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A REVIEW OF THE INFLUENCE
OF BACTERIAL INFECTION AND OF BACTERIAL
PRODUCTS (COLEY'S TOXINS) ON MALIGNANT
TUMORS IN MAN



*A critical analysis of 30 inoperable
cases treated by Coley's mixed toxins, in which diagnosis
was confirmed by microscopic examination
Selected for special study*

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TABLE OF CONTENTS

Introduction	Page 5
Table of 30 Inoperable Cases of Malignant Tumors	„ 16
Complete Case Histories.....	„ 21
Index of Various Preparations of Coley's Toxins Used, 1891—1953	„ 93
References	„ 97

INTRODUCTION

The treatment of cancer by injections of bacterial products is based on the fact that for over two hundred years neoplasms have been observed to regress following acute infections, principally streptococcal. If these cases were not too far-advanced and the infections were of sufficient severity or duration, the tumors completely disappeared and the patients remained free from recurrence. If the infections were mild, or of brief duration, and the neoplasms were extensive or of histological types which were less sensitive to infections or their toxins, only partial or temporary regressions occurred.

Of all the many investigators who studied this phenomenon, the late William B. Coley, M. D. is the only one who devoted a lifetime to the subject. His search for a systemic treatment of cancer began in the first year of his practice (1891) when he lost his first case (a bone sarcoma) in spite of early, radical and repeated surgery. This led him to study all the cases of sarcoma treated in the New York Hospital during the preceding 15 years.

His interest in the possible therapeutic value of infections or their toxins was aroused by one of the cases in this series of histories—a thrice-recurrent inoperable sarcoma of the neck, in which five operations had failed to control the disease. This patient recovered after two attacks of erysipelas and remained free from further recurrence seven years later (8).

Beginning in May 1891, Coley attempted to produce erysipelas in a twice-recurrent inoperable myxosarcoma of the tonsil and neck. After repeated trials, using four different cultures, he succeeded. The resulting severe erysipelas caused complete regression of the tumors except for cicatricial tissue from the former operations.

After attempting to induce erysipelas in nine other patients, Coley recognized the difficulties—either the patient might prove immune, or the infection fatal. He tried cultures of erysipelas sterilized by heating or by filtration, but these proved weak and ineffective.

In December 1892, he learned of the investigations of Roger on bacillus prodigiosus (*Serratia marcescens*) in association with other micro-organisms. These experiments suggested that bacillus prodigiosus or its toxins may increase

the virulence of other organisms with which they are associated in their proliferating stage. Coley therefore decided to mix the toxins of bacillus prodigiosus with those of erysipelas in order to increase the virulence of the latter. The first "Coley Mixed Toxins" were sterilized by filtration, and the first case treated by this preparation was a bedridden young man with an inoperable sarcoma of the abdominal wall and pelvis, involving the bladder. (See Case 1 for complete history.) The extensive growth disappeared and the patient remained free from recurrence until his sudden death in a subway station from heart disease, 26 years later (11).

The preparation then in use, however, was variable and not potent enough to produce cures in the more resistant types of neoplasms. Limited space prevents a detailed description of the more than 15 different formulae of Coley's toxins used in the past 60 years. Suffice it to say that it was not until the more potent unfiltered Buxton and Tracy preparations were available and were intelligently administered that the more resistant types of cancer were successfully treated. (Note: A brief description of these different preparations will be found at the end of this monograph.)

During the past 14 years we have been making a critical analysis of toxin therapy. The approach has been much more fundamental than merely to study the historical background of Coley's Toxins. The goal has been to gather available data on the effects of acute infections or their metabolites, and various forms of inflammation on malignant disease. This includes the beneficial effects of one intercurrent disease upon another; the effects of pyogenic, non-pyogenic or non-pathogenic bacteria or their toxins or enzymes; the effects of viruses; the effects of various inflammatory or antibiotic substances; the effects of physiotherapeutic or chemotherapeutic agents of non-bacterial origin; and all known cases in which so-called "spontaneous regressions" occurred.

Many of the questions relating to this study have received little consideration. For example, why is it that the incidence of cancer has increased much more rapidly since the advent of modern asepsis and public health than ever before? This increase remains apparent even if figures are corrected for improved methods of diagnosis and for age distribution. We believe this is because these technics have sharply reduced the incidence of surgical infections and infectious diseases. Shear, of the National Cancer institute, seems to agree with us, for in 1950 he observed that 75 per cent of the spontaneous remissions in untreated leukemia in the Children's Hospital in Boston occurred following an episode of acute disease. He asks: "Are pathogenic and non-pathogenic organisms one of Nature's controls of microscopic foci of malignant disease, and, in making progress in the control of infectious diseases, are we removing one of Nature's controls of cancer?" (94, p. 390). Jacobsen (1934) cited data which he claimed represented the uniform observations of experienced clinicians with reference to the low incidence of malignant disease in patients who had been victims of a common infectious process, i.e., in the actively tuberculous or osteomyelitic, and in patients with acute infectious

diseases in general, particularly those giving a history of typhoid, paratyphoid, scarlatina or diphtheria. Jacobsen concluded that the evidence tends to support the conclusion that the reticulo-endothelial system when sufficiently active, (as when stimulated by one or a number of infectious processes) may attain in a measure the ability to cope with neoplastic diseases in a similar, if not identical manner. He also believes that the present increase in malignant morbidity is due to the decreased resistive powers of the reticulo-endothelial system occasioned by the lessened incidence of exposure to and infection of the general public with those diseases which were widely endemic before the advent of modern public health methods. He believed that as acromegaly is a disease of the pituitary, so cancer should be regarded as a disease of the reticulo-endothelial system, and the hope of prevention and cure lies in toxin therapy (62). In an editorial in the J.A.M.A. (1934) this whole matter was discussed and it was concluded that further studies in this field seemed indicated in the light of the accumulated evidence (52).

As to experimental work which may support this theory, Teutschlander has demonstrated a definite decrease in the susceptibility of tuberculous fowls to Rous chicken sarcoma (106), and Bashford found mice convalescent from contagious diseases were refractory to tumor transplants. Schwartzman reviewed the literature bearing on the effects of intercurrent infections on animal tumors (97).

Many physicians believe that the chief therapeutic value of toxin therapy lies in the fever produced. Available evidence on this point has been carefully reviewed. It would appear that fever alone is not the most important factor in toxin therapy or in the effects of acute infections, because if it were, every infection, physiotherapeutic agent or chemotherapeutic substance which invoked fever should be equally effective. This is not the case. Nevertheless, the evidence accumulated by Shoulders (95, 96), Jares and Warren (63, 110), Delario (47), Doub (49, 50), Rohdenburg and Prime (90), as well as many earlier investigators using various agents which invoke fever or local heat, clearly shows that these factors definitely enhance whatever form of therapy is being given, and that therefore they are certainly beneficial, but that fever and heat alone cannot destroy human cancer without being used in such high degree as to be detrimental to the patient.—Byrne, 1895 (4); Westermarck, 1898 (111); Balfour, 1916 (1); Percy, 1916 (87, see case 30).

In addition to evaluating modern technics in the use of toxins, surgery, radiation or chemotherapy, we have abstracted some of the early monographs on cancer therapy here and abroad as practiced over a century ago (Tanchou, 104). It appears that these early physicians induced inflammation at the site of the neoplasm by a variety of methods, while at the same time they stimulated the organism as a whole, and that they persisted with the treatments for many months, changing the remedies as tolerance developed.

In studying all these apparently unrelated older and more recent approaches to the cancer problem, one finds they have certain points in common: a more or less

severe local inflammation, produced by an irritating or destructive agent such as radiation, diathermy, intratumoral injections of toxins, acute local infection, poultices, leeches or vesicants, occurring either alone or combined with a profound systematic stimulus. The systemic stimuli were produced by various means such as Coley's toxins or other bacterial or plant products injected remote from the tumor by the intramuscular, intraperitoneal or intravenous route, or by the systemic effects of severe bacterial infections. In addition to the above, cases were found in which spontaneous remissions occurred following an intercurrent fracture (109 a), burn, shock (1 a) or absorption of extensive pleural effusion, or ascites (60, 70, 109). In all these cases there also appeared to be both inflammation and a systemic stimulus such as fever or "stress".

Of all these combinations the largest number of successful results have occurred in two groups: a) in cases of malignant disease in which an acute erysipelas infection developed in or near the tumor; b) in cases treated by Coley's toxins, where a reasonably potent product was administered both into the tumor or its immediate periphery (to induce local inflammation and sensitize the tumor cells) and also remote from the tumor, in doses sufficient to elicit marked systemic reactions, fever and chills, the injections being continued until after the growth had disappeared in order to prevent recurrence or metastases. The results in patients with inoperable neoplasms so treated were uniformly good. (We do not include terminal cases in this category, although some of these also responded dramatically.)

Jacobi's work with bacterial filtrates (*B. typhosus*) on several types of animal tumors emphasizes the importance of sensitizing tumors by intratumoral injections. He elicited violent hemorrhagic and necrotic reactions followed by either complete sloughing and healing or by slow recurrence of tumor growth which again responded to further injections. This occurred in all the animals in which the tumor tissue was first "prepared" or sensitized by an intratumoral injection followed by an intravenous or intraperitoneal injection. In the controls in which saline was substituted or in which the filtrate was injected only intratumorally or only intraperitoneally, these effects were not obtained, and the tumors continued to grow, causing death of the animals. Duran Reynal's more extensive studies bearing on this problem were discussed in some detail in two of our earlier publications (78, 79). These findings may have an important bearing on planning the optimum technic of administration for treating human cancer (61).

Although Fogg observed inhibition of growth of sarcoma 180 cells in tissue culture with certain bacterial products (54), it was not generally recognized that bacterial toxins do not actually kill cancer cells *in vitro* (113) although they cause regression of cancer *in vivo*. This would seem to be a further indication that much of their curative action must be exerted indirectly, through stimulating the body's basic defense mechanisms (inflammation, alarm reaction, fever, etc.). However, both heat and inflammatory exudates do destroy neoplastic cells *in vitro*, as well

as causing regression of neoplasms *in vivo*, as indicated by the work of many investigators such as DeCourcy (46), Hodenpyl (60), Lohmann (68), Mackay (70), Okuneef (84), Overgaard and Okkels (85), and Tuffier (109).

If we consider that an erysipelas infection produces a more severe local inflammation with local heat as well as vesication and absorption of exudates than any other form of infection, and that in addition to these properties, it produces marked systemic reactions, including fever, we may have discovered the reason why the greatest number of dramatic disappearances and apparent cures of cancer have occurred following erysipelas, rather than after typhoid, pneumonia, malaria or some other infection. (Note: It is probable that the development of erysipelas in a given patient may depend not only on the virulence of the culture but also on the physiology of the host, local and systemic immunity factors, tissue permeability, response to inflammatory stimuli, etc.)

DIFFICULTIES ENCOUNTERED BY THIS METHOD

The treatment of malignant tumors by bacterial products has been associated with many difficulties. These included variation in bacterial strains, lack of a standard bio-assay to insure a definite potency of the products available for clinical use. This matter is discussed in greater detail in our earlier papers (78, 79). Unfortunately, all but four of the more than 15 different formulae of Coley's toxins available in the past 60 years were weak and variable.

Furthermore, at the very time when Coley's early studies were in progress, the new discoveries of x-rays and radium and their effects on neoplasms overshadowed all other approaches to the study of the treatment of malignant lesions. During the last half-century the effects of radiation have become fairly clearly delineated. X-rays have apparent beneficial effects on certain types of tumors, but the majority of highly malignant visceral tumors are affected little if at all by irradiation.

IMPORTANCE OF TECHNIC

It is now apparent that the neoplastic cell is most sensitive to bacterial products during the metaphase of division. It would seem, therefore, that anything which inhibits the rate of mitosis or decreases tissue permeability during toxin therapy may also slow down the destruction of tumor tissue by toxins or the protective substances they evoke in the body. Prolonged, heavy radiation or repeated surgical procedures which alter or destroy the vascular or lymphatic channels and produce fibrosis may be considered as deleterious if used prior to toxin therapy.

The evidence accumulated in recent years indicates that in order to produce consistently successful results, it is necessary to destroy the neoplasm completely before the patients or the tumor cells develop immunity to the bacterial product. Thus the most effective technic is essential. We are not dealing merely with an

antigen-antibody immunity problem, but also with the fact that the tolerance produced by repeated intravenous injections of pyrogenic materials is associated with the development of immunity to the Schwartzman phenomenon. In discussing this point Cluff and Bennett cited Benson's observations. They concluded that the resistance to Schwartzman phenomenon which develops when the reaction is elicited at short intervals is transient, disappearing after a rest period of 21—28 days. It was found that a transient state of non-reactivity could be produced by repeated inoculation of bacterial substances intracutaneously, intravenously or intramuscularly, evidence that the resistance is not dependent on the development of skin hemorrhage. The resistance which develops by repetitive injections could be overcome by increasing the provocative intravenous dose but not by increasing the preparatory intracutaneous dose (7).

These observations suggest that a series of three or more courses of toxin therapy of perhaps four weeks, alternating with a rest period of 21 days, may produce better results by allowing the patient to regain tolerance to the toxins, than to continue the toxins indefinitely. (Cases 8 and 29 are examples of cases so treated.) It should be emphasized, however, that if a "rest period" is given too soon, the tumor may again increase rapidly in size. (See Cases 23 and 24 for examples.)

One of the most serious disadvantages toxin therapy encountered was the lack of appreciation of the importance of technic. Many physicians, including Coley, allowed their house surgeons to make the injections on all hospital patients, and, as there were no standard forms for recording the technic used and reactions elicited by different types of toxins, it was difficult to evaluate the importance of various details of technic in determining success or failure. These included site, dosage, frequency, and duration of the injections, as well as degree of reaction elicited.

Another factor in technic which needs consideration is the disposal of large quantities of necrotic tumor tissue destroyed by toxins, in order to prevent toxemia from absorption. This is most often a problem in very extensive anaplastic soft part tumors that respond very rapidly to toxin therapy, and may be handled by the method Coley and other surgeons used, incision and drainage or aspiration. However, it may be possible now to utilize more modern weapons such as streptococcal enzymes (Streptodornase and Streptokynase), which may well have played an important role in the destructive effects seen when accidentally contracted streptococcal infections developed in cases of extensive neoplasms. These enzymes may liquefy the debris in a tumor regressing under toxin therapy, thus facilitating aspiration or absorption (107).

It is unfortunate that most physicians who gave Coley's method some thought, considered it as useful only in inoperable or desperate cases. Hence the number of operable cases who received toxins is small, probably not much over 400 patients. These cases were given injections before or after surgical removal, usually after, "as a prophylactic against recurrence". Because the tumor had usually been removed in such cases, most physicians (including Coley himself) did not appreciate how

important technic could be in administering toxins in the operable cases. If injections were given for at least four to six months, surgeons here and in Europe achieved 80 per cent five-year survivals—a considerably higher rate than that following surgery alone or combined with radiation (41). As regards this factor of duration of treatment which now seems so important in inoperable as well as operable cases, Coley stated in September 1935: "Dr. Calkins of Watertown, New York, who has the largest number of successes of any other surgeon, keeps up the treatment usually for a year" (41). Coley also began to appreciate the fact that more aggressive and persistent treatment was necessary to control or cure far-advanced cases. In commenting on the brilliant result achieved in 1926 by Christian and Palmer, Coley stated: "I believe this is one of the most remarkable cases of malignant tumor of the long bones that has ever been published, and I am quite willing to admit that, had the patient been under my care, he would probably not have been alive today. In the first place, 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 tumor of the stump. In the second place I am quite sure that I should not have dared to increase the dose to such a large amount. However, it was not until these large daily doses were given that the improvement continued until all the tumors had disappeared. I have learned more from this one case than from any other that I have personally treated, and I feel that many of the past failures might have resulted otherwise had larger doses and more frequent injections been given" (6, p. 196). See below for a complete history of this case, a reticulum cell sarcoma of the tibia, p. 84.

Toxin therapy (when reasonably potent products are administered with a proper technic) causes destruction of tumor tissue and apparent immunity to further recurrence or metastases. Experiments at the Wistar Institute, in Philadelphia, have shown that the optimum conditions for inducing immunity in rats are: a) That the tumor must actually grow in the host. b) That it must die in the host. c) That it must degenerate under conditions which permit relatively slow absorption of degeneration products. (103, Discussion by Dr Jonathan E. Rhoads, of Philadelphia.) In view of these findings, it would seem wise in treating future cases by various forms of toxin therapy to administer the toxins for a time *before* as well as after surgical removal in operable cases, in order to induce a more active immunity through absorption of necrotic tumor cells. This was successfully accomplished by Matagne of Brussels, Belgium from 1896 until his death. He seems to have been the only surgeon here or abroad to begin toxin therapy as a routine measure prior to operation (41, 46).

In discussing this same paper by Stone on the question of whether resistance to cancer may be induced, Dr John Jameson Morton of Rochester, New York, suggested that if we could attack "the enemy" at its lowest ebb, and use jointly extirpative as well as suppressive agents, there may be considerable gain therein, whether the suppressive agents are irradiation or chemotherapeutic agents. We

believe the results achieved by Coley and the many other physicians who gave toxin therapy a careful trial, show that this is true. The combination of surgery and prophylactic toxins has produced consistently much higher percentages of five-year survivals than surgery alone. Also cases treated by radiation and toxins show a larger percentage of permanent results than cases treated by radiation alone.

DISCUSSION

It now seems opportune to review the evidence which has been recently assembled and to re-discover the effectiveness of Coley's original concept. With more precise knowledge of bacterial chemistry, of immune reactions, of antibiotics, of the defense mechanisms of the body, including inflammation and the alarm reaction, it may now be possible to determine the basic biological factors underlying the remarkable effects which were achieved by Coley and others who were working more or less empirically.

In order to evaluate more clearly the actual results obtained by Coley's toxins and other forms of toxin therapy in cancer, we are now preparing a series of end-result studies of all known cases in which sufficient detail was available, and diagnosis was confirmed histologically. For a more detailed history of the early development of Coley's method, you are referred to the first two studies in this series (78, 79). Another more recent publication is a bibliography of approximately 500 references to the literature on the effects of actual infections, inflammation, fever or heat on malignant disease (80). We are also preparing a series of end-result studies according to anatomical sites. The first study comprises abdominal cancer. These cases have been sub-divided according to the organ in which the neoplasm developed wherever possible, and these in turn have been listed according to whether the patients were in the terminal, inoperable or operable stage when toxins were begun. The present monograph is a critical analysis of the method Coley developed with end-result studies of 30 inoperable cases treated by Coley's toxins. These cases indicate how the toxins worked on a variety of neoplasms, and includes cases showing the dangers of inadequate treatment. (Cases 22 and 27.) This group was selected from over 270 in which a complete regression was obtained, as being representative of what could be accomplished by toxin therapy in inoperable malignant disease.

Because the late Dr William B. Coley was put in charge of the Bone Tumor Service at Memorial Hospital, his practice after 1918 was largely devoted to bone cases, and therefore almost all his published papers in the last 15 years of his life deal with neoplasms of bone (34, 35, 36, 38, 43). Unfortunately, this gave the medical profession the erroneous impression that Coley's toxins were effective only in bone sarcoma. Actually, osteogenic sarcoma are very much less sensitive to toxins than neoplasms arising in the soft tissues. Coley stated this as early as

1895, but it was ignored. It is important to note that the osteolytic types of rapidly growing malignant bone tumors, such as endothelioma, reticulum cell sarcoma and plasma cell myeloma, as well as giant tumors of bone are all markedly sensitive to toxins. (See Cases 6, 8, 19, and 29 for examples.)

