COLEY TOXINS - THE FIRST CENTURY

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EDITORIAL COMMENT

We are pleased to be able to present this summary of the first century of Dr. Coley's toxins prepared by Helen Coley Nauts. We believe you will agree that this is an objective scientific presentation particularly when one considers the criticism, frequently unfounded, which has been given Coley's work in the past. Those reading this chapter and working in hyperthermia will find many parallels and similarities with their frustrations and peer criticisms as noted herein. Comparable modes of action will be found for those proposed to explain the benefits of hyperthermia. Possibly with today's more detailed understanding of the intricate complex immune system, a logical basis can be offered for the "dramatic cures" which in themselves caused skepticism, and Coley's results can be better understood. A study of Coley's life's work will lead to a better understanding of the problems, obstacles and potential solutions we have in hyperthermia and also I suspect that it will help our morale to realize that we are not the first or only ones to have criticisms heaped upon sound and meticulous work. It is gratifying that in recent years Coley is being recognized as the pioneer of cancer immunology.

In January, 1893, W.B. Coley, a young New York surgeon treated his first case of cancer with the mixed bacterial toxins of Streptococcus pyogenes and Bacillus prodigiosus (now known as Serratia marcescens). This bedridden male, aged 19, had an inoperable sarcoma of the abdominal wall and pelvis (16x13 cm.) involving the bladder with incontinence. Only biopsy had been performed. Injections in or near the tumor caused reactions up to 40oC. or more and complete regression occurred in four months. He remained well until death from a heart attack 26 years later (1, case 1).

In 1939, we began our analysis of Coley's method to

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answer the following questions: 1) Was there sufficient clinical and experimental evidence to justify the conclusion that the method had therapeutic value? 2) If so, what factors governed success or failure? 3) Why did the method not achieve wider recognition? 4) If the conclusions to these questions warranted further study we asked ourselves what can be done to make the Coley toxins consistently effective in most types of neoplastic disease (2). Some factors or data that seemed vital to success or failure were identified:

1. Variability of preparations used

No comprehensive text book on the method had been published by Coley, although he was working on one at the time of his death in 1936. He made every effort to obtain unequivocal diagnosis by eminent pathologists from the beginning. However he did not recognize the great importance of obtaining potent, stable preparations of the mixed toxins to avoid variability from different formulae or from batch to batch (1,2). Coley had no bacteriological training and relied on others to made the preparations.

The first observation brought out by our long term study was that at least 13 different preparations had been used during Coley's active years, (1892-1936) of which three were considerably more potent than the rest, Buxton VI, Tracy X and Tracy XI. Unfortunately the first two commercial preparations Parke, Davis & Co., IX and XII were very weak and the English preparation (Lister Institute VIII) was even weaker, so very few English surgeons achieved success (1,2). These weaker preparations did not produce adequate febrile reactions (3, Fig.1).

In 1902 a patient with recurrent inoperable lymphoma of the axilla reported to Coley that it took eight minims of the Parke Davis IX to give the same febrile reaction as 1/4 minim of the Buxton VI (6, page 79). Despite such a clearcut case, Coley does not seem to have attempted to remedy the situation, and may have been unaware of this problem until 1911 when he gave a lecture at Guy's Hospital in London and he discussed it briefly in his response to the vote of thanks, ending with the remark "success depends on the preparation..." Dr. Coley, in London in 1911, following recognition at Guy's Hospital for his work stated, "I am greatly obliged to you, gentlemen. What I have heard led me to believe that British audiences were cold, but I have never in my own country received such a hearty reception as you have given me today. Sir Alfred Fripp tells me that you have tried the fluid in the hospital. The trouble has been that a different preparation is sometimes used. Mr. Mansell Moullin of the London Hospital had five successful cases, and he said he got his successes with the fluid obtained from the Cornell Laboratory (Buxton VI). Middlesex Hospital had had three failures but in the fourth, they used the Buxton VI and the growth regressed to 1/14 in a few weeks...."

Finally in May 1915, Tuholske of St. Louis wrote him about a case of extensive sarcoma of the pharynx and nasopharynx with almost complete obstruction -- a tracheotomy was imminent (1, case 23, p. 68-72; 3, case 56, p. 131-135). Even massive doses of Parke Davis XII had had no effect at

all. Coley then sent him the Tracy XI (see below for details relating to technique). This case made him contact Parke Davis and get them to work more closely with Tracy and so Type XIII was made considerably more potent than XII (1,2).

