iron both in vitro and in vivo [17]. It has also been suggested that one of the beneficial effects of fever on the course of infection relates to the accompanying hyposideremia and consequent reduction of the availability of iron for bacterial cell growth [20]. The possiblilty that iron, bacterial infection, fever, and tumor regression are connected has not been sufficiently explored. However, recent studies in vitro and in vivo have shown that tumor cells utilize iron in a fashion possibly similar to bacteria and also through the expression of surface receptors for the iron binding protein transferrin [22,23].

The effective competition of bacteria for a nutrient indispensable for tumor cell growth could play an important role in the reported regressions of cancer associated with severe bacterial infections. In addition, recent work on the action of iron on a number of immunological functions tested in vitro [22; also cited in 4, 593, 593a] and on the immunological function of patients with iron overload has shown that both iron and ferritin have immunosuppressive effects on the macrophage and on T-lymphocyte function [19].

Thus a fine balance seems to have evolved between bacterial infection, iron deficiency, fever, immune function, and tumor cell growth.

If the incidence of infections is reduced, or the frequency of iron deficiency is decreased by use of iron-supplemented or iron-rich diets, and the immune system is partially suppressed by exposure to iron and other metals through occupational or environmental pollution, the balance will favor tumor development. These factors may all have contributed to the increased incidence of cancers observed in the last 90 years, since infections have been so largely eliminated or controlled and iron supplements have become so widely used in developed countries.

In summary, it is already known that iron inhibits some immunologic functions. Iron can be envisaged as critical to several steps of tumor growth and progression. In principle, intervention at each of the steps influenced by iron could arrest the growth of cancer effectively. In practice some evidence that this is the case is beginning to emerge from cancer treatment with monoclonal antibodies against iron-associated proteins (ferritin and transferrin receptors) [22,24–27].

Such studies are vital now to our understanding of the role of iron in immunity and cancer, and the work begun by de Sousa at Sloan-Kettering Institute in New York is fundamental. It will have wide ramifications, scientific and clinical, in the understanding and treatment not only of cancer but of other diseases such

as rheumatoid arthritis and heart disease. It will also have important consequences for nutrition and help our understanding of bacterial infections and the way we combat them.

DIETARY CONSIDERATIONS

A substantial amount of work in recent years has elucidated the deleterious biological effects of free radical reactions [25]. Generation of some of the most toxic end products of these reactions involve oxygen consumption and are drastically enhanced by the presence of iron.

In communities where iron intake from diet is adequate and where, for lack of serious bacterial infections, all available iron in the body is either used to make new red cells or stays in storage in the immune system, eventual accumulation with age is inevitable, particularly in men and postmenopausal women. It has recently been hypothesized that high iron stores are responsible for the higher incidence of heart disease that occurs in these two groups [28]. Thus dietary regimens reducing iron intakes and increasing the intake of antioxidants such as Vitamins A and C can be predicted to increase lifespan [25].

THE IMPORTANCE OF FEVER

At first the significance of the febrile reaction was not fully appreciated. Many patients, therefore, received inadequate doses of MBV given intramuscularly or subcutaneously producing a slowly rising temperature. We now know that "slow heating" seems to induce thermal tolerance in some neoplasms. When given more aggressively, the rapid change in temperature suppresses the ability of malignant cells to adapt to the higher temperatures.

What benefits do mixed bacterial vaccines offer which cannot be obtained by using whole-body hyperthermia produced by hot air or immersion in hot water or oil? The evidence we have assembled suggests that modern whole-body hyperthermia usually requires immunosuppressive anesthesia or tranquilizing agents. Some of these heroic procedures may in themselves be immunosuppressive. Local hyperthermia by radio frequency apparatus seems to offer greater promise and is more easily tolerated by the patient. *Neither type appears to offer sufficient duration of therapy for permanent results.*

We believe that even better end results may be possible by a judicious use of local hyperthermia given weekly combined with injections of a mixed bacterial vaccine, not only Coley's MBV, but other types such as that used by Waisbren given at least twice a week at first. These injections must be continued after the local hyperthermia treatments are completed in order to stimulate the host defenses to cope with absorption of necrotic tumor tissue, to promote healing, and to destroy any residual neoplastic cells which remain either at the primary site or elsewhere. Vaccine therapy can be administered on an ambulatory basis.

In conclusion, we hope that this review will stimulate you to combine modern localized hyperthermia (with or without radiation) together with bacterial vaccine injections; that you will recognize that caution is needed in administering iron supplements; and that if your patients are at risk of developing infections, you will rely on bacterial vaccines and supplemental vitamin C rather than only on antibiotics. Finally, oncologists using exogenous interferon may also consider the use of bacterial vaccines, since they have been shown to stimulate the production of endogenous interferon, in addition to their other host-stimulating effects.

ACKNOWLEDGMENT

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Experience With Diathermia-Induced Whole-Body Hyperthermia

Herbert Neumann, Hans-Ake Fabricius, Peter Burmeister, Roland Stahn, Matthias von der Tann, Rupert Engelhardt, and Georg-Wilhelm Löhr

Selective heat sensitivity of cancer cells has been proven by many in vivo and in vitro experiments [1,2]. One of the results of this basic experimental work is the enhancement of cytostatic drugs and clinicians have tried to transfer these results into clinical application. Local hyperthermia for superficial tumors, or hyperthermic perfusion of extremities, has already shown remarkable results [3–5]. By these locally effective methods tumoricidal temperatures up to 43°C can be reached.

The tumor chemotherapist, for the most part, faces patients with disseminated malignant diseases. In these stages obviously the application of hyperthermia must raise the temperature of all parts of the body including all metastases. Tumoricidal temperatures in whole-body hyperthermia (WBH) cannot be reached. Therefore, the rational therapeutic approach must be seen as an enhancement of chemotherapeutic effects by WBH.

METHODS

For the induction of WBH, different methods have been developed: the wax-bath method [6], the extracorporal heating of blood by a shunt of the femoral arteria [7], or a water blanket which can be perfused with hot water [8].

By all these methods temperatures up to 42°C can be reached. In these temperature ranges narcosis is required, and since the whole procedure involves a high risk for the patients [9–13] great efforts for control are needed.

In our clinic we are using the Siemens diathermia cabinet (Fig. 1) [14]. It consists of a Plexiglass cabin which is preheated with air at a temperature of 60°C to prevent temperature loss by convection. The head of the patient is positioned outside the cabin while the body is on a mattress in which a coil field