Our conclusions are based on a comparative analysis of over 1,200 cases treated by various forms of Coley's toxins and other bacterial products, and a group of 300 cases in which an intercurrent infection played a part. The cases have been listed according to the type of toxin used, the type of tumor, the anatomical site and the stage of the disease when the toxins were begun or infection developed, a procedure which facilitated analysis of the factors governing success or failure.

It is hoped that clinical studies will now be undertaken to determine whether one may achieve similar effects on cancer patients by using various bacterial products (57, 112), administered intravenously or intraperitoneally, combined with inflammation induced locally in the tumor area by a variety of means such as diathermy, poultices, etc. From available evidence, it would seem that bacterial pyrogens may be complex carbohydrates rather than proteins. Streptococcal enzymes and their possible role in helping to increase tissue permeability and dispose of necrotic tumor tissue also deserve serious study.

While such work is being undertaken and improvements in the products and the technic of administration are being effected, it is important to evaluate the excellent results which were achieved in the past when toxin therapy was properly administered. We believe that Coley's method has not been more widely used because the existing strong evidence was scattered and had never been presented in such a manner as to allow toxin therapy to compete with its more popular competitors, the x-ray machine, radium or some of the recently discovered chemotherapeutic agents.

We agree with Stone that whether the cancer cell as such (as an entity), or whether the cancer cell, as including an active virus . . . is the active causative agent in cancer is irrelevant to the question as to whether it can provoke a defense reaction. We believe that the evidence we have assembled indicates that such a reaction has been induced in the cases treated by various forms of toxin therapy.

Present and future studies in this field should include fundamental research on the relative importance of local inflammation of various types, and of the mechanism invoked by the systemic reactions as they may relate to the reticulo-endothelial system and the endocrine system, including the alarm reaction. Such studies should yield more concrete results than to continue to associate all the essential destructive action of bacterial toxins with the tumor-hemorrhage-inducing factor, as has been the case with most of the research done in the past 16 years (93, 94, 97, 98, 114, 115, 116). It is suggested that a broader physiological approach to the entire problem be undertaken now by many investigators.

The fact that blood-borne bacteria and antigens become localized in areas of inflammation and in tumors should be studied as it relates to developing the most

effective technics of administration (3, 75). Studies on modern concepts of inflammation have been made recently by many investigators including Burrows (3), Lohmann (68), and Menkin (74, 75). The last-named has isolated several factors from inflammatory exudates, one of which stimulates leukocytosis, another fever, another necrosis. It is possible that if these factors are used separately in connection with toxin therapy they may yield better results. However, through thousands of years Nature has evolved the complex phenomenon of inflammation as a defense mechanism. Perhaps the entire process must be evoked intensively together with systemic stimuli in order to destroy cancer and prevent recurrence. It is possible that individuals who develop neoplasms have lost the ability to elicit such reactions (46), and that toxin therapy, acute infection or inflammation restores or supplements these functions, thus enabling the patient to deal effectively with malignant disease.

TABLE OF 30 INOPERABLE
CASES OF MALIGNANT TUMORS, TREATED
BY COLEY'S TOXINS
SELECTED FOR SPECIAL STUDY

Table of Inoperable Malignant Tumors selected for Special Study which were treated by Coley's Toxins

Doctor (References)	Date	Age Sex	Site of Tumor	Type of Tumor*	Duration and Site of Injections	Immediate Result	Final Result (Years Traced)
1. Coley (9, 11, 12, 21, 22, 29, 41, 73, 102)	1893	M. 16	abdominal wall, pelvis involving bladder	spindle cell sarcoma	4 months (into tumor)	gradual steady decrease in size, complete regres- sion	no recurrence, very good health until death, chronic myo- carditis 1919 (26 years)
2. Coley (12, 13, 14, 29 42, 89)	1893	F. 29	abdominal wall, filling left abdomen, (cachexia)	fibrosarcoma	4 months (into tumor)	gradual steady decrease in size, complete regres- sion.	no recurrence, in good health, sudden death heart failure 1918 (25 years)
3. Coley (12, 13, 14, 18, 20, 24, 29, 72)	1894	F. 16	scapular region, extensive (13" x 7")	spindle cell sarcoma	9½ months (into tumor)	disappeared entirely by absorption	no recurrence, alive & well 1913 (19 years)
4. Griswold & Storrs (15, 16, 17, 20, 24, 29, 41, 77, 102)	1895	F. 42	breast, pectoral region, axilla, (lost 42 lbs.)	spindle cell sarcoma; rapid growth	3 months (into tumor)	disappeared completely by absorption & discharge of necrotic tumor through drainage points	no recurrence. Died 5/2/43 at 89, bronchopneumonia. (47 years)
5. Gruver (26, 29, 41, 77, 82)	1899	F. 49	cervix, extensive metastases, intes- tines	carcinoma	about 3 years (into tumor intramuscu- larly)	pain easier, then gradual complete disappearance of both metastatic masses.	no further metas- tases; died, 'flu, 1929 (30 years)
6. Pollak (Coley) (20, 23, 29, 41, 42, 77)	1902	M. 21	5 vertebrae, dorsal & lumbar, exten- sive, (lost 50 lbs., paraplegia)	giant cell tumor	about 3½ months (some into tumor)	enormous growth entirely disappeared, paraplegia ceased, normal function restored	no recurrence, led normal life; died coronary thrombo- sis, 1944 (42 years)
7. Winberg (Haggard) (24, 29, 43, 112)	1901	M. 40	upper jaw, recur- rent, extensive metastases liver	mixed cell sarcoma	5 months (3 in tumor)	rapid, complete disap- pearance of growths, im- provement in general health.	no further recur- rence; died alcohol- ism, nephritis 1907 (6 years)
8. Spencer (19, 29, 45, 99, 100)	1906	M. 33	entire lower abdo- men, infiltrating viscera, rectus muscles	spindle cell sarcoma, prognosis grave	6 months (3 courses total- ing 46 doses, intervals of rest, some into tumor.)	no effect from first course; diminished during periods of rest between courses; complete regression.	no recurrence, re- turned to active army life; alive & well 1912 (6 years)

9. Sanford (77)	1906	F. 9	upper jaw, recurrent, extensive	round cell sarcoma	7 months (in thigh)	fungating growth entirely disappeared	no further recurrence, alive & well 1953 (47 years)
10. Coley (24, 29, 41, 77)	1906	F. 11	tonsil & neck	round cell sarcoma	6 months (mostly in tumor of neck)	tumors disappeared completely	alive & well 1952 (46 years)
11. Coley (22, 24, 29, 77)	1907	M. 27	back & jaw	round cell sarcoma	8 months (5 in tumor of jaw)	tumors disappeared entirely	developed carcinoma viscera 1945, died 1946 (38 years)
12. Gibbon (2, 26, 34, 35, 41, 77)	1908	F. 17	humerus, recurrent	spindle cell sarcoma	several months (in arm near tumor)	recurrent tumor completely disappeared	alive & well 1947 (39 years)
13. Coley (29, 31, 41, 42, 73, 77)	1908	M. 21	inguinal & iliac, recurrent	lympho-sarcoma	8 months (6 in tumor)	tumors disappeared; recurrent; entirely disappeared a second time	no further recurrence; alive & well 1952 (44 years)
14. Bott (26, 27, 29, 41, 42, 77, 108)	1909	F. 39	both breasts, extensive metastases	carcinoma	2 years (in or near metastases)	marked improvement within 4 weeks; all metastases disappeared: regained health	developed another tumor axilla, 1925; died 1927 (20 yrs. after onset of first breast cancer)
15. Lagueux (14, 25, 29, 64, 108)	1909	F. 50	breast, axillary metastases	carcinoma	not stated	recurrence disappeared, edema arm subsided	no further recurrence, alive & well 1912 (3 years)
16. Barry (29, 41, 77, 108)	1909	F. 44	sternum recurrent	osteosarcoma	6½ months (a few in tumor)	growth entirely disappeared, sinus drained necrotic tumor tissue, then healed	no further recurrence; alive 1952—has gastric cancer (42 years)
17. Greenwood (29, 32, 41, 56, 77)	1911	M. 67	posterior triangle neck	malignant melanoma, recurrent	22 months (some in or near tumor)	growth entirely disappeared	no further recurrence; died acute bronchitis 1925 at 81 (14 years)

* Diagnosis confirmed by microscopic examination in each case.

Case 1 and 2 received the Type IV preparation of Coley's toxins (filtrates of erysipelas and bacillus prodigiosus).

Case 3—6 received Buxton's Type VI preparation of Coley's Toxins (mixed unfiltered erysipelas and bacillus prodigiosus).

Case 7 and 8 received Parke, Davis & Company's mixed unfiltered Coley toxins (Type IX).

Cases 9—11 received Tracy's Type X preparation of Coley's Toxins.

Cases 12—26 received Tracy's Type XI preparation of Coley's Toxins.

Doctor (References)	Date	Age Sex	Site of Tumor	Type of Tumor*	Duration and Site of Injection	Immediate Result	Final Result (Years Traced)
18. Coley (28, 29, 41, 73, 77)	1912	M. 52	soft palate	adenocarci- noma	over 12 months (mostly in tumor)	marked decrease in size, less diffuse, more discrete, harder; remains excised	no recurrence; well until death 1944, stroke (31 years)
19. Harmer (29, 41, 58, 59, 72, 77)	1912	M. 12	10th dorsal verte- bra, recurrent, 5"×4"×2"	giant cell tumor	7 months (abdominal muscles, later in tumor)	injections into tumor caused sloughing and complete disappearance	no further recur- rence; alive & well 1953 (40 years)
20. Burns (29, 40, 41, 42, 77, 108)	1912	F. 27	kidney, retroperi- toneal glands	round cell sarcoma	4 months (in buttocks)	rapid, complete disap- pearance extensive growth; gained 20 lbs.	no recurrence, alive 1952 (40 years)
21. Fowler (29, 31, 41, 73 77)	1913	M. adult	neck	round cell sarcoma	over 4 months (intramus- cular)	growth disappeared com- pletely; when dose or frequency decreased growth increased	no recurrence; died drowning about 1928 (15 years)
22. Coley (30, 41, 73, 83)	1915	M. 38	nasopharynx, both upper jaws, ethmoid (exophthalmos)	carcinoma	1st course 6 wks; second 4 months (pectoral gluteal muscles)	all evidence disease dis- appeared; toxins stopped; recurrence, again regres- sed; toxins again stopped; disease recurred, not again controlled	died of cancer about 1 year after first injection
23. Tuholske (41, 42, 77, 102)	1915	M. 28	pharynx & naso- pharynx	round cell sarcoma	1st course 3 1/4 months, 2nd course, 2 1/2 months intramuscular	completely disappeared in 6 wks., recurrence, brain involvement; all evidence of disease again disappeared under further Rx. (see his- tory for details)	no further recur- rence or metas- tases; died 1948, coronary occlusion (33 years)
24. Coley & Follansbee (41, 73, 77)	1916	F. 23	gluteus maximus muscle	round cell sarcoma	8 months (partly in tumor or surrounding tissues & gluteal mus- cles)	growth entirely regressed; toxins stopped; large re- currence; this entirely disappeared under aggres- sive treatment	no further recur- rence; had 3 more children, alive & well 1953 (37 years)

25. Calkins 5, 41, 77)	1916	F. 29	ovary, extensive metastases mesenteric glands, intestines, peritoneum, liver, colon	carcinoma	15 months (intra-muscular)	incomplete removal; patient dying; metastases regressed completely; gained 80 pounds	no further metastases; excellent health until death, cerebral hemorrhage 1936 (20 years)
26. Coley (2, 33, 34, 35, 36, 41, 43, 73, 77)	1917	M. 39	tibia, metastases, groin	osteogenic sarcoma	2½ years with rest periods	(patient also had 3 radon packs); complete regression	no further metastases; alive & well 1953 (35½ years)
27. Harmer (41, 58, 59, 72, 108)	1911	M. 46	back, axilla, metastases	malignant melanoma	11 months (some in tumors)	metastases regressed by absorption or by sloughing; some excised; no evidence of disease.	patient went on spree; returned quite ill; died disease 1914 (2½ years)
28. Pollak (53, 67, 76, 97, 98)	1924	F. 2	mediastinum, pressure on spine, paraplegia	angiosarcoma	11 days (gluteal muscles)	daily doses, violent reactions; again able to walk in 3 wks; growth slowly disappeared completely	no recurrence; alive & well 1953; married; had normal baby (29 years)
29. Christian & Palmer (2, 6, 35, 36, 37, 38, 73, 76, 77)	1926	M. 32	tibia, recurrent in stump, multiple metastases	reticulum cell sarcoma (formerly considered endothelial myeloma)	5 courses totalling about 23 months with periods of rest	at first decrease; when toxins stopped, tumor increased enormously, others appeared; toxins resumed in huge doses; finally all evidence disease disappeared	no further recurrence or metastases; alive & well 1953 (27 years)
30. Senecal (41, 73, 77, 91, 92)	1933	F. 38	ovaries (bilateral), metastases omentum, broad ligaments, liver, enormous growth, (cachexia, see complete history)	papillary cyst adeno carcinoma	1st: 6 mos. 2nd: 1 yr. (intra-abdominal)	abdomen decreased 9 inches in circumference in first 4 wks; gained weight, strength. Growth, apparently disappeared, then recurred when dose, frequency reduced; operation; toxins given for another year.	no further recurrence or metastases; in very good health, 1953 (20 years)

* Diagnosis confirmed by microscopic examination in each case.

Cases 27—30 received Parke, Davis and Company's preparations (Type XII and XIII), the only Coley toxins available in the United States from 1921 to 1946.

COMPLETE CASE HISTORIES

Note: This patient was the first case of any type of cancer to be treated by *Coley's mixed toxins*. The cultures of erysipelas and bacillus prodigiosus were grown separately, passed through a Kitasato filter (without heating), and mixed at the time of use. They were prepared by Dr Alexander Lambert at the Laboratory of the College of Physicians and Surgeons, New York. Coley stated that the streptococcus culture used was obtained from a fatal case of erysipelas and was exceptionally potent. The second case also received this product.

CASE 1: Inoperable spindle cell sarcoma of the abdominal wall and pelvis, involving the bladder, confirmed by microscopic examination by Dr Harlow T. Brooks, pathologist.

Previous History and Treatment Other than Toxin: J. F. F., male, age 16, born in Germany, living in New York City. The family history was negative for malignancy. There was no history of syphilis. Onset, about three months prior to admission to Memorial Hospital, pain developed in the abdomen. About two months afterward a hard lump was felt in the lower abdomen. This increased slowly but steadily in size. Occasionally the pain in the tumor was very severe, being intermittent in character. There was no loss of weight. Examination on admission showed a hard tumor measuring about $6\frac{1}{2}$ inches across by $5\frac{1}{4}$ inches and apparently being 5 inches thick. There was no fluctuation. The growth involved the entire thickness of the abdominal wall, was attached to the pelvis and judging from the symptoms and position evidently involved the bladder. (The patient was unable to retain urine when admitted.) The general condition was poor, the patient being confined to bed most of the time. An exploratory laparotomy was performed by Dr L. Bolton Bangs, Professor of Genito-urinary Surgery at New York Postgraduate Hospital and Medical School. The condition was found to be inoperable and the patient was referred to Dr William B. Coley.

Toxin Therapy: (Type IV). Injections were begun by Coley on January 24, 1893, and were given directly into the tumor mass. They were continued in

slightly increasing doses until May 13, 1893, or a little less than four months. The Memorial Hospital Records state: "These injections produced within eight hours a rise in temperature from 0.5° to 6° , the pulse running from 100 to 106. The chill and tremblings were extreme. For the severe headaches following the chill, Phenacetine was given. Aseptic precautions being successful, no pus was produced, in spite of the many needle punctures. The tumor gradually diminished in size, at times for a few days after injection it would be enlarged, but the final diminution was indisputable" (72). The dosage used varied between 0.5 and 1.5 cc. of erysipelas, and 0.25 and 0.5 of prodigiosus. Coley stated that the chill usually occurred within the first half hour after injection, though occasionally it was delayed an hour. Sometimes local redness and swelling accompanied the reaction. Usually both local and constitutional symptoms had subsided at the end of 24 hours.

Clinical Course: The patient was discharged on May 13, 1893, at which time the tumor was a fifth the size it had been on admission. No further treatment was given. At examination two weeks later the tumor was no longer visible. Palpation revealed a small movable mass, two inches in diameter at the site of the former growth. (When the toxins were begun the mass measured $5\frac{1}{4}$ by $6\frac{1}{2}$ inches.) The enlarged glands in the right inguinal region still persisted. The patient had gained ten pounds in weight in the previous four weeks. By August 1, the remains of the growth had almost disappeared, save for a small mass palpable in the right iliac fossa. The inguinal glands were still enlarged. The patient was kept under constant observation. He was able to resume his regular work and received no further treatment. He was presented before the New York Academy of Medicine, November 15, 1894. Six years later he developed a primary lesion of syphilis, which ran the usual course and was finally cured by mixed treatment. He was presented by Coley before the New York Surgical Society in 1900 and again on February 13, 1907, in perfect health (29, Case 57). He remained in very good health and free from recurrence until his sudden death on February 26, 1919, over 26 years after toxin therapy. Death occurred in the subway station at 42nd Street, (Grand Central Station), New York. The death was investigated by the Chief Medical Examiner and the cause listed as chronic myocarditis, a contributory cause being "fatty degeneration of the heart" (102, No. 8370).

References: 9, 11, 21, 22, 29, 41, 73, 102.

CASE 2: Extensive inoperable fibrosarcoma of the abdominal wall, confirmed by microscopic examination by Dr W. F. Whitney, Pathologist of the Massachusetts General Hospital, Boston. He reported: "A small dense, ill-defined, whitish-looking mass, which on

microscopic examination was found to be made up of large numbers of small cells with a tendency to form fibres... the diagnosis is fibrosarcoma" (12, p. 70).

Previous History and Treatment Other than Toxin: Mrs E. J. L., female, age 29, of Melrose, Mass. The patient's father had died of tuberculosis, but the family history was negative for malignancy. The patient had been married for ten years, and had one son born in 1884, when she was 20—a difficult delivery. She wore tight corsets during her pregnancy. The baby was said to be "under-nourished" at birth. Onset, she first noticed a small swelling in the abdominal wall in late April, 1893. This increased in size with considerable rapidity and was associated with pain in the left side. On August 16, 1893, the patient consulted Dr Maurice H. Richardson, of Boston, Mass. On examination he found a tumor filling the left side of the abdomen, which clinically he believed was connected with the Fallopian tube. The patient was pale and cachectic, there was no color in the face and rather a waxy look (13). On August 31, 1893, an exploratory operation was performed by Richardson at Massachusetts General Hospital, assisted by Dr Farrar Cobb. An incision directly over the median line revealed an inoperable tumor involving the abdominal wall but not the tubes. A second incision was made over the most prominent part of the tumor, revealing a firm growth, which Richardson stated "in its gross appearance . . . was clearly malignant". As the condition was inoperable a small portion was removed for microscopic examination. Richardson gave a very bad prognosis, but decided to refer the patient to Dr William B. Coley for a trial of the toxins.