2. Techniques of Administration

The Tuholske case illustrates the importance of a number of factors. First, the danger of stopping the injections too soon, even if complete regression has occurred. Although complete regression occurred in six weeks, the disease recurred on the opposite side in about three months with evidence of brain metastases. Second, the injections for the recurrence were given subcutaneously or intramuscularly in the deltoid or scapular regions with very poor absorption. Not until given in the abdominal wall did good febrile reactions occur, and the recurrence disappeared, but the symptoms of brain metastases persisted. The patient went into coma for 3-1/2 weeks. No further injections were given. With supportive treatment he regained consciousness and made a complete recovery. He remained well until death of a coronary occlusion 33 years later (3, case 56, p. 131-135). Although Coley published 143 papers or monographs on his method between 1893 and 1936, (8) he seldom gave sufficient detail on methods of administration; i.e., site, dosage, frequency, duration, and the desired optimum febrile reaction.

a. Site and Dosage of Injection

The type of reaction elicited depended on two things. The site of injection and the dosage. Injections given intramuscularly or subcutaneously remote from the tumor, required much larger doses to elicit a reaction of 101oF. or more than did an injection into the tumor or in a vascular tissue or intravenously. In the early years Coley used intratumoral injections into different parts of the tumors. These elicited not only fever but tumor necrosis factor and an inflammatory reaction all of which were more effective in causing destruction of the tumor thus imitating an erysipelas infection. (The most dramatic "spontaneous" regressions of cancer occurred during and following acute erysipelas injections which produce a more intensive inflammatory reaction than any other infection).

We found only one case treated by Senecal with intraperitoneal injections -- a huge ovarian carcinoma with widespread metastases in the peritoneum and ascites. Very dramatic regression occurred in four weeks. The case became operable and recovered. She remained well 27 years (1, pp 89-42, 8, pp 85-41).

Intravenous injections were not used by Coley until about 1925 and usually some intramuscular injections were given first. Very much smaller doses were needed, and these caused no inflammatory reactions. They were well tolerated.

Fowler in 1898 recognized the importance of site of injection. When given subcutaneously, the intensity of the general reaction varied with the dosage and site used. With subcutaneous injections a larger dose was required to produce

the desired reaction, whereas a few drops were sufficient for the intravenous route. "The vascularity of the tumors explains the ease with which a reaction can be produced by Coley's method of interstitial injections, the latter being quite analogous, if not identical with the intravenous method" (cited by Moullin, 9).

X-rays and radium were discovered in 1895, only a year after Coley read his first important paper before the American Surgical Association (8). He was one of the first surgeons in New York to use x-rays in his practice having persuaded Memorial Hospital in 1901 to procure an x-ray machine, paid for by one of his wealthy patients. He read his first report on the work before the American Surgical Association in June 1902 (11). The growing enthusiasm for both x-ray and radium quickly overshadowed Coley's method before it had been properly standardized, or its mode of action understood. Coley, anxious to prove that his toxins had a systemic rather than a local reaction such as x-ray, radium and surgery, stopped using intratumoral injections about 1906, and not until a year or two before he died did he come to realize the mistake he had made.

b. Frequency of Injections

In the early years Coley and other surgeons gave injections daily or every other day at first, which appeared to be more effective than less frequent injections, especially when treating inoperable cases. One surgeon who routinely used the Coley toxins in both his operable and inoperable cases, Calkins of Watertown, New York, gave the injections daily or every 48 hours for about six months, then twice weekly with occasional intervals of rest for another six months (12 pp. 42-43 & 53). Injections were given as an outpatient after the first two weeks. Calkins achieved 80% five year survival in using this technique over a 32 year period. Matagne also often gave injections daily. (See below).

Many surgeons, such as the Mayo brothers, did not wish to get involved in such long term therapy, so they advised the family physician who had referred the case to the Mayo Clinic to administer the injections after the patient returned home. As a result a considerable number of Mayo Clinic cases were successfully treated.

c. Duration

Coley did not recognize the importance of duration of treatment, especially in the inoperable cases until 1926 when Christian and Palmer succeeded in curing a reticulum cell sarcoma of the tibia recurrent in the stump after amputation with extensive metastases near the umbilicus and in the left inguinal region. In discussing this case in 1927 Coley stated "I am quite willing to admit that, had the patient been under my care, he would probably not have been alive today. ...I am almost certain that I should not have continued the treatment after three months when not only had no improvement been noticed, but marked increase had taken place in the metastatic

tumors and especially in the recurrent tumor of the stump (from 17-31 inches). In the second place I am quite sure that I should not have dared to increase the dose to such a large amount (2 cc). However, it was not until these large daily doses were given that the improvement continued until all the tumors had disappeared. ....I feel that many of the past failures might have resulted otherwise had larger doses and more frequent injections been given" (1, case 19, p. 84-89).

Our end result studies beginning in 1946 have shown that, if the injections were given for six months, 80% of inoperable sarcoma of soft tissues survived 5-88 years. (3)

In osteogenic sarcoma when the Coley toxins were given as an adjuvant to surgery for at least three months 85% survived and were traced up to 53 years later. Three other cases so treated died 4-13 years later of late recurrence or metastases, i.e., prolonged survival. If given for less than three months 36-43 percent survived. This was considerably better than the 10-15 percent survival from amputation alone in that period (4, Figure 2, p. 10).

d. Type of Febrile Reaction

Coley did not sufficiently appreciate the benefit of producing febrile reactions averaging 39o-40oF.) from the beginning of treatment. This did not occur if they used small doses intramuscularly or subcutaneously remote from the tumor, or when the very weak products were used. This factor was more important in treating inoperable cases. For example, in the soft tissue sarcoma 60 percent of the inoperable cases, whose reactions averaged 102o-104oF. with chills, were traced well 5 to 88 years, as compared to only 28 percent of those having reactions below 102oF. and no chills (3, Figure 2).

3. Stage (Operable vs Inoperable Cases)

In treating operable cases as an adjuvant to surgery very few surgeons began the treatment prior to surgery. This is unfortunate because preliminary toxin therapy, even for only a brief course, can counteract the immunosuppressive effects of anesthesia and surgery, due to stimulation of cytokines such as interferon, interleukins, tumor necrosis factor and others. In cases of amputation, it counteracts the psychic stress of losing a limb, which is also immunosuppressive.

The first physician to recognize that operable cases might benefit was Matagne of Brussels, Belgium. He first began using the Coley toxins in inoperable cancers, having observed a dramatic case cured following an erysipelas infection reported by Bidlot in 1891 (7, Ref. #39). In 1896 he gave a rather brief incomplete description of his inoperable cases and was soon criticized by a commission charged with examining it (14). This did not deter him from continuing his clinical studies and over the next 57 years he published 12 more papers interrupted by two world wars (8, Ref. #265-277).

In 1902 he reported on the use of Coley toxins in operable cases as a means of preventing recurrence, the first

physician to do so (14,15,16). In 1905 he presented a series of these operable cancers in which he had administered the toxins before operation, usually for four or five weeks, in some cases for three months. (17).

One extensive recurrent inoperable malignant melanoma of the upper arm in the region of the humeral artery with metastases in the axilla, received injections in the recurrent tumor for seven months in 1902 with rapid but incomplete regression of the recurrent mass, but the axillary metastases did not regress. Shoulder joint disarticulation was then performed. There was no further recurrence and the patient remained well over 41 years after onset (15,16,17).

Matagne prepared his own Coley toxins using the effective Buxton VI formula (17, p. 1389). He gave injections daily into the tumor beginning with a dose of 5 cg., gradually increasing by 2.5 cg. each day or every other day until a febrile reaction of 39o-39.5oC. or 40oC. was elicited. The reaction usually consisted of a violent chill which began 30 minutes after injection and lasted 30 minutes. Dosage was increased to 10 mg. in some cases, in others to 30, 40 or even 50 cg.