Toxin Therapy: Injections were begun early in October, 1893, using the mixed filtered preparation (Type IV). Local injections into the tumor were repeated daily for six weeks causing marked reactions. Within two weeks after the first injection, improvement was very evident. The patient's general condition suffered but little, and she was able to be up and about almost the entire time. Little reaction followed moderate doses, and it required very large doses to raise the temperature to 101° to 102° F. On December 22, Coley advised the patient to go home for a month to allow the inflammation caused by the local injections to subside, so that the exact amount of improvement caused by the treatment could be determined. Richardson found her improvement so marked after three weeks at home that he wrote Coley he saw no reason why she should not be permanently cured. She returned to New York on January 12, and remained under treatment another month. The tumor steadily decreased in size and had apparently entirely regressed at the time of her discharge about February 10, 1894. On April 3, 1894, the patient was carefully examined by Richardson and Coley, and they were unable to find any trace whatever of the tumor. All signs of inflammatory induration had likewise disappeared. She had gained several pounds in weight and her general health had never

been better (29, p. 91). This case was one of several reported before the American Surgical Association, May 31, 1894, and in the discussion of this paper Richardson stated: "In this case there can be no doubt, according to the accepted methods of diagnosis, that the woman had a malignant and necessarily fatal disease. The mass filled the right lower quadrant when I operated. I first incised in the median line, and came down upon the tumor. I then made an incision in the lateral region with the same result. There was nothing to be done surgically. I took out a section and had it examined. It was pronounced sarcoma. The patient was sent to New York in October: when she came back (in February) there was not the slightest sign that could be detected. Unless the diagnosis was entirely wrong, unless the history, gross appearance, and microscopic examination were entirely wrong, this was a case which must have died sooner or later." Whitney, in a personal letter to Coley, also stated that there was not the slightest doubt as to the diagnosis (41).

Clinical Course: On March 8, 1895, Richardson again examined the patient and found no trace of the tumor remaining, but at the site of the exploratory incision there was a ventral hernia. In writing Coley about this time Richardson stated: "I look upon this case as a most extraordinary one . . . which gives hope that we are on the verge of some great discovery in the treatment of this deplorable condition" (41).

The patient remained perfectly well until 1909 when she developed a fibroid tumor of the uterus, which Coley removed by abdominal hysterectomy. The abdominal wall at that time was found to be perfectly normal with no trace of the original sarcoma. The patient was shown before the Clinical Congress of Surgeons of North America November 12, 1912, in good health. She died in the spring of 1918, of "heart failure", having enjoyed good health until about three years prior to her death. She had complained of a slight stomach ache during the early evening. On going to bed she had some dyspnea, and then quietly passed away. The patient's husband requested the attending physician to make an examination of the abdominal region at the time of her death, thinking that perhaps there had been a recurrence, but the findings were entirely negative (41).

Note: In 1898 Richardson presented the case of J. R. before the American Surgical Association (89). This boy had a very extensive recurrent inoperable lymphosarcoma involving the axilla and scapula which was incompletely removed at operation. The remains of the growth then regressed completely following a very severe wound infection (see Monograph on Infections, Series A., inoperable series accidentally infected, in preparation).

In presenting this case Richardson stated: "The case seems of interest in connection with the subject of disappearance of malignant tumors under the influence of a general toxæmia, whether artificially or accidentally produced. The occasional cure of malignant disease by internal medication excites not only interest but incredulity. Scepticism 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."

"As an illustrative example I would cite one of the most extraordinary cures of sarcoma that I have ever seen. 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. After some months treatment with Coley, the tumor, though as large as a child's head, disappeared." (The abdominal wall had been infiltrated to a thickness of at least six inches, he added.) In conclusion he stated:

"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. I am convinced, however, that a considerable number of tumors, pronounced malignant, disappear under local or systemic conditions which are artificially produced. 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" (89).

References: 12, 13, 14, 29, 41, 89.

Note: The following four cases received Buxton's unfiltered toxins of erysipelas and bacillus prodigiosus (Type VI of Coley's various formulae).

CASE 3: Inoperable spindle-cell sarcoma of the scapular region, with extensive involvement of the chest wall, confirmed by microscopic examination by Dr H. T. Brooks, Pathologist at the New York Post-graduate Hospital (12).

Previous History and Treatment Other than Toxin: S. C., female, age 16, Jewess, of New York, New York. There was no history of malignant disease in the family. The patient's history was negative for tuberculosis, inflammatory or specific disease. She was born in England and had always been in good health. However, from the time she was very young she had always had to work very hard, carrying water, scrubbing and other manual labor (before the age of 10). At 13 she attended school for three years. She then worked as a nurse maid. Menses were normal. Onset, in March 1894, or four months prior to admission, she began to have pain in the left arm, shoulder and scapula. She then noticed a small tumor in her back over the left scapula. This rapidly increased in size, gradually extending both in front and behind, until it had involved the larger portion of the left thoracic wall. It was associated with constantly increasing pain and interfered with motion of the arm. The patient was admitted to Memorial Hospital on June 23, 1894, under the care of Dr William B. Coley (73, No. 2710, 1894; No. 3242, 1895). Examination at this time revealed a hard, fixed mass involving almost the entire region of the left thorax behind, extending from the clavicle to the lowest rib, the

vertical measurement being 13 inches. Horizontally, it extended from the median line behind to the middle of the sternum in front, and from one inch below the clavicle seven inches downward, involving a large portion of the region of the left breast. It was flat, being only about two inches thick over the most protuberant portion. The entire tumor was fixed to the scapula and to the ribs, apparently originating in the soft parts over the scapula (13). The skin over the growth was normal in appearance and not adherent. The growth was not painful on palpation. The left arm could not be raised to a horizontal position, being bound down by the new growth. Movements forward and back were correspondingly limited. Breathing was much diminished on the left side, both anteriorly and posteriorly. A biopsy was performed, and the specimen was carefully examined by Brooks, who reported: "typical spindle-cell sarcoma" (13). Because of the rapidity of the growth and the enormous extent, Coley did not believe even temporary arrest possible; nevertheless, he decided to try the injections for two or three weeks.

Toxin Therapy: (Buxton VI). Injections were begun at Memorial Hospital on June 23, 1894, by Coley, and were all made into the tumor over the lower part of the scapula, or within a radius of two inches. They were given daily or every other day and produced fairly marked febrile reactions, usually accompanied by a chill. However, the reactions were never severe enough to keep the patient in bed more than a few hours after injection. At times there was much pain in the growth. To Coley's astonishment, improvement was immediate and very rapid. Within three weeks, the arm could be raised to a vertical position, and within one month, the growth in front had nearly disappeared. The improvement continued without any interruption until the latter part of October 1894, 3½ months from onset of treatment, when no trace of tumor could be found in front or behind. The growth regressed entirely by absorption, without any breaking down or sloughing (13). Coley presented the patient before the New York Academy of Medicine, November 15, 1894, at which time there was not the slightest trace of the growth or any induration whatsoever. She had regained her normal health and strength. As a precaution against recurrence, injections were continued with intervals of rest until April 12, 1895, when the patient was discharged as cured (73).

Clinical Course: She was examined from time to time by Coley and his associates. In 1900, or six years after toxin therapy, she developed myositis ossificans in the pectoral region on the opposite side (73, No. 7895, 1901). She remained in good health and free from recurrence when last traced in December 1913, 19 years after treatment (29).

Note: In reporting this case in 1895, Coley stated: "This case is to my mind the most brilliant of the entire series . . . (Up to 1895). Here we have a tumor, the great malignancy of which was shown by the rapidity of its growth and the

extensive involvement that had occurred within four months, and the diagnosis of spindle-celled sarcoma established by the microscopic examination of a skilled pathologist, entirely disappearing with $3\frac{1}{2}$ months from the beginning of the treatment with the mixed toxins" (12).

References: 12, 13, 14, 18, 20, 24, 29, 73.

CASE 4: Inoperable, rapidly growing spindle cell sarcoma of the pectoral region and breast, confirmed by microscopic examination of material removed at biopsy by Drs B. H. Buxton, E. K. Dunham of New York, and William H. Welch, of Johns Hopkins Hospital, Baltimore.

Previous History and Treatment Other than Toxin: Miss E. E. F., female, age 42, of New Britain, Connecticut. The patient's paternal grandmother had died of carcinoma of the breast, but the family history was negative for tuberculous or specific disease. The patient's previous health had been good. Onset, in October 1895, she first noticed a hard lump below the left clavicle in the pectoral and axillary region. This grew rapidly and in two months had reached the size of an orange. It was firmly adherent to the deep vessels and extended well into the axilla. Her general health deteriorated and the patient lost 24 pounds in weight. She consulted Dr M. Storrs of Hartford, early in December, 1895. A consultation was held with McKnight, attending surgeon at the Hartford Hospital, and both surgeons regarded the condition as entirely inoperable. The patient was rapidly losing strength and weight. It was decided to try toxin therapy under Dr William B. Coley's direction.

Toxin Therapy: (Buxton VI). Injections were begun by Storrs and Dr R. H. Griswold on December 16, 1895, the day following the patient's admission to the Hartford Hospital. The initial dose was one drop, which was gradually increased to a maximum of 8 minims. The first chill occurred after the fourth injection, on December 29. Injections were given every two days until February 8, during which time 39 were administered, 18 of which produced distinct chills. The dose was 8 minims on February 8. The following day a more potent solution prepared from more virulent cultures was obtained and the dose was reduced from 8 minims to one minim. In spite of reducing the dose this injection produced the most violent chill. This more potent preparation was continued and caused chills in doses of 1 to 3 minims during the next five weeks, injections being given daily in this period. The patient reported: "Chills came on 30 to 90 minutes after treatment lasting 30 to 45 minutes. When the newer stronger toxins were used (February 9) had the worst chill of all; with that toxin the chill would come on sometimes half an hour after the treatment. The days I had a chill, I had less pain and felt better after the chill than the days when I had none..." (77). (This patient did not take her

temperature regularly, and the few times she did take it, half an hour after the injection, it was usually about 100° F, so the maximum febrile reactions in this case are not known.) The patient remained in the hospital only a short time; thereafter the injections were made at home or in the doctor's office

The tumor began to shrink shortly after the injections were begun. It was incised nine times during the course of the treatment, in order to facilitate the drainage of necrotic tumor tissue. The discharge increased after the more potent toxin was used. All the incisions were thoroughly irrigated every time an injection was made for nearly three months. (This was a painful process, and it is doubtful whether such a procedure should be employed in treating future cases.) During the treatment the patient's appetite was not very good, but she ate in order to maintain a little strength. A total of 76 injections was given in three months.

Clinical Course: By the latter part of March 1896, or a little over three months after the toxins were begun, the growth had entirely disappeared and the patient had gained rapidly in flesh and strength, so that she soon regained the 25 pounds she had lost prior to toxin therapy. Coley presented her before the New York Surgical Society on November 11, 1896, and also before the Clinical Congress of Surgeons of North America, November 11, 1912 (29). She remained in good health, married and when last traced by Coley shortly before his own death, she was well except for pain in her knee joints. In 1939 she developed a small basal cell epithelioma at the left side of her nose (77). She died on May 2, 1943, at the age of 89, of bronchopneumonia and decompensated arteriosclerotic heart disease (102). This was 47 years after the toxins were administered.

References: 15, 16, 17, 20, 24, 29, 41, 77, 102.

CASE 5: Inoperable carcinoma of the cervix, with metastases in the small and large intestines, confirmed by microscopic examination by Dr James Ewing of a specimen removed by Thompson, of Scranton, Pa.

Previous History and Treatment Other than Toxin: Mrs R. G., female, age 49 in August 1899, of Stroudsburg, Pennsylvania. The patient was one of a family of eleven children, three of whom had died in infancy. One sister died of cancer of the intestines at the age of 45, another of carcinoma of the esophagus at 65, another of carcinoma of the breast with metastases at 73, one brother of carcinoma of the stomach at 44 or 46, and the maternal grandmother died of cancer of the uterus at 43. The family history was negative for tuberculosis, diabetes, arteriosclerosis or allergies. The patient's previous personal history was negative, except for the usual diseases of childhood. Menses began at 18; the patient was married at 24 and had three children. At the age of 41 she began to have intense pain in the lower abdomen at intervals of every two days to a week, with much nausea, vomiting and

headache. This continued for two years, the symptoms increasing in severity. During this period there was no disturbance of the menstrual cycle. A diagnosis of malignant cervix was made and the patient was admitted to the New York Hospital on May 9, 1893. Physical examination at this time showed tenderness on pressure over the left side of the abdomen. The cervix was very hard and the external os was surrounded by a ring of hard nodules. Dr William T. Bull operated, removing a growth the size of a goose egg, together with the cervix. A specimen of this growth was reported as "normal cervical tissue". The patient was discharged on May 20, 1893. She made a good recovery and remained in good health. During this time menstruation practically ceased, or was irregular, occurring at longer intervals. Three years later the abdominal symptoms recurred, with occasional bloody discharges from the uterus. This continued for three years and by 1899 there was much nausea, retching and even vomiting of feces, occurring intermittently at intervals of about a week. An exploratory laparotomy was performed by Dr Charles Thompson of Scranton, and a specimen removed and sent to Ewing, who reported it to be carcinoma. The mass in the right lower quadrant was found to be inoperable. The patient was readmitted to New York Hospital on July 18, 1899, and physical examination at this time revealed two growths, one on each side of the abdomen, attached to the small and large intestines. These masses had been growing rapidly for about six months. The region of the cervix was hard and eroded, the uterus enlarged and firmly fixed. A diagnosis of inoperable carcinoma of the cervix was made, with a prognosis of not more than 18 months of life. The patient was discharged unimproved on July 20, 1899. Dr William B. Coley was then consulted. He confirmed the diagnosis and the prognosis, but nevertheless recommended trying the toxins as a last resort.

Toxin Therapy: (Buxton VI). The patient returned home and the injections were begun in early August by her son, Dr Charles D. Gruver and Dr Joseph Shull. They were made deeply, directly into the masses, and were given twice a week for about six months, and then once a week for over a year. After an interval of rest they were resumed, the total duration of treatment being about three years. The initial dose was 0.5 minim, which was increased to a maximum of about 5 minims. Some injections were given into the abdominal wall and gluteal muscles. In describing the results Gruver stated: "Each injection caused a full reaction: elevation of temperature, redness and swelling, the patient remaining in bed 24 hours. Improvement was noted after the first month of treatment—pain easier and intervals between painful attacks longer" (41). Gruver added that the growth had been increasing rapidly in size before the toxins were begun, and that after the injections were given, it remained stationary and then gradually regressed. At the end of a year it was scarcely palpable (77). There was decided improvement in the general health as well as in the local condition, and the patient was able to resume her normal activity, doing all her own housework.

Clinical Course: There never was any recurrence. The patient remained in unusually good health. During the last five years of her life there was some swelling of her ankles and some dyspnea, but these symptoms did not incapacitate her nor did they require treatment. While visiting her son in Asheville, North Carolina, she was very active during an influenza epidemic in the household, contracted pneumonia and died in 72 hours, on January 7, 1929. She would have been 80 years old the following October. This was 30 years after toxin therapy (77).

References: 26, 29, 41, 77, 82.

CASE 6: Very extensive inoperable giant cell tumor of the dorsal and lumbar vertebrae, with paralysis of the bladder and rectum and the lower extremities, and loss of 50 pounds in weight, confirmed by clinical and microscopic examinations. The case was reviewed in 1932 and again in 1946, by Dr Fred Stewart, of Memorial Hospital.

Note: The original diagnosis in 1902 had been "round cell sarcoma", by Dr Harlow Brooks, Pathologist at Bellevue Hospital, New York (20).

Previous History and Treatment Other than Toxin: D. G., male, age 21. The patient wrenched his back while wrestling in the autumn of 1898, causing some pain and stiffness for three days. Later, pain and discomfort again recurred at the site of the injury. The patient entered the Montefiore Home for Incurables in April 1901, at which time examination revealed a large swelling in the back and lower dorsal region. He was unable to walk, but there was no true paralysis of the lower extremities. Six months later a tumor was noticed on either side of the spinous processes of the lower dorsal and upper lumbar vertebrae. This gradually increased in size until February 1902, when it was exceedingly large, involving all the vertebrae from the eighth dorsal to the third lumbar. The muscles of the thigh were markedly atrophied, and there was great general emaciation, with total paralysis of the bladder and rectum. The patient was unable to turn over in bed and had lost 50 pounds in weight. At this time Dr William B. Coley saw the patient in consultation with Dr Virgil P. Gibney. The latter regarded the prognosis as absolutely hopeless (20).

Toxin Therapy: (Buxton VI). Injections were begun by Dr Alfred W. Pollak, the house surgeon, with little hope of giving more than temporary relief. The initial dose was 0.5 minim injected into the buttock on February 22, 1902. The dose was increased daily by half a minim. Two days after the first injection the tumor seemed smaller and there was no redness or irritation of the skin. The first chill occurred on February 27 following a dose of 3 minims, with a temperature of 103.4° F., accompanied by pain, nausea and vomiting; the pulse was weak and rapid, the respiration rapid, and there was blood-stained diarrhea. The condition was so bad

that injections were not resumed for a week, when 3 minims again caused a reaction of 103.4° F. accompanied by pain, emesis and chills. The same result followed this dose given March 18 and 20. In the meantime everything possible was done to stimulate the patient's appetite. On April 2 the injections were resumed, the dose being $1\frac{1}{2}$ minims, which produced little reaction. Another marked reaction occurred on April 11, following an injection of $2\frac{1}{2}$ minims (103.4° F.) and on April 12, following a dose of $2\frac{3}{4}$ minims (104.2° F.). The maximum temperature occurred following a dose of 3 minims on April 14: 108.8° F. (Coley considered this to be the cumulative action of the toxins following a series of daily injections. However, it is possible that this injection reached a vein.) In spite of this excessive reaction, an injection was given the following day and caused a febrile reaction of 100° F. Injections were continued with intervals of from one to three days' rest up to May 15. At no time did the patient develop tolerance to the toxins, which is usually observed when they are given for a long period. The last dose, on May 15, produced a febrile reaction of 104.6° F. with severe chills.