The first surgeon to save a limb by using Coley toxins following surgery was Owens in 1894 in a highly vascular giant cell tumor of the proximal tibia following curettage. This was the first case of giant cell tumor in which the limb was saved (19). In two-thirds of the giant cell tumor cases involving long bones, the limb was saved by the use of curettage and toxin therapy combined, in some cases, with radiation. The remarkable regeneration of bone destroyed by the tumor following toxin therapy was especially evident in Series A, Cases 8,11,13,26 and 40 (22).

Coley began using his toxins in operable cases as early as 1895 (20). The first published case was an osteogenic sarcoma of the femur. The patient remained free from recurrence or metastases for 53 years. (4, Case 1, Table 1). Other American surgeons soon followed, including Ochsner in 1915 and Calkins in 1917, for breast carcinoma and sarcoma (6) and Meyerding of the Mayo Clinic for osteogenic sarcoma and Ewing's sarcoma of bone.

4. Early Criticism: Limiting Types of Tumors Treated

Between 1891 and 1896 Coley published 16 papers describing his method (8, references 42-64). Editorials began to appear in 1894 with the first negative report entitled "Failure of the Erysipelas Toxins" (21). In 1895 Abbe, the President of the New York Surgical Society, suggested that the method be tried in different hospitals: a fair proposal, but no enthusiasm was shown. It is a great pity that such a plan was not carried out, but it is not surprising that a group of surgeons were reluctant to pursue a medical approach to the treatment of cancer. In October 16, 1895 Coley read a paper before the New York State Medical Association entitled: "The indications for the non-operative treatment of tumors. The value of Toxins". This was published in reprint form in 1896

(19) and caused more concern among surgeons and a few more negative reports (5).

To editorials, mostly unfavorable, Coley responded objectively on December 29, 1894, "That a few physicians in a very limited number of cases with indifferent preparations of the toxins have failed to obtain good results will not... have great weight in the minds of the scientific portion of the profession in determining failure or success of this method of treatment of sarcoma" (20).

In 1915 Harmer of Boston published a critical report on 134 microscopically proven cases treated by Coley's toxins (21). He concluded that they are of value in certain cases of inoperable sarcoma. Although his conclusions were somewhat negative he noted that in a small number of cases they produced striking relief of pain. Coley's many surgical friends in England and in the United States urged him to limit his use of the toxins to sarcomas since the early experiences with his weaker preparations in advanced carcinomas or melanomas had not proved successful.

Other surgeons had successfully treated metastatic cervical carcinoma (1, Case 5), extensive metastatic breast carcinoma, (1, Case 14, 15; 23, p. 232) giant cell tumor of vertebrae (1, Cases 6, 20), recurrent malignant melanoma (1, Case 17), ovary, metastatic (1, Cases 25, 30; 12, Cases 20, 21). These reports encouraged Coley to use his method on many other neoplasms; testicular cancer (24), breast cancer (23), lymphoma and Hodgkin's disease (25,26), malignant melanoma (27), multiple myeloma (28), Ewing's sarcoma (29), neuroblastoma (30), colon cancer (31) and renal cancer (32) with a great many remarkable results (1,33).

5. Animal Experiments

In 1907 Beebe and Tracy published the results of their studies (34) in which they stated: "The striking results attained (by Coley) in an increasing number of cases have diverted the attention to the possible significance of the Bacillus prodigiosus in the preparation. ...It seemed important to study with some care the effect of inoculation, not only with the Bacillus prodigiosus (now known as Serratia marcescens) but with other bacterial toxins as well.....with the hope of determining the rationale of this method of treatment, and if possible of placing it on a more scientific basis". They used B. prodigiosus, Streptococcus pyogenes, Staphylococcus aureus and Bacillus coli communis (now known as Escherichia coli; also the mixture known as Coley toxins. They treated with these preparations lymphosarcoma grown in dogs transplanted from a spontaneous tumor.

They reported that B. prodigiosus alone and Streptococcus pyogenes alone as well as the mixture of these two (the Coley toxins) caused regression of this tumor in the dogs. Staphylococcus aureus given into the tumors caused fever to 105.9oC., but no real regression. E. coli in one dog caused steady regression; all tumors disappeared in five weeks. They used different sites of injection. The intratumoral

injections caused much more rapid regression (34). In conclusion they stated that, "though the action is chiefly local, it is at the same time something more than this for it was repeatedly observed that tumors at a distance from the site of injection undergo regression simultaneously while in one dog all the injections were given remote from the tumor" (34).