Clinical Course: From May 15 to June 5 there was a daily rise of temperature, often as high as 104° F., apparently due to the absorption of large quantities of necrotic tumor tissue, for the tumor had shown a steady diminution in size. By June 5 the improvement was so marked that it was not thought advisable to give further treatment. By the end of September 1902, the total paralysis had been replaced by fair motor power and ability to walk. The reflexes were normal and the areas of sensory disturbance had diminished in extent and intensity. There was still some urinary retention and constipation. Gibney applied a plaster jacket which the patient wore for a number of months. Improvement continued until by early 1903 he had entirely recovered and the plaster jacket was discarded (20, 23, 29). The patient resumed his regular occupation, married, and had three children. He was seen periodically by Coley. In 1914 an x-ray examination by Dr Byron C. Darling was reported as follows: "Between the twelfth dorsal and the third lumbar vertebrae there is now a bony outgrowth extending at least one inch on both sides of the spine and posteriorly about one inch to a plane corresponding to the ends of the spinous processes. On the lateral view there is absence of the body of the first lumbar vertebra, i.e., a kyphosis. The condition is more that of a productive lesion than a destructive lesion. The x-ray appearance is consistent with a new growth in which the process has ended in a deposit in a soft destructive tumor, rather than a bony tumor from the beginning." The patient was presented at the Memorial Hospital Bone Tumor Clinic in 1926. In reviewing the case at this time, Coley stated that the sections showed a large number of giant cells of uniform size, and quite different from the usual type of benign giant cell tumor. He added that this tumor had attained a greater size than he had ever seen in giant cell tumor, involving five vertebrae, and that it showed a degree of local malignancy which he had never seen or found in the literature (42). After having remained well for 28 years, the patient

developed a recurrence of his symptoms at the site of the old tumor. These persisted and he became bedridden and was taken to the Harper Hospital in Detroit. X-ray pictures were taken by Dr Clark D. Brooks and were sent to Coley. At this time the patient had difficulty in urinating. A urological examination was made, following which he developed acute pyelonephritis. The urological condition was considered a cord lesion bladder, due to the old tumor of the spine, but Brooks did not believe that there was a recurrence of the tumor. The condition cleared up. On July 1, 1932, the patient was reexamined by Coley at the Hospital for Special Surgery, New York. X-rays taken at this time showed extreme destruction of the body of the first lumbar vertebra with considerable destruction of the twelfth dorsal and second lumbar. The intervertebral discs had also been destroyed and there was marked angular kyphosis. Calcification had been laid down all about this region, uniting the bodies from the eleventh dorsal to the third lumbar into one solid bony mass. There was no suggestion of recent activity. The patient continued to lead a normal life, his only complaint being diabetes, which he developed in 1935 and which was controlled by insulin. During the autumn of 1943 he developed coronary disease. He died suddenly while on a vacation, on August 19, 1944, of coronary thrombosis, 42 years after the toxins were administered.

References: 20, 23, 29, 41, 42, 77.

Note: The following two cases received Parke Davis and Company's preparation of Coley's toxins, mixed unfiltered, known as Type IX.

CASE 7: Recurrent inoperable mixed cell sarcoma of the right superior maxilla involving the antrum, with metastasis in the liver. In commenting on the case in 1902 Dr William B. Coley stated: (112) "This case is so extraordinary that it is most important that the diagnosis should be placed beyond question. The mass removed on May 9 was examined by Dr J. L. Rothrock, of St. Paul and pronounced sarcoma. This was confirmed by Dr Schadle. Microscopical examination was also made by Dr George D. Haggard, of Minneapolis, after removing another section, August 11, and pronounced spindle cell sarcoma. All agreed that it was clinically sarcoma and absolutely inoperable. Sections were also examined by Drs B. N. Buxton and James Ewing, Professor of Pathology at the Cornell Medical School, New York, and finally by Dr William H. Welch, of Johns Hopkins. Welch's report is as follows: "The section shows a tissue composed mostly of closely packed cells without definite arrangement. The predominant cells are fairly large oval spherical or irregularly polyhedral cells, with not very abundant cytoplasm, and with round or

oval nuclei larger than those of ordinary lymphocytes. In addition, there are some fusiform cells and smaller cells of the lymphoid type. The cellular outlines are not readily made out. The intercellular stroma is scanty, but in places a fibrillated intercellular substance is recognizable. There is considerable fragmentation and distortion of nuclei, especially in certain places, and in one area there is necrosis of the tissue. Hemorrhages are present in a few places. Small acini and ducts of an acinous gland occur irregularly, distributed in different parts of the section. These are generally widely separated by intervening tissue of the tumor. They are lined by one or two layers of low cubical epithelium. Blood vessels with definite walls are not readily made out, but vessels with endothelial lining immediately surrounded by the tumor cells, can be seen. Diagnosis: Round cell sarcoma. He added: 'There is perhaps enough diversity in the cells to justify the designation mixed cell sarcoma, but round or oval cells greatly predominate. The tumor has the histological elements of malignancy.' (signed) William H. Welch" (112).

Previous History and Treatment Other than Toxin: A. Y., male, age 40, born in Sweden. The patient, a veterinary surgeon, with good family history, and in excellent health, was struck over the right superior maxilla by the horn of a bull early in February 1901. Two or three weeks later he had severe pain over the site of injury, and to relieve this the canine tooth was pulled. Pain continued, and the patient went to St. Paul in the middle of April and consulted Dr J. E. Schadle, who made a diagnosis of sarcoma. The first bicuspid tooth was pulled and the antrum explored without any evidence of an abscess being found. Excision of the upper jaw was proposed and performed on May 9 by Dr C. K. Wheaton of St. Paul, assisted by Drs Rogers and Dennis. A letter from Rogers to Coley describing the operation, states: "There was found a large tumor involving the antrum and almost the entire upper jaw. Ferguson's incision was made but an attempt to remove the entire growth proved unsuccessful. Thorough curetting and cauterizing of the remaining portions was done. There was also a mass the size of a hen's egg underneath the ear on the opposite side. This was completely removed. The patient having partially recovered from the effects of the operation, returned to his home, Lake Park, Minnesota on May 18, partially relieved of the pain" (112). After a few days the sarcomatous growth again began to increase in size, invading the nose and extending along the palate into the pharynx, and also involving the parotid region. On June 25 he returned to St. Paul and consulted Schadle, under whose care he remained until July 18. Only palliative measures were used, however, at this time, and Schadle wrote Winberg on July 13 that he felt the prognosis was very unfavorable. He added: "The disease is undoubtedly sarcoma and will eventually destroy

him" (112). Before returning home the patient consulted Haggard of Minneapolis, remaining under his care from August 1 to 11. Haggard stated that the patient had difficulty in retaining food and also in obtaining action of the bowels. He advised a trial of the Coley toxins, although others had strongly discouraged their use, considering the case altogether hopeless. Haggard further noted: "From August 1 to 11 weakness was progressive. Having been able to walk daily from one to two miles, he now became barely able to walk from the door to the carriage. Pulse 130. Jaundice, at first slight, became more pronounced. Dullness and tenderness appeared in the hepatic region. Nausea and vomiting increased. Stools constipated and clay-colored, urine dark with bile." He added: "From these conditions we decided metastasis had occurred in the liver" (112). At this time the right nasal cavity was occluded, the soft palate retracted and thickened by a tumor mass in its substance. This was ulcerated in the center, the ulcerated cavity being $1 \times 1\frac{1}{2}$ inches in size. The tumor extended from the right malar eminence to the bridge of the nose, with which it was even in height, and downwards to the edge of the maxilla. From the higher portion of the tumor at the side of the nose Haggard removed a section (part of this tissue was later sent to Welch). The patient returned to Lake Park on August 12; Winberg found that the disease had progressed rapidly; jaundice had become more profound, and the liver was enlarged. Pulse 140 to 150, irregular and intermittent. At this time speech was difficult to understand and the odor from the disintegrating portion of the tumor was repulsive. Winberg stated: "His condition was such that I hesitated to use the toxins, but the patient still kept up his courage and muttered: 'The practice of medicine is like fishing. Sometimes a sucker bites and sometimes he does not. Let us try the toxins'" (112).

Toxin Therapy: (Parke Davis IX). Winberg, who administered the toxins, reported: "The first injection of $\frac{1}{2}$ minim was made into the tumor on August 12, 1901. August 13, 1 minim was injected. Patient's condition grew worse, and there was no apparent effect from the toxins. On the 15th the patient's condition was so desperate that no treatment was given. It was thought best to abandon further use of the toxins. The patient threatened to get another physician if I would not continue. August 16, $1\frac{1}{2}$ minims were given. The urine became very scant. Patient had severe pain in the stomach and his general condition was even more alarming. On the 17th, 2 minims of a fresh bottle of Coley's toxins, obtained from Parke Davis & Co., were injected. Patient's eyesight began to fail; he had suppression of urine, and no nourishment of any kind could be swallowed. The teeth had become so tightly closed that it was impossible to cleanse the mouth. The swelling underneath the left jaw had become the size of an English walnut, and the original tumor of the right superior maxilla had reached the size of a man's fist. August 18: pulse 155 to 165, weak and irregular; temperature 100.8° F. Patient unable to see and rarely able to make himself understood. Jaundice greatly intensified. Large doses of nitroglycerin, gr. 1 to 50,

digitalin, gr. 1 to 50, strychnia, gr. 1 to 25, were given every four hours as symptoms of heart failure had appeared. At this time he was in a stupor . . . That night he was able to swallow a little champagne . . . August 19 he voided 4 oz. of urine, and he passed some more in the afternoon. An injection of 2 minims of the toxins was given into the abdominal wall. On the 20th, 3 minims were given also into the abdominal wall. Patient seemed slightly improved. Daily doses were given, always, except the first three injections, into abdominal wall, the amount being slowly increased. The improvement, which at first had been very slight, became more and more marked. The jaundice gradually disappeared and was entirely gone at the end of three weeks, at which time the tumor in the left submaxillary region had also disappeared, and there was marked decrease in size in the primary tumor of the right superior maxilla. Improvement in general health was rapid and continuous. Toxins were kept up in large doses up to January 4, 1902; in all 102 injections were given; 12 in August, 20 in September, 21 in October, 22 in November, 24 in December, and 4 in January. The toxins were always diluted with 15 cc. of water (and were given every day for six days and then none for two days), the dose was increased as rapidly as the patient could possibly bear it" (112).

Winberg added that the patient weighed but 113 pounds when the injections were begun, and that he gained 11 pounds during the first three weeks' treatment, and had a voracious appetite. On September 12 he rode 30 miles on a professional call, and since that time attended to a very large veterinary practice, which often called him away both night and day. On January 4 he weighed 143 pounds, a gain of 30 pounds in five months.

Clinical Course: On January 12, 1902, the patient made a trip to New York in order to show Coley the result obtained with the toxins, and on January 13 Coley presented him before the Surgical Section of the New York Academy of Medicine. At this time no trace of the tumors could be found either in the neck or face or jaw, and abdominal examination showed nothing abnormal. For photographs see (112) or (24), Figs. 8—9.

The patient remained in good health and free from recurrence until 1907, six years after treatment, when he died of acute nephritis following alcoholic excess (24).

Note: This case is of especial significance, because it is reported in such complete detail, and also because it may have done much to persuade Coley that systemic injections could be relied upon to produce successful results. This is indicated by his remarks at the end of Winberg's report (112). Apparently, he did not notice that the first three injections were made into the tumor itself for he states: "Aside from the extraordinary recovery of a patient so near death from inoperable sarcoma, the case is remarkable from the fact that the cure

was obtained by injections remote from the tumor. Therefore, the effect upon the tumor was entirely due to systemic rather than local action. Although I have personally had a few successful cases of inoperable sarcoma in which the injections were made remote from the tumor, in nearly all the successful cases the injections have been local, directly into the tumor itself. I have always maintained, however, that the curative action of the toxins is systemic as well as local. This case fully demonstrates the correctness of this view and disproves the position taken by a number of writers that the action of the toxins is merely local in character, in the nature of an escharotic" (112).

(A study of over 1,200 cases of various types of neoplasms treated with the toxins indicates that the site of injection apparently is of importance in determining the success or failure of the treatment. Undoubtedly, the toxins do exert a favorable effect on tumors through intramuscular or intravenous injections remote from the growth, but these alone take longer to accomplish the complete destruction of the neoplasm and, in the interim, the patient or the tumor may become immune to the toxins before the disease has been destroyed.)

References: 24, 29, 43, 112.

CASE 8: Inoperable spindle cell sarcoma of undetermined origin, occupying the entire lower abdomen, infiltrating the peritoneum, involving the rectus muscles, and firmly attached to the symphysis pubis. The diagnosis was confirmed by microscopic examination by Lt. Col. C. Birt, R.A.M.C. For microphoto see (99).

Previous History and Treatment Other than Toxin: C. W. L., male, age 33. The family and previous personal history was non-contributory. There was no history of venereal or malignant disease. The patient had always been a healthy man. He was a sergeant in the Royal Field Artillery, having been in the service 13 years. He had had enteric fever in India in 1895. The patient was admitted to the hospital at Bulford on July 21, 1906, complaining of a hard, painful swelling in the lower abdomen, and frequent and somewhat painful micturition. He had been operated for right inguinal hernia in September 1905, and believed the tumor and "weakness of the bladder" had developed shortly after that operation. The patient was a thin, spare man with a rather anxious expression. The general health was good except for loss of weight. He slept well and had a good appetite. Examination revealed a large, very hard swelling in the lower part of the abdominal wall, reaching from the pubes to within 1½ inches of the umbilicus, in the median line, and measuring about three inches across. It was apparently firmly attached to the symphysis pubis and was slightly tender. The overlying skin was free. Micturition occurred every three or four hours with some pain at the end. The urine contained some albumin, but was otherwise normal. During the following three weeks the patient seemed to be getting

thinner, but no increase in the tumor could be made out, though it became less tender. He was transferred to the Queen Alexandra Military Hospital at Millbank, England, on August 20, 1906. On admission the condition was as described above except that the urine was normal, the frequency of micturition less, and on rectal examination a hard mass could be felt in front of the prostate, evidently forming part of the tumor. An exploratory laparotomy was performed by Major C. G. Spencer, R.A.M.C., on September 5, 1906, and revealed a growth involving the recti muscles, firmly attached to the symphysis pubis and extending down in front of the bladder where it could be felt per rectum. Because consent to a dangerous operation had not been obtained, only a section was removed and the wound closed. Six days later an attempt at removal was made, but the peritoneum lower down was found to be widely involved and the operation was abandoned. The wound healed by primary union.

Toxin Therapy: (Parke Davis IX, a fresh supply, 99, p. 154). On September 22, or 11 days after the second operation, an initial injection of 0.5 minim was made into the substance of the growth, and this dose was increased to 3 minims, which caused a sharp febrile reaction with headache and chills two hours later, lasting four hours. There was marked local pain and tenderness at the site of injections. The latter were given alternate days, and after 12 had been administered, treatment was discontinued, as no appreciable effect had been produced on the size of the tumor and the patient's health was markedly effected. He had lost weight and suffered a good deal of local and general reaction after each dose.

Clinical Course: He left the hospital on October 13, 1906, with a very bad prognosis. He returned two months later, improved most strikingly in general health, having gained 15 pounds in weight and being able to take active walking and cycling exercise without inconvenience. The tumor was distinctly smaller and softer above the symphysis, though the hard mass felt per rectum was still present. The patient stated that "a fortnight after the injections were stopped he felt sore in the tumor, as if it were ulcerating", and he then noticed that it was getting smaller, softer and more movable.

Second Course of Toxin Therapy: Injections were resumed on December 16, 1906, and continued until January 11, 1907, in doses of 1 to 6 minims. Treatment was suspended because the growth had become very tender, and the general health had deteriorated in the same manner as during the first series of injections. The tumor had also continued to regress.

Clinical Course: The patient was again sent out on furlough for a month and returned February 20, his health again much improved and the growth further diminished in size. All bladder symptoms had disappeared.

Third Course of Toxin Therapy: A third series of injections were made consisting of 19 doses of from 1 to 3 minims, making a total of 46 injections in the three series.

Clinical Course: The patient was discharged April 3, 1907. The tumor had diminished very greatly in front, above the pubes, but the mass felt by the rectum seemed unaffected, as the injections did not directly reach it. From time to time reports were received that the patient was in good health but he was not again seen by Spencer until December 1908, at which time no trace of tumor could be found, either in the abdominal wall or by rectal examination. The operative scar was firm. The patient had returned to active army life, and he stated that he had been in the best of health ever since leaving the hospital. He remained well and free from recurrence when last traced in 1912, six years after toxin therapy (29, p. 138).

In the discussion which followed the presentation of this case, Spencer stated that he had also observed two cases of recurrent fibrosarcoma in which this method had been used apparently with success. One of the tonsil, which had recurred following each of three attempts at surgical removal, in which the man's life was beginning to be threatened from pressure on the trachea, was given toxin therapy by Peake, of Henley. Spencer states that "following Coley's directions (Peake) gave a full dose, producing a severe attack of toxemia, lasting four days. In ten days the patient consented to have another dose, and the treatment so continued, temporarily arrested the pressure on the trachea so that the man desired to resume his occupation, but could not do so because the treatment could not be stopped. In this way the condition was kept stationary for about twelve months" (99). Spencer had not heard of the later progress of the case so the end-result is unknown.

The second case, also a fibrosarcoma, had been under his care in the Westminster Hospital. The growth was in the sheath of the femoral artery (with tumor thrombus), and had recurred twice, and the only possible operation was amputation at the hip-joint. As an alternative he had been treated recently with repeated injections of Coley's fluid, which certainly prevented any increase in the size of the growth. There was still some persistent thickening around the femoral artery, but it was doubtful whether this was inflammatory or a true recurrence. In this case a rigor was only occasioned if an excessive dose was given, but a severe local reaction could be brought about which on one occasion threatened to cause suppuration, but the swelling subsided after the application of fomentations for a few days. Both the cases had been examined microscopically and reported to be fibrosarcoma.

In the course of the discussion following Spencer's paper, Pearce Gould stated that at the Middlesex Hospital in London they had not been very fortunate in their results in most of the cases in which Coley's injections had been used.

Usually the tumors had been practically unaffected by the injections, and some of the patients had been very ill after the treatment. Most of the experience to which he referred was, however, obtained soon after Coley first introduced the method, and at that time it was almost impossible to obtain in London such well-prepared toxin as was now available, so that possibly this might partly explain the unsatisfactory results. He had certainly never seen a case in which such a favorable result had occurred as in the present one (99).

Unfortunately, in addition to the fact that the preparations used in England prior to 1909 were weak and variable, few physicians realized the importance of using an aggressive technic of administration, in order to produce favorable results, and most of the cases treated were very far advanced, often moribund (45). As to the importance of aggressive treatment, Coley stated in 1906: "In every case there is a certain stage of equilibrium. There is a natural resisting power in some individuals, which may prevent the disease from advancing, and if we can by means of the toxins, do anything else to increase this resisting power and turn the scales... we get success... many of the failures have been due to not giving enough of the toxins."

References: 19, 29, 45, 99, 109.

Note: The following 18 cases received Tracy's preparations of Coley's toxins (mixed unfiltered). The first three had Type X, the others Type XI.

CASE 9: Recurrent inoperable small round cell sarcoma of the superior maxilla, confirmed by microscopic examinations. Sanford stated: "There is absolutely no question as to the diagnosis. Two microscopical examinations were made in the New Haven Hospital and one at St. Raphael's Hospital" (77).

Previous History and Treatment Other than Toxin: T. H., female, age 9, of Branford, Connecticut. The family history was negative for malignancy, tuberculosis or venereal disease. The child fell on her face on the ice in the winter of 1905—1906. A tumor developed on the upper jaw just to the left of the median septum. Dr Leonard Sanford stated: "Two different attempts at removal were made, one before the patient came into my hands" (by Verdi, at St. Raphael's Hospital, New Haven). "The growth when I first saw it was the size of a marble, protruding from the gum in the location of a molar tooth. I tried to take out the entire upper jaw, but abandoned the operation on account of hemorrhage. The child ought to have died on the operating table but she didn't. I broke off the growth at its attachment with a heavy pair of forceps. In the two weeks following, its recurrence was so rapid that you could watch its increase from day to day. The child not only could not close her mouth but her jaws were distended to a maximum" (77).