6. Radiation and Toxin Therapy

Ewing became medical director of Memorial Hospital about 1915 and he was an ardent advocate of radium, a large supply of which had been given to the hospital by Dr. Douglas. At that time Coley had been appointed Chief of the Bone Tumor Service. Ewing insisted that every single ward case should receive radium or x-ray prior to amputation and, despite the fact that Coley believed this to be a dangerous protocol, he had to comply. In 1927 Coley published the end results (35). Not a single patient so treated had survived, while in his private patients to whom he gave the toxins following surgery 50 percent had survived. If injections were given for three or more months, 85 percent survived four - 40 years later (4). The Mayo Clinic also achieved 50 percent five year survival in their toxin-treated cases, while other surgeons here and abroad were curing only 10-15 percent with amputation alone.

Matagne, as well as Coley, became interested in utilizing radiation in his practice and he acquired some radium at considerable expense which he used especially in epitheliomas. Like many other surgeons he felt constrained to use it to justify the expense incurred, as a result fewer patients were treated with the toxins thereafter.
Coley treated one of his first cases with x-ray therapy in 1901. He irradiated an inoperable lymphosarcoma of the cervical, axillary and mediastinal nodes which was producing dyspnea and edema of the lower extremities. Marked regression and increased mobility had occurred following toxin therapy alone, but then control was lost and the patient became bedridden, with severe dyspnea. X-ray was then given 4 to 6 times weekly causing remarkable regression in three weeks and complete disappearance in six months. No further toxins were given after radiation was begun. The disease then reactivated with hundreds of pea to egg-sized nodules over the entire body. Death occurred in June 1904, 5-1/2 years after onset. Coley believed the radiation had lowered the resistance of this patient to her tumor (6).

In contrast, an eight year old boy had had amputation for a fungating Ewing's sarcoma (later regarded as a reticulum cell sarcoma) of the fibula with metastases to the inguinal and iliac lymph nodes. Toxins (Tracy XI) were begun immediately after amputation and given two months with marked reactions. Soon after the injections were stopped a 15 cm. mass in the iliac fossa and lung metastases developed. All disappeared after one radium pack to the groin (10,109 mch). The child remained well and free from disease until death from an emergency appendectomy 15 years later (36, 37).

7. Radiation Protection

About 1958 a number of investigators began reporting on the protective effect of bacterial endotoxins against radiation injury (39-41). This occurred if injections were given prior to the radiation, optimally 24 hours before.

Thomson (1962) reported "bacterial endotoxins prepared from Salmonella typhosa, Escherichia coli, Serratia marcescens and Proteus morganii all promoted hematopoietic recovery when given before or after whole body radiation. Post radiation infection is appreciably reduced, hematopoietic tissues regenerate and survival is enhanced" (39).

Ainsworth, of the Cellular Biology Branch of the U.S. Naval Radiobiological Defense Laboratory, San Francisco, published several reports in one of which he noted that low pyrogen doses are known to produce a more rapid rise in resistance than larger doses, i.e., 50 mcg. was not as effective as 2 mcg. of pseudomonas in increasing survival time to lethal radiation (40). At our request in 1962 Ainsworth screened the Coley toxins as a potential radioprotectant on x-irradiated mice. In this experiment the smaller dose was more protective. Data from this unpublished work follows:

Effect of Coley Toxins on Survival of Irradiated Mice

Method: Typhoid-paratyphoid vaccine was used to compare Coley's Toxins since previous data had shown that TAB is highly effective in reducing the radiation mortality in mice. The mice used were CF1 females, 100 days old, weighing 19-24 grams. Total body x-irradiation was delivered from a 250 kv Westinghouse x-ray machine operated at 15 ma and a distance of 40 inches. Added filtration consisted of 0.5 mm Cu and 1 mm Al.

8. Modes of Action

In addition to radiation protection and potentiation of tumor response, the Coley toxins produce fever which we know is beneficial, they also stimulate the reticuloendothelial system, activate macrophages, increase hematopoiesis, increase production of prostacyclin, endogenous interferon, endorphins, tumor necrosis factor, interleukins and growth factors (44, 45). Interleukin-1 for example, induces a profound hypoferremia which assists the patient in withholding iron from the cancer cells. Weinberg has summarized some of the numerous papers in regard to this subject including Torrance et al. (45a,45b).