Toxin Therapy: (Tracy X). Coley's treatment was started by Sanford about two weeks after the operation, or on March 2, 1906. Injections were made into the thigh, and were given twice a week, the initial dose being one minim. The dose was increased rapidly so that marked reactions were produced almost from the first injection. Sanford stated that he aimed at a minimum febrile reaction of 103° F., and a maximum of 105° F. A chill occurred following most of the injections. The patient remained at the New Haven Hospital for about two months during which time Sanford administered the injections. At the end of this period the growth had regressed completely. The patient was allowed to go home, but the injections were continued there by Tenney until October, or a total duration of seven months. It required 20 minims to produce a reaction temperature of 102° F. towards the end. The treatment given at home did not make it necessary to keep the child in bed.

Clinical Course: She regained her former health and there was no further recurrence. Sanford reported: "I saw her some twenty years later. She wore a plate which supplied the loss of two or three teeth. Coley never knew that this little girl grew to adult womanhood. He did, however, know that a year or more after the treatment she was entirely well — one of the most remarkable cures it was ever my good fortune to experience" (77). The patient was last traced in excellent health and free from recurrence in January 1953,—46 years after toxin therapy. She had married in 1920, had a son in 1923, a daughter in 1926. Her only illness since 1906 was a ruptured appendix in 1926.

References: (77)

CASE 10: Inoperable round cell sarcoma of the tonsil and neck, confirmed by microscopic examination of specimens of both tonsil and neck tumors by Dr Bertram H. Buxton, of the Loomis Laboratory, New York.

Previous History and Treatment Other than Toxin: A. L., female, age 11, of Hartford, Connecticut. The family history was negative for malignancy. The patient had always been in good health, except that she had frequent attacks of tonsillitis and the usual childhood diseases. She had a congenital cleft palate and hare lip. In 1905 she developed a small swelling in one of the glands on the right side of the neck. In early September 1906 considerable enlargement was noted in this region, which increased rather rapidly. When examined by Dr William R. Porter in the latter part of October, he discovered a large tumor apparently originating in the right tonsil and nearly blocking up the pharynx. She was examined by McKnight and a number of other physicians in Hartford, and all considered the tumor inoperable. The patient was referred to Dr William B. Coley on November 9, 1906. Physical examination at this time showed a growth the size of half a hen's

egg, on the right side of the neck, involving the pharynx wall and tonsil, nearly blocking the passage. On the opposite side of the neck, just below the angle of the jaw, there was a tumor about the size of a small hen's egg, fairly movable, smooth in outline, fairly firm in consistency; the skin was not adherent.

Toxin Therapy: (Tracy X). The toxins were begun by Coley on November 9, 1906, and continued with two or three intervals of rest up to the middle of May 1907, the patient receiving in all between eighty and ninety injections, nearly all of which were given into the tumor of the neck, but none into the tonsil. She was rarely able to tolerate more than 2 or 3 minim doses without a severe chill, followed by a temperature of 103° to 105° F. The maximum temperature was 106° F. After two or three weeks' treatment, there was a marked softening of both neck and tonsil tumors. Examination was made in consultation with Dr W. L. Culbert, who removed a portion of the tumor of the tonsil. It was found that the central portion of this tumor had become necrotic, and several drams of broken-down tumor tissue were curetted out. Coley also removed some tissue from the tumor of the neck, which also proved softened and necrotic in the center. Microscopically, it was noted that the tumor cells were much swollen and there was a good deal of degenerated, intercellular substance.

In two months the tumor of the tonsil and the neck had entirely disappeared. Shortly afterward a new swelling developed in the neck, about one inch higher up. The patient also developed a small glandular tumor on the other side of the neck beneath the sternomastoid muscle. In February, while taking treatment, she developed a severe attack of herpes, involving the right pectoral region and entire right arm. This was extremely painful and she was unable to take treatment for about three weeks. In the early part of May there still remained some swelling on both sides of the neck, rather deep-seated underneath the sternomastoid muscle, and Coley decided to explore under ether. He found the swelling consisted entirely of broken-down necrotic material which had not found an easy exit. Some of the tissues from both sides were sent to Tracy at the Loomis Laboratory and microscopic examination showed no evidence of sarcoma remaining. The wound quickly healed (29).

Clinical Course: The patient was shown before the Clinical Congress of Surgeons of North America, in November 1912, in good health and thereafter Coley examined her periodically for the next twenty years (41). Between 1920 and 1925 a considerable number of operations were performed by Dr Frederick B. Moorhead of Chicago, for reconstruction of the cleft palate and hare lip. Moorhead reported: "The palate was completely gone and we succeeded finally by using adjacent structures, in building up a fairly good soft palate but did not complete the hard palate." Apparently the result obtained was good, because in February 1943, following examination, Dr F. Gorham Brigham of Brookline, Massachusetts

reported: "Your mouth, all things considered, was in a healthy condition. Certainly there was a remarkable job done when you had the palate taken care of. There was a small amount of tonsillar tissue but it looked healthy. The scars . . . on your neck were healthy and firm" (77).

In 1930 the patient developed rheumatic fever, following a neglected cold. She recovered without any heart lesion, but was subject to colds thereafter. In April 1933, she was operated by Dr Robert Greenough of Boston, for an ovarian cyst and gallstones. About 1939 or 1940 she developed a chronic abscess in the right breast. This was operated upon by Dr Grant R. Taylor. The condition recurred from time to time during the next six years. In February 1943 she received a careful general examination by Brigham. The general condition was found to be good, except that there was slightly high blood pressure and the patient was somewhat overweight. Under diet and vitamin therapy, she lost 12 pounds and by July 1944, the blood pressure was normal. The patient was last traced in September, 1952, 46 years after onset. There had never been any recurrence of the sarcoma of the tonsil and neck (77).

References: 24, 29, 41, 77.

CASE II: Recurrent inoperable "large round cell sarcoma" of the muscles of the back, with metastasis to the lower jaw, confirmed by microscopic examination of the primary growth by Dr John Funke, Pathologist at the Jefferson Medical College, Philadelphia, Pennsylvania. (Jefferson Hospital Records, 1907).

Previous History and Treatment Other than Toxin: C. E. C., male, age 27, of Tamaqua, Pennsylvania. The family history was negative for malignancy or tuberculosis at that time, but in 1944 one sister died of carcinoma of the colon. The patient had always been in good health. Onset in September 1907 a tumor was first noticed in the lower lumbar region at the sacro-iliac junction. It increased in size very rapidly and two operations were performed in rapid succession in September and October 1907 by Dr J. C. Biddle of Fountain Springs, Pennsylvania. At the operation in September a tumor the size of two fists was removed. It was of muscular origin, did not involve the bone, but extended down to and round the spinal nerves. A metastatic tumor then developed in the lower jaw. At this time Biddle regarded the prognosis as hopeless and sent the patient home. In November 1907 he was referred to Dr William B. Coley by Biddle. At this time he was greatly emaciated and unable to walk without help. In view of the very rapid growth of the tumor with such early metastasis, Coley also gave a very bad prognosis. Examination at this time showed an unhealed wound in the lumbar and gluteal region 6 by 8 inches in diameter, the unhealed portion being an excavation about an inch lower than the surrounding tissue. The lower

jaw showed a tumor beginning about an inch to the left of the symphysis, extending nearly to the angle of the jaw on that side, and apparently occupying the entire thickness of the jaw (22).

Toxin Therapy: Injections were begun by Coley on November 19, 1907, the initial dose being $\frac{1}{4}$ minim given in the gluteal region. The dose was gradually increased until a febrile reaction of 104° F. was obtained following the third or fourth injection. Five injections of Tracy's filtrate (Type X F) were given into the tumor of the jaw in doses of $\frac{3}{4}$ minim, the remaining being given in the gluteal region. In describing the effects of the toxins the patient stated that a few days after the injections were given into the tumor of the jaw "I thought I could feel the growth disintegrate. It may be that the total of all the careful treatment from the start was making itself manifest." The highest dose of the unfiltered preparation which was tolerated was 8 minims. The injections were given four or five times a week. The tumor of the jaw slowly became smaller and much softer. When it became fluctuating Coley made an incision over the most protuberant part and found a highly vascular tumor extending down to the periosteum. The patient's general condition slowly began to improve under treatment. At the end of the first month there was but slight improvement, while two weeks later the improvement was marked. By early January the patient had gained five pounds. From that time on the tumors melted away with great rapidity until at the end of ten weeks there was no trace left either in the back or on the jaw. Three months after treatment was begun, or on February 8, 1908, the patient had regained his lost weight and most of his strength and was allowed to go home. The toxins were continued by the family physician twice a week for two months and once a week 'until July 1908, a total duration of about eight months. During the last three months of treatment the Parke Davis Filtrate (XII F) was used. No other form of treatment was given.

Clinical Course: The patient was seen periodically by Coley. He remained in good health and free from further recurrence or metastases. By July 1909 he had gained 69 pounds, and thereafter he maintained a weight of 206 pounds for some years. Coley presented him before the Clinical Congress of Surgeons of North America on November 12, 1912 (29). In March 1942 the patient reported that he had been very active since 1908, the previous 12 years as a bank executive without vacations except for a few days at a time. He further stated: "My judgement from observations is that the toxins must be used with skill and care; that the dose and the frequency of the injections are important..." (77). In June 1944 one of his sisters died of carcinoma of the colon, and within a few months a brother died. That autumn the patient's health, which had been very good until that time, began to deteriorate. He lost about 45 or 50 pounds in weight during the next year and became quite nervous, with anorexia and faulty digestion. In March 1946 he was admitted to the Pottsville Hospital where he remained under

observation for two weeks. Various tests were made and the family was told that these were all negative for cancer or for gastric ulcer. On May 23 he was admitted to the Temple University Hospital in Philadelphia, under the care of Dr William W. Babcock. A colostomy was performed as obstruction had developed. The condition was inoperable. Babcock stated that "apparently carcinoma had developed internally at the site of the original growth in the lumbar region in 1907, and had involved all the abdominal viscera." The patient was discharged 13 days later and died at his home on June 11, 1946, at the age of 73. This was 38 years after toxin therapy had caused complete regression of the sarcoma (77).

References: 22, 24, 29, 73, 77.

CASE 12: Recurrent spindle cell sarcoma of the humerus, confirmed by microscopic examination by Dr John Funke at Jefferson Hospital (Case No. A 6836). Dr James Ewing said it appeared to be a fibro-sarcoma of the periosteal type. Also confirmed by x-ray examinations at Jefferson Hospital, Philadelphia, and by the Committee of the Bone Sarcoma Registry (2, Case No. 413).

Previous History and Treatment Other than Toxin: I. R., female, age 17, Roumanian factory worker. The family history was negative for cancer, tuberculosis or venereal disease. The patient had always been in good health until onset. She had had measles as a child. Menses began at 14, and were regular and painless. Six weeks prior to admission the patient was scratched along the upper portion of the right arm. A week later she noticed that the arm ached on arising in the morning. It pained but slightly on motion, and the patient remained at work for two weeks after onset. She then noticed that the arm was swollen and tender on pressure on the inner side, about two inches above the elbow. Local treatment consisting of applications of iodine was given, which caused severe irritation of the skin, but the pain and tenderness increased steadily during the next three weeks. Examination on admission to Jefferson Hospital, on February 13, 1908, revealed nothing abnormal except for a hard swelling on the inner side of the lower end of the upper arm. This mass was very tender, and there was local heat but no edema. The x-ray showed an oblong shadow in close relation to the humerus with some thickening of the periosteum. An operation was performed by Dr John A. Gibbon on February 15, 1908. A nodular tumor mass, the size of an egg was found with considerable infiltration of the muscular tissues. The whole mass on the inner side of the lower end of the humerus was excised and the thickened periosteum was chiselled away. The wound was packed and left open with the intention of using roentgen ray and toxins in the event that amputation was refused. The patient was willing but the family would not consent to amputation.

Toxin Therapy: Injections were begun by Gibbon on February 19, 1908, using the Parke Davis preparation (Type XII). They were made into the arm near the tumor. The initial dose was $\frac{1}{4}$ minim and this was increased slowly. No reaction occurred until a dose of $3\frac{1}{2}$ minims was reached on February 28. This caused a temperature of 101° F. with a sensation of chilliness. The following day the more potent Tracy product was substituted (Type XI), the initial dose being $\frac{1}{4}$ minim which caused a reaction of 102.2° F. Examination on March 6, showed a distinct local recurrence anterior to the wound, involving the muscles. This recurrence was larger than the original tumor but it caused little pain. Injections were continued steadily. They were given in the early evening, after dinner. The patient stated that the reaction caused pain in the arm and in the tumor, and chills, and at about 4:30 a. m. profuse sweating, whereupon her condition would rapidly become entirely normal. She stated that she received several x-ray treatments lasting about ten minutes each. The details of these treatments are not recorded in the Jefferson Hospital records. Under continued toxin treatment the recurrent tumor regressed completely and there was no further recurrence.

Clinical Course: Gibbon examined the patient on November 13, 1909, twenty-one months after the toxins were begun, and stated that the girl had apparently been perfectly well for eight or ten months. She was presented at a meeting of the Interurban Orthopedic Club by Gibbon on November 4, 1910, in excellent condition (34, 35). In June 1911, the patient was married and four healthy children were born between 1912 and 1921. She remained in very good health between 1909 and 1944. However, in May 1944, her younger son who was in the service was sent overseas. This upset the patient very much and she became very nervous. A neurodermatitis appeared over the affected arm and during the next months four areas opened and ulcerated. The general condition deteriorated, and she became very despondent. As soon as she heard that her son was safe and was on his way home, her symptoms subsided completely. (The patient also had developed a neurodermatitis at the site of these old x-ray burns during each of her pregnancies, and at the time her first grandchild was born.) She wrote in June 1947 that her weight had increased from 154 to 184 pounds, and that she had consulted a physician who put her on a diet. She then lost 26 pounds and stated that she "looked nice and felt splendid" (77). Attempts to trace this patient since 1947 have failed, as she moved and left no address. (No record of her death has been found in Pennsylvania.) She therefore was traced over 39 years after onset and recovery under toxin therapy.

Note: This case is of interest because it is one of a group in which the toxins were not administered sufficiently aggressively during the first ten days or month of treatment to prevent a recurrent growth from developing, but in which when

treatment was stepped up, using a better preparation or larger dosage, ultimate control of the disease was effected.

References: 2, 26, 34, 35, 41, 77.

CASE 13: Recurrent inoperable lymphosarcoma of the inguinal and iliac glands, confirmed by microscopic examination by Dr J. F. Butler, of Springfield, Massachusetts, who described it as a small round-cell sarcoma. (Memorial Hospital records, Nos 14998, 15215, 1908.)

Previous History and Treatment Other than Toxin: E. C. T. B., age 21, of Riverton, Connecticut. The family history was negative for malignancy, tuberculosis or venereal disease. The patient had had the usual diseases of childhood (measles, pertussis and mumps). He had always been in good health. He was struck in the left groin by a lever on January 14, 1908, while working as a blacksmith. Onset, one week later, he noticed a swelling at the point of injury. This increased steadily in size until February 2, 1908, or three weeks after the injury, when a tumor was removed by Dr Dudley Carleton of Springfield, Massachusetts. A recurrence took place shortly afterwards in the inguinal and iliac glands. The patient was referred to Dr William B. Coley for toxins. Examination at this time showed that the general condition was good. The inguinal and iliac glands were enlarged but the overlying skin was not adherent and there was no tenderness. The tumor was of moderately firm consistency. The patient was admitted to Memorial Hospital on March 26, 1908.

Toxin Therapy: (Tracy XI). Injections were begun by Coley on March 26, 1908. During the next 42 days he received 27 injections, all but two of which were the unfiltered Tracy product (XI), in doses ranging from 0.5 to 5 minims, followed by well-marked reactions; there were at least two chills and the maximum febrile reaction was 104° F. Most of the injections were given in the buttocks, but at least six were given into the tumors. The patient was allowed to go home on May 7, as the tumors had almost completely disappeared. He was advised to have the toxins continued at home for six months. He remained home two weeks and in this period four injections of Tracy's toxins were given in the buttocks. He was readmitted to Memorial Hospital on June 1, 1908. Examination revealed an indefinite swelling beginning 2½ inches below the left crest of the superior spine, and about one inch above Poupart's ligament, extending downward toward the pubes. Below Poupart's ligament the swelling shaded off into indurated tissue extending perhaps four or five inches. Injections were resumed by Coley on June 1, and given more aggressively in daily doses of 4 to 9 minims into the tumor and 4 to 14 minims in the buttocks. He received 19 injections in the next 25 days. One severe chill followed a 7 minim intratumoral injection on June 10. As the general condition was good, the patient was allowed out on pass almost

daily. He was then sent home and urged to have the treatment continued for another three or four months by the family physician. This time the toxins were continued for six months, but those given at home did not produce severe reactions. The growth regressed completely (31, Case 26).

Clinical Course: There was no further recurrence. The patient was followed periodically. The family physician reported in 1944 that the patient had been in perfect health since 1908. He was last traced well and free from recurrence on September 22, 1952, over 44 years after toxin therapy was begun (77).

References: 29, 31, 41, 42, 73, 77.

CASE 14: Inoperable carcinoma of both breasts, recurrent following bilateral mastectomy, with extensive metastases in the supraclavicular and cervical glands, confirmed by microscopic examination by Dr James Ewing, Memorial Hospital, New York, New York (73, Case No. 12325 and 13961).

Previous History and Treatment Other than Toxin: Miss E. D., female, age 39, of Palmyra, New York. The patient's paternal aunt died of cancer of the breast at the age of 84, and several other members of the family had had cancer. The patient had a bad fall when she was five years old. A year later she developed infantile paralysis which caused a very bad scoliosis of the spine. Because of this condition she had worn a brace and corsets ever since her fifteenth year. Her left breast had received constant pressure and irritation from the aluminum corset worn at that time. The curvature caused a marked deformity of the chest, one lung being compressed into a very small space. Onset, early in 1905 a small swelling the size of a pea was first noted in the left breast at the site of the irritation. There was occasional discharge from the nipple. For a year prior to operation there was pain of a sharp stinging character. The nodule was not attached to the deeper structures and the overlying skin was freely movable. The patient was referred to Dr William B. Coley by Weigel, of Rochester, New York, in November 1905. Coley removed the growth under cocaine on November 22, and it was diagnosed histologically as a cyst with no evidence of malignancy. A year later another small nodule appeared in the same region, which was also removed by Coley, requiring a more extensive operation under ether on May 16, 1907. Clinically this tumor appeared the same as the first, but microscopic examination revealed a small portion in which carcinomatous degeneration had taken place. Another operation was performed a week later and the entire breast was removed. The axilla was not explored as the patient's condition did not permit prolonging the anesthesia. A year later a third nodule appeared in the upper part of the other breast. It was exceedingly small when first detected, being hardly larger than a buckshot. It seemed slightly harder than those in the other breast and the

skin showed the faintest evidence of adhesion. Therefore the entire breast was amputated by Coley without exploring the axilla, in February 1908. The following December, or nine months later, the patient again consulted Coley. He found a well-marked recurrence in the pectoral region, with involvement of the glands in the left cervical region as well. The condition was clearly inoperable. As an experiment Coley tried Dr Silas P. Beebe's thyroid extract for a few weeks. The tumors continued to increase in size, and when Coley examined her in February 1909, there was a hard carcinomatous mass occupying the entire left pectoral region with involvement of the glands from the clavicle nearly to the mastoid. Coley gave the family a very grave prognosis, stating that he did not believe the patient could live more than six months. He was asked if it would be any use to try Coley's toxins in such a case, and he replied that nothing could be gained other than possibly slight retardation of the growth, that there was no hope of cure. In spite of this, the patient's sister was very anxious that the treatment be tried, as she did not want the patient to feel that nothing was being done. By this time the patient's weight had decreased to 80 pounds, with beginning cachexia.

Toxin Therapy: The injections were given by the family physician, Dr W. J. Bott, of Palmyra, under Coley's direction. In order to lessen the discomfort associated with the local irritation of the unfiltered toxins, Coley asked Bott to use the filtrate (Tracy's XI F), which he considered to be about half the strength of the unfiltered and very much less irritating. The patient proved to be very susceptible to the toxins. The initial dose was 0.5 minim, which was gradually increased to 3 minims. The injections were made into the cervical tumor or in the pectoral region on either side. Very small doses were sufficient to produce moderately severe reactions. Within four weeks Bott wrote that marked improvement had occurred and that the tumors were steadily decreasing in size. At this time the more potent unfiltered product was begun (Tracy's XI). Improvement continued steadily and in August 1909 Bott wrote that the pectoral, axillary and cervical tumors had practically entirely disappeared. At this time a bottle of Parke Davis XII (unfiltered) was used, and in September 1909 Tracy's XI (unfiltered) was again used.

Coley examined the patient on February 24, 1910, and could find no trace of cancer either in the pectoral or cervical regions. The patient regained her normal health and stated that she had never felt better. There were no glands palpable in the axilla and no swelling of the arm. During the previous year she had received 104 injections of Coley's toxins, ranging from 0.5 to 3 minims. Although the patient objected to continuing the treatment, Coley persuaded her to do so, and the injections were therefore continued, with intervals of rest, until February 1911, a total duration of two years, during which time 160 injections were given. Tracy's XI (unfiltered) appears to have been used during most of the second year of treatment, except for a bottle of Parke Davis filtrate (XII F) in October 1910.

Clinical Course: This case was first reported before the American Cancer Research Society in April 1911, by Coley. The patient was presented before the New York Surgical Society on March 13, 1912. At this time she weighed 100 pounds, her maximum normal weight (27). Coley examined her from time to time during the next 13 years. She remained well and free from recurrence until March 1924, 15 years after the toxins were begun. At this time a tumor developed in the anterior margin of the right axilla. Apparently the patient did not consult a physician for a year, or until March 1925, when Dr Walter A. Calihan of Rochester, New York, examined her. At this time the growth was about an inch in diameter, spherical in form and hard. There was definite attachment of the skin, with dimpling in the center. Calihan wrote Coley stating: "The question of metastases arising over 18 years after onset is of great interest. The tumor has been present one year with increase in size and skin dimpling within the past two months. I am rather of the opinion that this is probably a malignancy developing in a piece of aberrant breast tissue." This tumor was removed and a specimen was sent to Coley. Ewing examined it and pronounced it a highly malignant carcinoma. The patient refused further toxin therapy at this time. The disease progressed, causing death from general carcinomatosis of all the skeletal bones 18 months later, at the age of 57. This was 21 years after onset of the first breast cancer.

Note: In reporting this case in 1912, Coley cited Lagueux's two reported cases of carcinoma of the breast (inoperable), successfully treated by the toxins, and traced well and free from disease three and five years. Coley stated that these were of particular interest for the reason that, as far as he knew from his own experience, and from a careful review of the literature, "they were the only cases in which an inoperable recurrent carcinoma with glandular metastases, and with the clinical and microscopic diagnosis unquestioned, had ever disappeared under any method of treatment, and where the patient had remained well for a period of three or more years" (27).

Coley added that although during his early experiments with the living streptococcus of erysipelas he had tried the effect of inoculation upon carcinoma as well as sarcoma, after substituting the mixed toxins of erysipelas and bacillus prodigiosus he had practically limited the method to cases of inoperable sarcoma, believing it wise to first establish its value in one class of cases. Among his earlier patients, however, there was one case of inoperable carcinoma of the floor of the mouth, involving the lower jaw, where the diagnosis was confirmed by microscopic examination, in which the disease entirely disappeared and the patient was traced well and free from recurrence at last observation, six years later. Coley felt that these few cases justified a further and more thoroughly systematic study of the effects of toxin therapy on inoperable carcinoma, particularly because his earlier experiments were carried out with preparations much inferior to the product used on the above case and those of Lagueux. The results in these cases, Coley

further suggested, furnished sufficient grounds for advocating the adoption of routine systematic toxin therapy after all primary operations for carcinoma (29, p. 21). This plan had been adopted by a number of surgeons, he noted about 1930 (42). Coley added that the treatment could easily be carried out by the family physician, and need not interfere with the patient's occupation or usual routine of life. One of the surgeons who used the method as a routine in all his cases of sarcoma or carcinoma following complete or partial surgical removal, Dr F. R. Calkins, of Watertown, New York, stated that he had produced 80 per cent five-year survivals by this combined treatment (77).

Coley believed that sufficient recognition had not been given to the cases in which accidental acute erysipelas infections had caused marked or complete regressions in malignant tumors of all types. These observations further justified the conclusions he had offered. He believed it advisable to make a more systematic study of the effects of toxin therapy upon inoperable carcinoma (29, p. 126). A few years later he added the following note: "Pressure of work and the rapidly increasing interest in the treatment of carcinoma by x-rays and radium have prevented this. However, I have continued the use of the toxins wherever possible as a prophylactic after primary operations for carcinoma (and sarcoma), as well as a certain limited number of inoperable cases" (42). Coley was not fully aware of the fact that the only preparation available for use from 1921 until his death on 1936 was weaker than those used in the above case. Only by an aggressive technic could successful results be obtained in this later period in advanced cases of carcinoma. (See Cases 28, 29, 30 for examples.)

References: 26, 27, 29, 41, 42, 77, 108.

CASE 15: Recurrent inoperable carcinoma of the breast, with axillary involvement, confirmed by microscopic examination.

Previous History and Treatment Other than Toxin: Mme C., female, age 50, of the Province of Quebec, Canada. A grandfather had died of cancer of the throat. The patient was operated upon in August, 1908 by Dr Pierre Lagueux of Levis, P. Q., for cancer of the left breast of four years' duration. Recurrence developed in the cicatrix with limitation of motion of the left arm. There was also a mass the size of a goose egg in the right breast, the nipple was retracted and oozed a liquid serum of very foul odor. The general condition was very bad. The patient had no appetite and had headaches and a general feeling of lassitude. She was admitted to the hospital at Levis on May 29, 1909.

Toxin Therapy: (Tracy XI). Injections were begun by Lagueux on that day and were continued daily for a period of three weeks. All pain disappeared almost from the first injections. The recurrence in the cicatrix disappeared and the swelling

in the left arm began to subside. The tumor in the right breast decreased to half its former size, in the first month of treatment. On June 20, the patient returned home where the injections were continued by the family physician. (The exact duration of treatment is not recorded.)

Clinical Course: The patient was reported well and free from further recurrence when last traced three years after the toxins were begun (64). Lagueux stated in reporting this case to Coley: "The remarkable feature of the treatment was... the pain entirely disappeared almost from the first injection. My experience has shown me that it is not necessary to lose time by giving small doses but the more quickly we reach a temperature reaction the more often we have success." His patients stated that they felt much better as soon as the temperature returned to normal. Lagueux added that he did not wish to seem more enthusiastic about the treatment than Coley himself, but that he believed that at least 60 % of the cases of inoperable sarcoma or carcinoma so treated were successful. The two cases he reported were seen by several physicians and were treated with the help of Doyon of San Sebastian (64).

Note: Lagueux's wise perception of the importance of aggressive treatment should be emphasized. Note also his observation of the beneficial effect of the toxins on pain, a factor that was reported by many other surgeons who used the method, including Finney, of Baltimore (14). Lagueux continued to use the toxins for many years, as shown by his letters to Coley and by Tracy's records. In June, 1911, he wrote Coley as follows: "The greater part of the time I had (inoperable) carcinoma to treat... I must say that the progress of the disease was always modified, always I got a prolongation of life, and *pain* always disappeared after the first injections. I must say that your toxin is not known enough in this country, for I believe numbers of patients would benefit from its advantages" (41).

Modern research has indicated that in order to produce complete and permanent results in the less anaplastic tumors, such as carcinoma, it is necessary to use injections in or near the growth alternating with injections remote from the tumor (intramuscular or intravenous). Lagueux's experience indicates that even when using a less favorable technic temporary regression and palliation may occur.

References: 14, 25, 29, 41, 64, 108.

CASE 16: Inoperable osteosarcoma of the sternum at the costosternal junction, about the fourth rib, confirmed by microscopic examination in the laboratory of the Harvard Medical School, and also by roentgenologic examination by Dr E. G. Brackett, of Boston, Massachusetts.

Previous History and Treatment Other than Toxin: G. J. D., male, age 44, born in Scotland, of Whitinsville, Massachusetts. The family history was negative

for tuberculosis, allergy, diabetes, or any form of malignancy. The patient worked in an iron foundry as an iron molder. He was married in 1897 and had five children prior to December, 1907, and an unusually happy family life. He had always been in good health until November, 1908, when he received a sharp blow on the chest from heavy iron tongs, while at work. Two weeks later "inflammation" set in and the injured area began to swell. Dr E. W. Barry was consulted in December and in January, 1909, the patient was operated for what appeared to be an abscess of the sternum, but which, on pathologic examination proved to be sarcoma. After four months the wound healed and the condition appeared normal, without swelling, for five weeks. Then a recurrent growth appeared two inches above the original site, which finally broke down and discharged from a little sinus.

Toxin Therapy: (Tracy XI) (108). Injections were begun by Barry on July 7, 1909, and were given every 48 hours, mostly intramuscularly into the back and hips. The patient stated that he could not stand injections into the tumor as they caused great swelling and pain. The initial dose was $\frac{1}{4}$ minim, which was gradually increased until 10 to 14 minims were given at each injection. Several chills occurred, some of which were severe. The patient was treated as an ambulatory case, and went every day to Barry's office to have the wound dressed and for an injection. By October 21, the wound, which had been steadily discharging necrotic tumor tissue, was healing rapidly and had almost closed up. By October 27, the patient was feeling very well and he returned to light work at the foundry four days later. He received only one injection of the toxins between October 27 and November 8. In this brief period in which the toxins were suspended and the patient returned to work, there were signs of renewed growth in the tumor, and the wound which had almost closed, enlarged to the size of a silver quarter. Barry advised the patient "to give up this type of work and get outdoors", which he did. Injections were continued until January 25, 1910, or the duration of $6\frac{1}{2}$ months, but it was not until February, 1910, that the wound again showed signs of healing. From February until April improvement was rapid; the appetite improved, and the patient felt better in every way and looked better. He received a total of about 55 or 60 injections.

Clinical Course: The patient wrote Coley in April, 1911, that he had been entirely well for a year, and working hard as janitor of the public schools, "in charge of 14 rooms and ten fires". He remained in excellent health with no further recurrence (29, Case 87 in Table). His weight in 1948 was 140, the height being $5' 7\frac{1}{2}"$. He wrote in July, 1948, that he was "still strong enough to plant two vegetable gardens, including about a bushel of potatoes". He remained in good health until the winter of 1950 to 1951 when he developed some symptoms of gastric distress. This increased somewhat and finally the patient was admitted to a hospital in Worcester, Massachusetts, in January, 1951. An exploratory laparotomy revealed an inoperable cancer of the stomach. No attempt at removal was

made. The patient's condition improved somewhat after his discharge and he wrote that he felt very much better. His condition remained fair when last traced in October 1952. This was over 43 years after his recovery under toxin therapy (77).

Note: This case indicates that improvement may be very slow during the first two months of toxin therapy if the injections are all made in the back and hips intramuscularly remote from the tumor, with slight reactions. The persistence with which the treatment was continued, despite the discouraging lack of improvement at first, finally resulted in a complete regression. The case also indicates the danger of suspending treatment or allowing a patient to return to work too soon.

References: 29, 41, 77, 108.

CASE 17: Recurrent inoperable malignant melanoma of the right posterior triangle of the neck, confirmed by microscopic examinations by Dr W. Gough, who stated: "The tumor has a fibrous stroma, containing large numbers of irregular cells containing black pigment. The tumor is a typical melanoma" (56).

Previous History and Treatment Other than Toxin: J. N., male, age 67. The patient was strongly built and in fairly good health when he first consulted Mr H. H. Greenwood, F.R.C.S. (Eng.), of Leeds, England, on February 2, 1911, complaining of a lump on his right shoulder, which he had first noticed about December 1, 1910. A month after onset it began to grow painful, and by February 1, the pain caused by the irritation of his braces interfered with his work. The lump, one inch in diameter, was at the base of the posterior triangle at about the middle of the clavicle. It was fairly hard and fixed, adherent to the skin, which was normal in appearance, save for a black speck as large as a pinhead. There was no obvious inflammation around it but the growth was increasing steadily in size. On March 1, Greenwood excised a small portion under local anesthesia. It proved to be solid, the cut surfaces coal black in color. Sections were examined microscopically and reported as above. On March 3, two days later, the growth was dissected out. It proved to be very extensive, about three inches in diameter and black throughout. Toward the middle line, although the carotid sheath was stripped clean, there remained small, inaccessible portions burrowing in front of the vertebrae. The wound was closed without drainage. When the sutures were removed on the seventh day the wound was found soundly healed. Three days later black growth was found breaking down the scar, pushing through the suture marks. Eight days after recurrence was first noted, the cavity was filled by a mass as large as the original growth.

Toxin Therapy: (Tracy XI). Injections were begun by Greenwood on March 21, 1911, the initial dose being $\frac{1}{2}$ minim of Tracy's product (Type XI) diluted with 20 minims of sterile water, and injected deeply into the pectoral muscles below the right nipple. Half an hour after the injection the patient had a slight rigor, with a temperature of 101° F. He was in collapse, with a feeble, rapid pulse. An hour later profuse perspiration occurred. In four hours the temperature was normal and he felt well enough to eat a hearty meal. The injections were continued every 48 hours in increasing doses, the site being gradually nearer to the tumor. Nux vomica was administered by mouth throughout the first two weeks, as the pulse was weak and irregular, and in one of his letters to Coley, Greenwood stated that the administration of nux vomica had an "unmistakable benefit". After the first month the injections were given twice a week, the regular dose being about 10 minims. At the end of a year an injection was given once every two weeks, and finally once a month. On three occasions the general reaction was so severe that the injections were stopped for 7, 11, and 14 days respectively. Locally, each injection gave rise to a hard, brawny swelling as large as a walnut, which subsided in 10 to 14 days. On November 14, after an injection into the tumor site, the reaction was so severe that the patient collapsed and was semiconscious for four hours, although the temperature was only 103.4° F. Following this reaction he was confined to bed for three days and away from work for a fortnight.

In describing the effects of the toxins Greenwood stated: "On May 2, 1911 (or 7 weeks after injections were begun), the visible black portions of the growth had disappeared and the growth was manifestly smaller. He returned to work on this day and except for the fortnight referred to above has worked uninterruptedly since. The injections have been given in the afternoon, and he has been fit for work next morning. (He was granted a half-holiday on his injection days.) Now one and a half years after treatment was begun, there is no sign of recurrence, his general health is excellent, his weight has increased slightly, and his monthly injection causes little general reaction." He added: "It will be conceded, I think, that 1) the growth was, as evidenced by the rapidity of recurrence, of a high degree of malignancy; 2) the action of the toxins is not due merely to local necrosis—shrinking of the growth was discernible before any injection was made into the tumor; 3) a certain degree of immunity is acquired . . . ; 4) the treatment can be carried out at the surgery, or in the out-patient department—the patient should be supervised for four hours after each injection. It is desirable that the general health be attended to during the treatment. An overdose produces its most obvious effects on the cardiovascular and nervous systems . . .

"It seems reasonable to conceive of malignancy arising from lack or excess of some internal secretion, and that Coley's fluid provokes the laggard secretory organ to renewed activity or restrains the exuberance of the faulty gland." He added, "It certainly is disappointing that the enormous mass of research work during the last ten years is a literature chiefly of destructive criticism" (56).

Greenwood further described the effects in this case in his letter to Coley: "The severity of the reaction was very precise and could be prophesied exactly: 1) the nearer the neck, the quicker and more severe the reaction. 2) The longer the interval, the quicker and more severe the reaction. 3) Only when injections were given daily and steadily increased did anything like a cumulative effect occur, and then it seemed rather that the patient had not had time to recover his strength. The reaction usually lasted about two to four hours, according to the dose—but immediately the sweating stage was over, he got up and ate a hearty meal" (56). He added that the temperature usually rose to 101° F. in half an hour, which was sometimes followed by a rigor, varying in intensity.

Summary of Toxin Therapy: The patient had a total of 105 injections over a period of about 22 months. Site: at first intramuscular, or subcutaneous, gradually working nearer the tumor and finally injections in and near the site of the former growth. Dosage: at first every other day, April to August, 1911, 10 minims three times a week; then twice a week, August, 1911, to January, 1912; 10 minims once a week during the whole of 1912; 5 minims at first once a week, and later once every two weeks, and finally once a month.

Clinical Course: Coley received word from Greenwood in July, 1913, that the patient remained absolutely free from recurrence or metastases, that he was in splendid health and weighed twelve pounds more than he had at the beginning of toxin therapy (32). He stated that the site of the tumor was marked by a hollow, covered by a clean scar with no trace of pigment. The patient was carefully followed by Greenwood, and he remained free from recurrence (29, p. 136). He died of acute bronchitis in 1925 at the age of 81, or 14 years after onset. His family physician, Dr Lacey Bathhurst, reported: "There was not the slightest suspicion of a neoplasm either primary or metastatic in his chest" (77).

Greenwood, in reply to a final letter regarding this brilliant case of recurrent malignant melanoma and a question as to whether he had ever used toxin therapy in other cases, stated that shortly after treating this patient he had become a surgeon in Lord Moynihan's hospital in Leeds, and when demobilized in 1918 he was at once appointed Surgeon to the Orthopedic Hospital. He continued to specialize in orthopedics until his retirement in 1945, so that cases of cancer were no longer referred to him. He added: "I only regret that I cannot report further successes, which I am sure await those who conscientiously use this weapon of attack . . . I cannot help thinking that the dosage usually employed is inadequate" (77). (Compare this successful result with Harmer's case of malignant melanoma in which one of the less potent preparations was used, Parke Davis XII—see Case 27.)

References: 29, 32, 41, 56, 77.

CASE 18: Inoperable adenocarcinoma of the soft palate, confirmed by microscopic examination by Dr James Ewing, after the operation on August 1, 1912. Dr W. C. Clarke reported: "composite groups of epithelial cells arranged in alveoli in a stroma resembling cartilage tumor", following the biopsy May 30 (38).