Certain infections such as erysipelas (13) and the Coley toxins also stimulate wound healing (1) and regeneration of bone destroyed by tumor (23). For example, a case of an extensive giant cell tumor of the proximal femur with complete destruction of 17 cm. including the neck and trochanter with pathologic fracture, recovered under Coley toxins in or near the tumor given for 7-1/2 months combined with two radium treatments. The first was given after one week of toxins,

the second seven weeks later. Complete regression of the tumor and regeneration of the hip joint occurred, with 14 cm. shortening; the patient remained well until death 45 years later of coronary occlusion. A second case involved the neck, both trochanters, with complete destruction of the acetabulum and ischium and pathologic fracture. He received one radium treatment (9000 mch) three days before toxins were begun. Complete regression occurred. The limb was kept in traction and the hip joint and femur regenerated without shortening (22, Case 20, pp. 46-50). In another giant cell tumor of the distal radius involving the ulna, the extensive tumor regressed completely under toxins alone and the bone regenerated with perfect function (22, Case 36, pp. 53-57).

9. Dramatic Cures Promote Skepticism

One form of criticism occurred as a response to dramatic cures. Richardson of Boston in reporting a remarkable case he had referred to Coley in 1893 stated: "Skepticism may be so extreme that carefully observed cases are thrown out for one reason or another, though I cannot but think chiefly for the reason that they were successful. In this case Dr. Garland and myself at the time of operation made the diagnosis as hopeless malignant disease of the abdominal wall. Dr. Whitney made a careful microscopic examination of the tumor and reported it as fibrosarcoma". In October 1893 she received local injections daily into the tumor for six weeks with marked reactions. Within two weeks improvement was very evident. The patient's general condition suffered but little and she was up and about most of the time. She returned home for Christmas, a second four week course was given in January. Richardson concluded: "The tumor, though as large as a child's head, disappeared. ....If a cure by means other than surgical is from the very fact of cure, declared sufficient proof of a mistaken diagnosis. There seems little use in presenting evidence. ....The curative influence of micro-organisms upon malignant growth, whether during the course of an accidental wound infection, or under the influence of deliberate toxin injection is a hopeful indication of far-reaching possibilities for good". (1, Case 2, pp. 22-25; 3, Case 3, pp. 3, pp. 51-53).

In July 1920 Codman, who had organized the Bone Sarcoma Registry in 1920 with Ewing and Bloodgood of Johns Hopkins, wrote Coley, "You have probably more living cases than any man in the world. That your treatment has a profound systemic effect I have no question but I am inclined to attribute the successful cases to errors in diagnosis. Yet I must admit you have more to your credit than anyone else".

In May 1934 Codman was Chairman of a Bone Sarcoma Symposium held at Memorial Hospital, and summarized Coley's paper on Ewing's sarcoma of bone stating. "This paper will give great satisfaction to Dr. Coley's many friends who have admired his courageous, tireless fight to overcome the skepticism of his colleagues. ...His six registered cases of five year cures are alone enough to sustain his argument. ....Just as it seemed quite justifiable for the Memorial

Hospital during the last decade to test out the value of radiation alone in inoperable cases or in patients opposed to operation, so it seems even more indicated that some great clinic should try out Coley's toxins during the next decade. Unquestionably they produce a profound constitutional effect. ...It is time for some great hospital to apply its laboratory resources to the wholly justifiable and distinctly hopeful purpose of giving this treatment a fair trial under favorable conditions. Certainly, in cases of Ewing's tumor one would hardly feel justified in not recommending the use of the toxins. The question of whether also to give radiation is the difficult one. Dr. Coley quite logically suggests that the combination of the two may be a bad one, for the rapid destruction caused by irradiation may open up channels for further invasion. Radiation in small amounts stimulates lymphocytosis, and its use in this way was advocated in 1918 for the treatment of malignant tumors by Dr. James B. Murphy, of the Rockefeller Institute, after some very convincing experimental work on animals. Large amounts of radiation, on the contrary, destroy the lymphocytes whose formation it at first stimulates. A series of cases treated by the toxins without the concomitant use of radiation, in which the blood reactions are carefully followed, might prove of great value. There must have been many, many cases in the past treated by these toxins on the hit or miss principle by the family doctor, without careful study, such as is possible in the modern clinic. Yet under these disadvantageous circumstances, occasional miracles have occurred and in Coley's own undiscouraged hand these miracles have not been infrequent". (46)