Previous History and Treatment Other than Toxin: W. D., male, age 52, of Brooklyn, New York. The patient had always been well until about January, 1911, when he first noticed a small mass just behind the soft palate. This was treated by Dr William F. Dudley, but the growth increased in size under local treatment. Physical examination by Dr William B. Coley in June, 1912, revealed the soft palate pressed forward and distinctly bulging into the cavity of the mouth. The space behind the cavity was practically filled with a large tumor which interfered considerably with speech and swallowing. On palpation a smooth, rounded tumor was found, moderately firm in consistency, situated behind the soft palate on the right side and extending backward. The condition was inoperable, but four masses of tissue were scooped out under novocaine anesthesia by Downes on May 30, 1912.

Toxin Therapy: (Tracy XI). Injections of the toxins were begun by Coley on June 6 and were made for the first week in the right and left pectoral regions, causing slight reactions. The initial dose was 0.5 minim, which was gradually increased to a maximum of 6 minims by the intramuscular route. The first good reaction occurred on June 14 (102° F. and a slight chill). Thereafter, about half the injections were given into the tumor. The tumor showed marked diminution in size and became less diffuse and more discrete, so that its outline could be more easily defined. It also became harder in consistency, so that the needle entered with difficulty. The local injections produced marked reactions, a temperature of 102° to 104° F. being obtained with 0.3 to 0.5 minim doses. The patient was allowed to go home for five days on July 3. He received a total of 29 injections at Memorial Hospital. In view of the decrease in the size of the tumor, Coley attempted removal on August 1, 1912, under ether anesthesia, after preliminary ligation of the external carotid. An oblique incision 2½ inches long was made through the soft palate and a tumor was found about the size of a small egg and fairly well encapsulated. It extended backwards and downwards about two inches. It was found impossible to remove the capsule and curette and scissors had to be employed. Microscopic examination of the tissue was made and the condition was again diagnosed as adenocarcinoma by Ewing (73). The wound healed very rapidly and the patient was sent to the country for two weeks to recuperate, after which he resumed his regular occupation. The toxins were kept up for more than a year by the family physician, who gave two injections a week. The treatment did not interfere with the patient's regular routine of life.

Clinical Course: The patient was presented before the New York Surgical Society on April 9, 1913, at which time there was no evidence of the disease; nothing but normal scar tissue remained at the site of the former growth and the patient weighed more than he ever had (29). He was again examined by Coley on January 10, 1914, well and free from recurrence. He remained in very good health during the next 30 years, and was examined for follow-up purposes by Dr Walker E. Swift in May, 1943. His health remained excellent until March 3, 1944, when he suffered a stroke. Death occurred three weeks later, on March 22, 1944 (77).

Note: This case is an example of those in which the toxins rendered the tumor operable, lessening the danger of metastases from tumor cells liberated at the operation, and the long prophylactic treatment after operation insured a permanent result.

In discussing the report of this case before the New York Surgical Society in 1913, Dr Howard Lilienthal stated that his experience with the toxins both in inoperable sarcoma, and as a post-operative precaution against recurrence in carcinoma, had convinced him of its value. He added that he felt "the treatment had not received the credit it deserved" (28 p. 560—561).

References: 28, 29, 41, 73, 77.

CASE 19: Recurrent giant cell tumor of the tenth dorsal vertebra, confirmed by microscopic examination by Hartwell, Pathologist at Massachusetts General Hospital, who reported: "Highly cellular tumor composed of spindle cells with numerous giant cells. The cells are very atypical and their richness varies in different areas of the tumor, some places being quite fibrous. There are scattered necrotic areas in the tumor tissue" (72).

Previous History and Treatment Other than Toxin: A. J. M., male, age 16, of Woburn, Massachusetts. The patient's father and sister were living and well, his mother died of phthisis. There was no family history of cancer, venereal disease, diabetes or allergy. The patient had had pertussis, measles, also malaria at ten. A double hernia had been operated upon at the Children's Hospital four years before (1908). In March 1912, the boy fell and injured his spine at the lower dorsal and upper lumbar region. He did not lose consciousness and was able to ride home. The next day there was pain and tenderness in this region which gradually increased in severity. This was treated in the Out-Patient Department at Massachusetts General Hospital by strapping, but with no relief. A swelling was first noted in May, or two months after the injury. On June 10, 1912, the patient was admitted to Massachusetts General Hospital (72), (Orthopedic XX, 67, 1912). Pain and tenderness had persisted and for two weeks there had been numb-

ness over a large area of the external and internal surface of the right thigh with absolute loss of sensation. The boy walked with slight instability, complained of weakness of the right knee, stepping with great care, as the slightest jar caused excruciating pain in the lower dorsal region of the spine, shooting up to the head. There was a slight depression in the region of the tenth dorsal vertebra and a swelling about the size of one's hand in the posterior subcostal region. Both legs could be raised about a third of the normal arc, beyond which pain was produced in the back and to the side of the spine. X-ray examination was negative. A neurological examination was made on June 21, by Baldwin, who found double ankle clonus and Oppenheim with disappearance of tactile and pain sense over the right anterior crural distribution, his diagnosis being partial paresis of traumatic origin. The patient was then seen by the surgical department and it was suggested that the condition was an abscess under the lumbar spinae muscles, as fluctuation could be felt. Incision was advised. An aspirating needle was inserted into the growth on June 26, but a dry tap resulted (72), (Surg. W. S., Vol. 761, p. 161, 1912). On June 26, 1912, an exploratory operation was performed by Porter under ether anesthesia. A bluish, rather tense, fluctuant mass was exposed beneath the muscles of the back. It was incised and a quantity of dirty liquid escaped, which was found to have been encapsulated in a rather definite sac with thickened broken down material in the walls. The vertebrae were involved. The mass was curetted, the transverse process removed, the bone curetted, and the capsule trimmed as much as possible. Bleeding was profuse, due to the vascularity of the tumor tissue, and the cavity was tightly packed. The patient was in very poor condition after operation, requiring stimulation, but he recuperated rapidly.

Toxin Therapy: (Tracy XI). Injections were begun July 2, 1912, by Dr Torr W. Harmer, of Boston, or six days after operation, and they were given every other day. While still at the hospital the patient received 15 injections in doses of $\frac{1}{4}$ up to 11 minims. These caused only one marked reaction: 104.6° F. after a dose of 9 minims on July 24, followed by a chill. (That night there was a good deal of pain in the back.) A plaster jacket was applied on July 20 and seemed perfectly comfortable. About a week later a window was cut over the wound and "granulations were cut down". The patient was allowed up in a wheel chair. There was no evidence of recurrence as seen through the window at the time of his discharge on August 1, but the surrounding skin was very hyperesthetic. Injections were continued by Harmer after the patient was discharged, being given twice a week. The site was intramuscular, into the abdominal wall, the legs and the arms. Despite this treatment, a recurrence developed locally, and grew to be larger than the primary growth: $5\frac{1}{2} \times 3\frac{1}{2} \times 2$ inches in diameter. This caused paresis of the leg on lying down and pain on the slightest jar of the spine. Injections were then made directly into this growth, causing violent reactions. The mass began to slough extensively in several places. The patient showed

improvement from this time on and by the middle of January 1913, the growth had entirely disappeared and there was no evidence of sensory disturbance in the limbs. The final injection was made on January 29, 1913, a total duration of seven months (58).

Clinical Course: The patient was examined by Harmer every two weeks for two years after the toxins were discontinued. He gained steadily in strength and weight and there was no evidence of further recurrence by x-ray or physical examinations. The scars were soft and not adherent to the underlying structures. The patient was shown before the International Society of Surgery at Massachusetts General Hospital on April 27, 1914. (See 58, Fig. 7, for photograph of scars.) At that time he had been working many months as a chauffeur, but had recently obtained a job in a tool and lathe company. In June 1914, a routine x-ray examination revealed a small mass apparently arising from the lateral surface of the third lumbar vertebra. This was not evident from inspection or palpation and was producing no symptoms and the boy appeared to be in excellent health. Porter excised this mass which proved to be a circumscribed bone cyst, with no evidence of malignancy. The patient was followed by Harmer periodically until 1931, and he remained in excellent health (41). He married and had one child. He continued to work as a mechanic in factories or garages. He was last traced in very good health in January 1953, over 40 years after treatment (77).

Note: This case seems to indicate the danger of using small doses which do not produce reactions, given only twice a week remote from the tumor by the intramuscular or subcutaneous route. Such a technic is not aggressive enough to control the disease or to prevent recurrence. Note, however, that when injections were made directly into the growth followed by severe reactions, the recurrent tumor regressed and there was no further recurrence. This case suggests that toxin therapy should be instituted in such cases before attempting surgical removal, in order to reduce the extent and the vascularity of the growth, thus making a less radical procedure possible, or perhaps eliminating the need of operation altogether. It is unfortunate that few physicians realized that even after a recurrence or metastasis has developed that the disease may be permanently controlled by aggressive and prolonged toxin therapy. Incomplete surgical procedures, especially where there is free hemorrhage, appear to stimulate the growth rate.

References: 29, 41, 58, 59, 72, 77.

CASE 20: Inoperable cancer of the kidney, involving the retroperitoneal glands, confirmed by microscopic examination by Dr W. A. Lindsay, Pathologist at the Victoria General Hospital, Halifax (formerly at Edinburgh University).

Previous History and Treatment Other than Toxin: Miss M. P., female, 27, of Kentville, Nova Scotia. The family history was apparently negative as regards

malignancy in 1912, but in 1945 the patient's mother had a radical mastectomy and the patient's sister had a cyst in her uterus requiring a hysterectomy. The youngest sister had tuberculosis. In the winter of 1895, at the age of 10, the patient was injured in the back over the right kidney region while skating. Following this she developed jaundice and that summer had "blood-poisoning" in her right hand. Two or three years later she had scarlet fever and her attending physician told her that the "glands in the neck and the kidneys were injured". In 1902 she had pertussis. Menses began at 12 and were very irregular for three years, with severe headache, constipation, nausea, some pain and excess flow. Thereafter until menopause, menstruation was normal. Onset, early in 1912 the patient's health rapidly began to deteriorate. In the latter part of August, or nine months later, the family physician found a large mass in the ileo-lumbar region. The patient was taken to Halifax and consulted Drs H. K. MacDonald and John Stewart (a pupil of Lord Lister). An exploratory operation was made, through a loin incision, and the kidney was exposed. The upper and middle third were found to be apparently normal, the lower pole being occupied by a large tumor which was adherent to a much larger growth anteriorly. A section was removed for microscopic examination. The patient was then turned upon her back and a laparotomy done, disclosing a large retroperitoneal mass which could not be removed. The patient made a very poor operative recovery and a sinus developed at the site of the loin incision. The condition was regarded as absolutely hopeless, and she was removed on a stretcher and special car to her home. No one believed that she would survive the journey (29 p. 144).

Toxin Therapy: (Tracy XI). Injections were begun by MacDonald about September 21, 1912, or around three weeks after the exploratory operation. They were given intramuscularly in the buttocks. MacDonald stated that her condition at this time was so bad that the toxins were used as a last resort, and he thought that "if they were of no benefit, they would perhaps have the other effect and put the patient out of her misery". However, after the first injection she began to improve. When a dose of 4 minims had been reached, the sinuses in the lumbar region closed. Marked reactions occurred after each of the injections, which were given in the morning: the temperature would rise to about 105° F., dropping to normal in the late afternoon. The tumor began to show marked decrease in size. After 18 injections had been given Dr Arthur S. Burns, of Kentville, Nova Scotia, the family physician, stated that the mass in the loin had practically disappeared, that the patient was rapidly putting on weight and in every way showed marked improvement. The toxins were discontinued on November 9. By January 23, 1913, four months after treatment was begun, the patient had gained 20 pounds in weight. She ate and slept well, was up and around the house and was making steady improvement. Careful examination by two physicians failed to reveal any evidence of tumor or enlargement of any kind. Dr William B. Coley advised that the injec-

tions be continued until the end of January. The recovery was so rapid that the family physician did not consider this necessary (29 p. 144).

Clinical Course: Improvement continued, and by the middle of the following June the patient had gained 32 pounds. She was examined two or three times a year by Mac Donald, who reported to Coley on her condition. In 1927, or 15 years after toxin treatment, the patient developed multiple fibroids, requiring a supra-vaginal hysterectomy and oophorectomy (41). At this time MacDonald made a very complete and thorough examination of the abdomen, particularly at the site of the former tumor, and found no evidence of disease of any kind. MacDonald stated that she made a good operative recovery and has since enjoyed excellent health. However, the patient stated in reviewing her history in June 1947 that she had never been extremely well since 1912, that she had had several operations on her bowels due to obstruction and adhesions resulting in loss of muscle tone and chronic constipation. There was no evidence of recurrence when the patient was last traced in February 1952, over 40 years after onset (77).

Note: This case indicates that a permanent result may be obtained in far-advanced nephrogenic cancer when a potent product is aggressively administered.

References: 29, 40, 41, 42, 77, 108.

CASE 21: Recurrent inoperable round cell sarcoma of the neck, confirmed by microscopic examination by two pathologists, one of whom was Dr William H. Welch, of Johns Hopkins.

Previous History and Treatment Other than Toxin: P. V., male adult, born in Italy, a physician, of Brooklyn, New York. The family history was negative for cancer, tuberculosis or venereal infection. The patient had always been well until early in 1913 when he noticed a swelling in the neck midway between the chin and the thyroid. This reached the size of a hen's egg five days after onset. It was considered at first to be inflammatory and was opened by Dr Russell S. Fowler, of Brooklyn, New York. A few drops of pus were obtained. Several days later Fowler removed the whole mass. After microscopic examination this was pronounced "infective granuloma", but this diagnosis was later revised to round cell sarcoma. Four weeks after operation a recurrence developed in the right cervical region. This grew rapidly, soon reaching the size of a fist, extending from the mastoid to the clavicle. It was regarded as inoperable.

Toxin Therapy: (Tracy XI). Injections were begun by Fowler on April 10, 1913, the initial dose being $\frac{1}{4}$ minim, which was increased daily by $\frac{1}{2}$ minim until a dose of $14\frac{1}{2}$ minims was reached. The tumor responded at once to the injections by decreasing in size. It also softened and opened spontaneously, discharging

necrotic material. Early in May the patient's general condition appeared to be poor, apparently due to absorption of considerable necrotic tumor tissue. As the tumor had disappeared except for infiltration in the lower portion of the sternomastoid, Fowler decided it would be best to ease up on the treatment. Accordingly, he diminished the dose by half a minim daily until it was $8\frac{1}{2}$ minims, a decrease of 6 minims, whereupon the tumor began to increase again rapidly and some thickening appeared at the upper end of the sternomastoid on the anterior surface, the lower infiltration which had remained having disappeared. Fowler immediately began increasing the dose again by $\frac{1}{2}$ a minim a day, and on May 15, referred the patient to Dr William B. Coley. Physical examination at this time revealed a mass on the anterior portion of the neck, beginning a little to the left of the median line and extending downward to the angle of the jaw. This measured about three inches in diameter laterally, and was very firm in consistency and much harder than ordinary sarcoma, more like carcinoma. There were several other small and discrete tumors in the cervical and supraclavicular region. The skin was adherent only in the region of the cicatrix and was not reddened. The tumor was not attached to the trachea or to the thyroid cartilage. The general condition was good, but the patient had lost 15 pounds in weight. He was admitted to Memorial Hospital on May 16, 1913, where he remained a week, receiving five injections, given in the pectoral muscles. These caused reactions of 100° to 101° F. The tumor regressed markedly during this week; having been $3 \times 2\frac{1}{2}$ inches on admission, it reduced to a small nodule $1 \times \frac{3}{4}$ inch in diameter. The Memorial Hospital records state: "In the right cervical region the irregular mass, apparently consisting of masses of glands, some very hard, other rather soft, are fairly discrete, in contra-distinction to the firm hard mass there a week ago" (73, Case No. 20450, 1913). The patient returned home and Coley urged Fowler to push the treatment to the limits of safety. Under increased dosage, given daily or every other day, the patient's condition quickly showed signs of improvement. In advising Fowler regarding this case Coley wrote in June 1913: "I have been more than pleased with the very rapid decrease in size of the tumor in the submental region and a general disappearance of the indurated area, in the whole right cervical region. I believe that with a judicious adaptation of the dose to this case we are going to get a complete cure. It is very important not to stop too soon. I would give him daily doses when he gets no reaction and when he does, give an interval of rest, one day... No matter what happens, it seems a remarkable illustration of the inhibitory action of the toxins in a case of extreme malignancy" (41). The improvement continued, and when Coley again examined the patient on July 17, 1913, the tumors in the cervical and submental regions had almost completely disappeared, and the general condition was good. At this time the dose had been increased up to 20 minims given in the pectoral region. Coley again wrote Fowler on September 11, 1913: "I have just seen Dr V. and am perfectly delighted to find that every trace of the tumor has disappeared from the neck and that he has gained

12 pounds since I examined him on July 20... I would strongly advise not to stop the toxins altogether at present, but to continue at least once a week, in moderate doses — not enough to cause a severe reaction. I should say that about five minims would be about right. If this does not give any reaction at all, you might increase the dose. Usually after a week or two of rest the susceptibility returns, and one cannot give as large doses as when the patient is taking the treatment regularly. I think very probably he would not have any more trouble if we stopped, but I have had a number of recurrences which I feel would probably have been averted had I continued longer with the toxins. On the basis of this experience, it is my present policy to go on with the treatment for a long period after the disappearance of the disease" (41). Examination on January 20, 1914, showed the neck to be entirely normal, with no suspicion of enlarged glands. The patient's weight increased from 212 to 222 pounds.

Clinical Course: There was no further recurrence. The patient remained well five years, and then died suddenly by drowning. There was no evidence of the sarcoma at the time of his death (41).

Note: This case is important because it clearly illustrates the narrow margin between success or failure to gain complete control of the neoplasm. Fortunately the details of technic are carefully recorded. It appears that definite amounts of toxin must be administered before a soil unfavorable to neoplastic growth is produced in the system, thus preventing further recurrence or metastases. Dosage and frequency must therefore be maintained, and not decreased too soon, in order to produce permanent results. It is possible that when a tumor is destroyed rapidly, thus liberating large quantities of partially necrotic tumor cells, that these produce growth-stimulating substances, which have to be neutralized by aggressive toxin therapy until they are entirely absorbed. The slower-growing tumors that respond less rapidly to toxin therapy would not present this problem.

Fowler, apparently recognized the importance of technic for he stated in a letter to Coley in 1916: "The few cases in which I have had the opportunity of encouraging the patients in the use of the toxins have been for the most part successful. I believe the matter to be one of dosage in relation to tumor, and am glad to add my testimony to the efficiency of the treatment, when properly carried out, in a sufficient number of cases to warrant its trial in all" (41).

References: 29, 31, 41, 73.

CASE 22: Inoperable recurrent carcinoma of the nasopharynx, involving both superior maxillae, ethmoid, sphenoid and frontal bones, confirmed by microscopic examination by Dr James Ewing, from a section removed in Louisville, September 1914. Ewing reported: "...the general appearances are those of a carcinoma with

poorly differentiated epithelial cells. An origin from the lining cells of the mucosa seems probable. Of the malignant characters of the process there can be no doubt" (41).