10. The Coley Toxins after Coley

After Coley's death in 1936, his son Bradley L. Coley, M.D., became Chief of the Bone Tumor Service and he and his associate Higinbotham continued to produce excellent results with the toxins in Ewing's sarcoma, reticulum cell sarcoma and some osteogenic sarcomas of bone. B.L. Coley and Higinbotham served in the Army from 1942 to 1946. Upon their return, chemotherapy became a priority. The Medical Director, Rhoads, without consulting the Bone Tumor Service, wrote Parke Davis & Company in 1950 telling them to stop making the toxins. A typical administrator's callused and unethical act against a number of patients who were receiving them. For a time Rhoads had the toxins made at Sloan-Kettering Institute (SKIxiv) and eight reticulum cell sarcomas were successfully treated with this product, combined with x-ray therapy in some cases. In inoperable cases with metastases the limb was saved in all these, one was a Mayo Clinic case (37).

In 1939 we began a half century of study on Coley's work. We found the factors affecting success were very concrete as outlined above, but they had been largely ignored by Coley and most of the other men using the method. Matagne was an exception. He made his own toxins so they did not have to be shipped and lose potency in transit before the days of airmail, and he administered them wisely. In 1953 we founded Cancer Research Institute, to provide incentive and

support for investigators in this field of cancer immunology. The first two investigators we funded were Johnston and Havas at Temple University, Philadelphia, Pennsylvania, Johnston's laboratory prepared the Coley toxins for clinical use and for a special study at New York University (50,51). Havas also prepared the toxins but did not use them clinically (52,53).

Between 1954 and 1963 a number of physicians and surgeons became aware of our studies, requested reprints and obtained toxins (Johnston XV). We also sent them detailed directions for administration and toxin therapy record sheets to facilitate analysis of results. Successful results were obtained by several including Johnston (50, 51). Rank in Texas, breast cancer (23); Fowler, in Connecticut, multiple myeloma (54) and colon cancer (31), and Nicholson in Philadelphia, reticulum cell sarcoma (37).

Following the tragedy of thalidomide in Europe in 1963, the Kefauver bill was passed enabling the Food and Drug Administration (FDA) to establish very stringent regulations regarding clinical trials of new drugs. Though the Coley toxins were 70 years old, the FDA ruled it was a new drug requiring special permits and endless red tape to use it clinically, hence all those who were using it stopped. Despite this terrible blow we continued to assemble data and to edit and to publish 22 monographs after 1963 (8). We also read papers at 11 international cancer conferences (8).

One study was undertaken with an F.D.A. protocol at Memorial Sloan-Kettering Cancer Center in June 1976 by Kempin et al (50). Patients with advanced non-Hodgkins lymphoma were randomized to receive or not receive one subcutaneous injection of mixed bacterial vaccine (MBV) five days before each cycle of chemotherapy. There were 40 nodular poorly differentiated lymphoma, five nodular mixed lymphoma, three nodular histiocytic lymphoma, Stage II, five cases, Stage III, 23 cases, Stage IV, 21 cases. Radiation therapy was given to initial areas of bulky disease or to nodal or extranodal sites responding only partially to chemotherapy. The MBV treated patients had a higher rate of complete remission (73 vs. 44 percent) longer duration of remission ($p=0.005$) and longer survival ($p=005$).

The product they used was made in Germany by Bayer, and they used only subcutaneous injections at infrequent intervals which caused little or no febrile reactions. Despite these factors the MBV did improve remission and survival, although a few years later the survival curves merged due to late recurrences. Thus the study was not continued, although the authors had reported in 1981 that the study strongly suggested a potential role for MBV therapy in the management of these tumors (50).

Another physician working independently in Milwaukee, Wisconsin, began in 1972, after having worked in a regional burn unit for nine years where he treated 3,000 cases with a mixed bacterial vaccine he had made up to prevent the virulent

infections these patients develop. His vaccine made isolation and antibiotics unnecessary. In 1972 he decided to treat his cancer patients with the vaccine which was made in his own laboratory. By 1986 he reported on 139 patients. They received BCG, transfer factor and MBV -- all were advanced cases that had failed under chemotherapy or refused it (54). His results suggested that combined immunotherapy is well tolerated and safe and that it had a salutary effect on a number of patients. His best results were in lung cancers and in operable breast cancer given the treatment as an adjuvant to surgery: none of the 30 cases so treated has died (55).

11. PRELIMINARY RESULTS OF MIXED BACTERIAL VACCINE IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA AS ADJUVANT

In 1981 Guo, a pediatric oncology surgeon at Beijing Children's Hospital became interested in using the method for his patients. He also was impressed by a case of very extensive sarcoma of the thigh that had recovered following a severe staphylococcus infection with complete recovery (44). He also had read our first monograph (1) which was in his Medical School Library. He wrote us and we provided the end result studies on pediatric malignancies, the directions as to preparing and administering the toxins and kept in close touch. We went to China in October 1983 and brought Guo to New York that fall, so he could visit Memorial Sloan-Kettering Cancer Center's excellent pediatric division. We emphasized the need for more space in the ward, an area for play and more nurses. We also stressed the need to allow the mothers to be with their children as much as possible to reduce stress which is immunosuppressive. We provided the toxins prepared by Havas in Philadelphia for part of the time.

In the past 7-1/2 years he has treated 49 cases in children. Of the inoperable cases receiving ten or more injections, eight were successful, traced up to eight years after onset. There were 16 inoperable failures, of whom six received 7 to 10 injections - too brief a period.

Of the 22 operable cases, only two have died, one of which was recurrent when toxins were begun. Twelve have remained free from disease up to six years after onset, seven more recent cases remain well and one equivocal case is probably cured but awaits a "second look".

Guo is the first surgeon since Matagne in Belgium to use the toxins before as well as after surgery. His results indicate how successful this technique can be: No primary operable case has died. He used injections intratumorally, intradermally over the tumor site, and intramuscularly (57).

Guo has also treated a considerable number of adults in another hospital, but it is too soon to evaluate the results.

In Shanghai at our suggestion, Tang a very well-known liver cancer surgeon, has been using the Coley toxins provided by Havas of Temple University. From May 1985 to December 1987

patients received hepatic arterial ligation plus cannulation for 30-40 consecutive days, including 12 cases with second stage resection, and 34 patients with palliative resection. These cases were randomized. The controls did not receive mixed bacterial toxins (as the Coley toxins are now called, MBV). One group had cis-platin, one group had MBV and radiation, one group had all three. The patients receiving MBV had 47.8 percent survival versus 35 percent for the controls. In the second look resection 9/25 survived versus 3/20 in the controls. Remarkable lymphocyte infiltration was found in the tumor specimen after second look resection in the MBV cases. (Zhao You Tang, Hai Yan Zhou, Gang Zhao, Li Mian Chai, Ji Zhen Lu, Kang Da Liu, Havas, H.F., Nauts, H.C.).

It may be of interest to some readers that there is currently a clinical trial testing the effect of mixed bacterial vaccines (MBV) upon the immunocompetence of patients with far advanced cancers and its toxicity and potential benefits to the patient. The vaccine has been registered with the Food and Drug Administration and the principal investigator, Dr. Rita Axelrod, possesses IND #BB-2016 for testing this drug. The protocol is quite broad and general so as to maximize the accrual of patients; however, in order to qualify the patient must have failed all standardized treatment modalities or be unacceptable for such management. The patients studied to date, with the exception of one patient, has shown acceptable toxicity to the vaccine and a number have shown gratifying improvement in some of their immune parameters. Dr. Axelrod is located at Temple University Medical School, Philadelphia, PA.

12. Conclusions

We believe that the factors outlined in this review indicate why the Coley Toxins never acheived wider recognition. Since the mistakes of the past are now more clearly understood, there is a real opportunity to organize cooperative studies. Not only for inoperable cancers but as an immunoadjuvant to potentiate the response to the usual modalities and protect against their immunosuppressive effects. The Chinese studies have already shown that this is possible.

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