Previous History and Treatment Other than Toxin: O. R., male, age 38, of Kentucky. The family history was negative for malignant, tuberculous or specific disease. A Wassermann test was negative. The patient had a complete congenital cleft palate, and wore a plate for this condition. For two years prior to onset the patient, a mining engineer, had worked in mines in Colorado in which there was considerable powdered granite in the air. This may have caused irritation to the congenitally malformed structures. He first noticed difficulty in breathing through the nose in early August 1914, also weakness and loss of weight. On August 15, he consulted a physician who found a tumor blocking up both nostrils and extending into the nasopharynx. On August 18, two specimens were removed, but these were lost in the mail. Two weeks later another specimen was removed and sent to Louisville, Kentucky, for microscopic examination. The report was simple adenoid tissue. Clinically, Thorpe regarded the condition as malignant. The tumor grew with great rapidity and on September 3, Thorpe operated, removing as much as possible of the tumor. A recurrence took place almost immediately and the disease extended upwards into the region of the nose and the frontal sinuses. A second operation was performed by Thorpe on December 12, 1914, with electric cautery. This operation was an extensive one, though incomplete, and the patient lost a good deal of blood. The tumor grew more rapidly after this operation, the pain became more intense and the general health failed steadily. In October the patient noticed that the jaws did not come together and the upper jaw in the region of the cleft in the hard palate had begun to spread; he was no longer able to wear the plate. On December 28 he consulted Ray of Louisville, a nose and throat specialist (who was then President of the American Academy of Ophthalmology and Otolaryngology). The latter stated that the tumor was undoubtedly malignant, and that it was too extensive for any treatment and advised the patient's wife to take him home and make him as comfortable as possible. The condition progressed and by the middle of January the patient was confined to his bed. He began to have hemorrhages from the tumor, sometimes losing several ounces of blood at a time. At the suggestion of the patient's brother in Chicago, Dr John B. Murphy was consulted on January 24, 1915. The latter considered the condition entirely inoperable and referred the patient to Dr William B. Coley for toxin treatment. He was admitted to Memorial Hospital on January 27, 1915, in a very weak and anemic condition, unable to walk without support. There was intense pain in the head, especially marked in the frontal region, requiring $\frac{1}{4}$ grain doses of morphine. The whole contour of the forehead and upper portion of the face was markedly distorted. The tumor involved both nasal cavities, both superior maxillae, and the ethmoid and

sphenoid bones, producing a pronounced broadening of the bridge of the nose, which was two inches in width, as well as a bulging of the whole frontal region. The right malar bone was much more pronounced than the left but both were enlarged. There was also marked exophthalmos of the right eye, with dislocation outward for one inch or more, causing inability to focus. He had not been able to read for more than a month. The growth extended as far as the upper lip. The superior maxillae had been separated by the tumor causing a space one inch wide in the center. Through the cleft in the palate, a large fungating tumor could be seen, occupying the whole space between the soft palate and the pharynx. The tumor bled very easily, and the patient had had severe hemorrhages. He had lost 24 pounds in the preceding five months. The disease was so very extensive and the general condition of the patient so bad that Coley at first declined to treat him, but finally consented to try the toxins at the urgent request of the patient's wife.

Toxin Therapy: (Tracy XI). The injections were begun by Coley on January 27, 1915, the initial dose being half a minim injected into the pectoral region. This was increased daily by half a minim. After the first week it was increased by 1 minim a day. On January 29, there was a slight bleeding from the tumor behind the palate. Hemorrhage increased and on February 3 he lost 7 ounces of blood. On February 5 there was considerable bleeding which was only partly controlled by spraying with adrenalin and packing. On February 6 one dose of horse serum was given subcutaneously (10 cc.) after which the hemorrhages temporarily decreased until on February 11, he lost 6 ounces of blood in the morning and 4 later on in the day. Another dose of 10 cc. of horse serum was administered. On February 12 he lost 12 ounces of blood. On February 13 the bleeding continued at intervals of twenty to thirty minutes during the day. On February 14 there was slight bleeding from the mouth. By this time the dose of toxins had reached 6 minims, causing a slight temperature of 99° F. but no chill. On February 16, with a dose of 7 minims, the first chill occurred, which lasted 20 minutes, followed by a temperature of 101° F. *From this time on he had no further hemorrhages.* "The pronounced local and general improvement, which had been noticeable at the end of one week's treatment, continued. There was a marked diminution in the size of the external tumors, as well as a decrease in the size of the tumor in the nasopharynx. 8 minims on February 19 produced no chill, nor did the next three doses of 9½ minims each, given February 20, 21, and 23. On February 24, 9½ minims produced a chill. February 26, 10 minims, no chill. February 28, 10½ minims, no chill. On March 1, 10½ minims injected into the pectoral region produced a very severe reaction, as the patient had not entirely recovered from the depression of the preceding day. One hour after injection, he had a chill, lasting 40 minutes; one hour after this, a second chill occurred, which lasted an hour. The temperature rose to 104° F., immediately after the first chill. One hour after the second chill it was 104.6° F. and the patient was in a state of collapse. Instead

of being cyanotic he became unusually red, the pulse 136 and very weak: respiration 32. He was not given any stimulants. Two hours after the second chill, the temperature was 102° F. and next morning both pulse and temperature were normal. The patient was very weak, but was up and about the room. On March 3, (two days later), a very remarkable change had occurred in the tumor as well as the contour of the face; the eyes were much closer together, nearly normal. The exophthalmos which had become much diminished had practically disappeared; the bulging in the frontal region had nearly subsided, and for the first time in three months the jaws came together in their normal position." The patient was then given a rest for three days, after which treatment was resumed, in smaller doses (5 minims). He received 22 injections during his six weeks in the hospital. The patient's wife stated: "The improvement was so rapid that day after day it was like turning the pages of a book. In three weeks the eyes and jaws that had been badly dislocated were normal and Mr R. weighed more than he had weighed in his life" (41). The hemoglobin was 80 % on admission on January 27, but fell to 68 % by March 9, the day of his discharge. The resident surgeon noted on that day: "The swelling of the bridge of his nose, between the eyes has entirely disappeared: eyes appear to be in normal position; the cleft in the palate is much narrower; there is now room for only one tooth in the gap in the upper jaw — (on entering the hospital this gap was one inch wide); there is no evidence of any tumor... teeth now meet properly for the first time in months. Except for a little thickness over the nose, the subjective symptoms have entirely disappeared. Patient has gained markedly in weight and strength" (30). By February 27, or after four weeks' treatment, he was able to breathe through one nostril and by the first week in March, through both—for the first time in seven months.

Three x-ray treatments were given in the early part of February, and these caused no reaction. Three x-ray plates were taken at Memorial Hospital, the first one, soon after the toxins were begun, showing a general confused blurring of the whole plate, the outlines of the different bones being lost. The second, taken March 18, by Holding, showed remarkable changes, several bones had nearly recovered their normal outline. Between March 9 and March 25, the patient received small daily doses of 3 to 7 minims of toxins, given at Coley's office. During this period he gained 14 pounds in weight. On March 25 he returned home to Kentucky at Coley's suggestion. On his way he stopped in Louisville to see Ray. The latter wrote Coley shortly thereafter and stated: "It certainly was not an operable case, as no form of surgery could have completely eradicated the growth with any hope of success. He dropped in to see me on his way home, ten days or more ago. I wish to bear witness to the wonderful result" (41).

There was a delay of one week in resuming the injections after the patient returned home, because the toxins did not arrive. Thereafter, doses of 2 or 3 minims were given three times a week, but these small doses failed to produce any reaction.

Clinical Course: At the end of three weeks the patient wrote to Coley, that a small lump had appeared just behind the angle of the jaw on the right side of the neck, and that he had a slight return of the headaches, with gradually increasing obstruction of breathing through the nose. Coley urged him to return at once, but he was unable to do so until April 26, when he was readmitted to Memorial Hospital.

Examination showed a smooth globular swelling, the size of an English walnut, just behind the angle of the jaw, on the right side of the neck and underneath the border of the sternomastoid muscle. The tumor was freely movable and of the consistency of round cell sarcoma. A slightly smaller mass was present in the left cervical region. The right eye showed a slight return of the exophthalmos and the upper jaw at the line of the teeth again showed nearly an inch separation. He had also begun to lose weight. There was no increase in the width of the bridge of the nose and only slight return of fullness in the frontal region, but there was a slight return of the tumor in the cleft behind the soft palate. No air could be forced through either nostril (72).

Second Toxin Therapy: (Tracy XI). The patient was immediately put on toxins, beginning with $4\frac{1}{2}$ minims and increasing $\frac{1}{2}$ minim daily. He proved much less susceptible than during the former period of treatment and did not get any chill until 25 minims had been reached. During early June the patient seemed very depressed. The dose at this time was 23 minims, apparently given in the gluteal region. These doses did not produce a chill, but caused nausea, vomiting and depression. He continued to lose weight and the headaches remained about the same, until severe reactions were produced during the third week in June (he had two severe chills), when he again showed very remarkable improvement, the headache disappeared, and he gained two pounds in weight in three days. By July 1, 1915, the appetite had returned, the separation in the jaw had decreased over half an inch, and the gland under the angle of the jaw was one-fourth the size it had been on April 26. During June he received five injections a week and by July 1, the dose was 27 minims. In addition to the toxin treatment, he had four x-ray treatments during this second stay in hospital. He was discharged from Memorial Hospital on July 31, 1915. On August 3, no trace of tumor could be found. The exophthalmos had again entirely disappeared, as well as the enlarged glands on both sides of the neck. The separation of the superior maxillae had reduced to normal, and the patient again could breathe freely through both nostrils. The patient had regained most of his lost weight and felt well. During August and September the patient convalesced in Sharon, Connecticut, to be near Coley. He received about two injections a week during this period. On August 27, 1915, the condition remained normal.

In August, 1915 (3) Coley stated: "This case is especially noteworthy and instructive for the following reasons:

1. After a very-far-advanced and inoperable malignant tumor had apparently disappeared under toxin treatment, a quick recurrence followed a reduction in the size of the dose from 10 minims to 2 or 3 minims.

2. The recurrent tumors, both primary and metastatic, grew rapidly and showed no signs of control until the dose of the toxins had been increased to more than double the amount tolerated during the first period of treatment.

3. Under these large doses and severe reactions all evidence of both primary and metastatic tumors again disappeared, and the patient's general health was restored" (30).

Clinical Course: In early September the growth again began to increase in size, following a rest period, in which no toxins were given for about three weeks, because the patient's stomach had become upset. About October 1, he was readmitted to Memorial Hospital. The disease could no longer be controlled. Death occurred in December, 1915, at the hospital (73).

Note: This case indicates the grave danger of decreasing the dose or the frequency or suspending the injections for even a week during the first few months of treatment in such advanced cases of carcinoma. The more far-advanced the condition, the more prolonged must be the treatment in order to insure a permanent result. Note that no intratumoral or intravenous injections were given, although it is probable that the injection on March 1 may have entered a vein. It is of interest to note that the most remarkable improvement occurred after this and other severe reactions. As the patient became immune to the effects of the toxins, it was no longer possible to control the disease. This indicates the importance of aggressive treatment in order to destroy all the tumor cells before immunity develops. Noon has indicated that immunity is produced more rapidly by subcutaneous and intramuscular injections, rather than intravenous, intraperitoneal or intratumoral (83).

References: 30, 41, 73, 83.

CASE 23: Inoperable round cell sarcoma of the right pharynx and nasopharynx, confirmed by microscopic examination after open biopsy by Professor Tiedemann of the Jewish Hospital, St. Louis. Sections were also examined independently by the pathology departments of Washington University and St. Louis University, Dr Lister Tuholske, of St. Louis stated, and "by three of our ablest pathologists" (42). Sections were sent to Dr William B. Coley, who had them examined in New York by Dr James Ewing of Memorial Hospital, who confirmed the diagnosis (41).

Previous History and Treatment Other than Toxin: M. B., male, age 30, of St. Louis, Missouri. The family history was negative for cancer or venereal

disease. The patient's father had died of chronic alcoholism, one brother of tuberculosis. The patient did not have a tendency to colds or sore throat, nor did he have bad teeth. He did not remember having had any childhood diseases. He was married at 19 and had one son born about a year later. There was no history of antecedent local trauma or infection in the nose or throat. When first seen by Tuholske, having been referred by Kaplan, the patient had a tumor of the right pharynx and nasopharynx of such size that it caused almost complete obstruction. A tracheotomy had been advised by Kaplan. This did not seem to be immediately necessary, so after determining the nature of the tumor, following biopsy, Tuholske decided to try Coley's toxins, as the growth was inoperable because of its size, location and involvement of the surrounding tissues. He had become familiar with the method while at the Augustana Hospital in Chicago, under Drs Albert Ochsner and Nelson Percy.

Toxin Therapy: (Type XII). Tuholske sent for some toxins directly from the main office of Parke Davis & Company and began the injections in May 1915. However, in spite of massive doses, apparently given intramuscularly, remote from the tumor, he was unable to get any reaction whatever. After a few week's trial, he wrote Coley and told him of his unsatisfactory experience with this preparation (41).

Toxin Therapy: (Tracy XI). Coley then sent a supply of Tracy's XI. The first injection of this product caused a very violent reaction: chills and a high fever as well as necrosis in the center of the tumor. The patient was treated at the Jewish Memorial Hospital. Between May 15 and June 23, injections were given daily or every other day in doses of $3\frac{1}{2}$ to 15 minims. The details as to the febrile reactions elicited are not recorded except on two occasions, when the temperature was 102.5° and 103° F. Tuholske stated that within six weeks the extensive growth had entirely disappeared. The patient was discharged from the hospital on June 28, 1915, feeling perfectly well. The injections were continued twice a week for another two months, and then the patient left the city (41).

Clinical Course: Sometime during the autumn a recurrence developed on the other side of the pharynx. The patient did not return until November 11, at which time there was a good-sized tumor apparent. He was immediately readmitted to the Jewish Memorial Hospital. Examination revealed that the left pupil was slightly smaller than the right, with a tendency to a rectangular shape. Both pupils responded well to light and accommodation. There was partial paralysis of the left abducens nerve. The patient could carry the eye outward about 30 degrees. The fundus and discs were normal in outline and color.

Further Toxin Therapy: Tuholske resumed the injections on November 13, giving 15 minims daily for a week, without getting any reaction, either local or

general, and the tumor continued to grow rapidly. On November 18 he wrote Coley asking if intratumoral injections would be advisable (41). (Whether any were given is not evident from the subsequent correspondence.) On November 30, Tuholske again wrote stating that he was very happy to report that in the preceding two weeks a very remarkable improvement had been evident. Prior to November 15, injections had been made into the patient's arms, except for the first which was made into the back and which was so painful that the patient pleaded that further treatments be given in the arms so that he could lie comfortably on his back. As the arms became somewhat indurated, Tuholske felt that this induration interfered with the proper absorption of the toxins, for they failed to act. On November 16, therefore, he began giving the injections into both thighs, on alternate days, and also into the superficial layers of the abdominal wall. These produced quite severe reactions and a wonderful improvement in the patient's condition. In fact, he considered himself cured on November 30, after only two weeks. The injections were continued about every other day until the last week in January, or almost three months (41). By this time all manifestations of the sarcoma had disappeared except the abducens nerve paralysis, which was supposed to be due to sinus involvement.

Clinical Course: About January 25 the patient began to vomit and was drowsy most of the time, becoming irrational at night. There was no elevation of temperature. His kidneys and bowels continued to function normally but he gave the impression of being in a toxic state. No injections of toxins were given during this period, and only such nourishment as he was able to retain: glucose proctoclysis, hypodermoclysis and neutral camphor; and stimulants: strychnia and digitalis.

The patient remained in a coma for $3\frac{1}{2}$ weeks, during which time the temperature frequently remained as low as 95° for hours at a time. Tuholske held little hope for his recovery. During the worst period early in February, the patient weighed only 89 pounds. By the last week in April he had gained 28 pounds, and he was then discharged from the hospital. A careful examination of the nose and throat by Kaplan, the laryngologist who had referred the case, failed to reveal any abnormalities, barring scars. The patient's speech, hearing and sight were normal. The paralysis of the left abducens nerve had cleared up and the movements of the eye were normal. Tuholske reported: "The period of one month was a perfect blank to the patient: he had no recollection of what had happened except that he fell asleep, worrying about his tumor, and when he woke up it was gone" (41). The patient also stated that when he returned to consciousness he noted a considerable change in his skin: it was dry and scaly, and there was no hair below the neck, and the testicles were considerably atrophied.

One interesting feature regarding this case was the polyuria, which Tuholske

was unable to account for. The patient passed an average of 6,700 cc. of urine in 24 hours for about six weeks, the specimens showing nothing abnormal except occasionally a few pus cells and a trace of albumen.

About May 8, 1916, the patient returned to Tuholske, who found a suspicion of a small swelling just below and posterior to the left mastoid process, with no palpable glands. This was considered as possible localized edema. No biopsy was made, but about six doses of x-ray therapy were given, with complete disappearance of the swelling. Tuholske stated that in 1918 the patient was presented before the St. Louis Surgical Society and a report of the case was then read (41).

The patient was admitted to the Jewish Hospital on July 17, 1930. Examination at this time revealed that the skin was pasty and waxy and the testicles were almost completely atrophic and pubic and axillary hair growth had not been restored: there were only a few fine hairs on the pubes and scrotum. The hair on the face and scalp had not changed much, except possibly for a decrease in amount and a finer texture. The patient stated that since his illness in 1915 he "felt chilly all the time, needing plenty of covers except in hot weather." He rarely perspired on the palms, and he had evanescent swellings of the hands, face and feet. The facial features were small, the chin rather receding. The atrophy of the testicles was associated with several of the symptoms of hypothalamic pathology. Dr Louis Cohen, an endocrinologist, then tried various preparations of male sex hormones, pituitrin, thyroid, etc., for about a year, but without any apparent effect. The patient discontinued treatment of his own accord, because he felt that the treatment was more of a nuisance than the symptoms for which he was being treated, and to which he had grown quite indifferent (77).

Tuholske examined him again in 1942 and found a mild hypertension of which the patient was not aware. The symptoms of hypothalamic pathology still persisted at this time. He was again seen in 1946 at which time Tuholske reported: "He has a moderately advanced arteriosclerosis, as a result of which he had a slight hemiplegia last year (1945) from which he recovered. He has recently been at work daily" (77).

The patient died of coronary occlusion and arteriosclerotic heart disease on November 23, 1948, at the age of 63 (102). This was 33 years after his recovery from sarcoma of the pharynx and nasopharynx with hypothalamic metastasis following toxin therapy.

Note: This history deserves careful study because it emphasized several important points regarding toxin therapy: a) the difficulty of obtaining favorable results with a weak preparation (Parke Davis XII); no effect whatever was noted, even with massive doses; b) the danger of stopping the injections too soon, even though the neoplasm may have regressed completely; c) the important role that the site of the injection plays in determining success or failure; unless absorption

is rapid and complete, a good result may not be obtained even with a potent product; d) this patient appears to have had a brain metastasis, as evidenced by the abducens nerve paralysis and the coma; no other case has been found in which brain metastases was present and regressed completely following toxin therapy.

It is now apparent from Coley's correspondence files and records that he used Buxton's or Tracy's preparations in the majority of his own cases and was therefore not fully aware of the comparative weakness of the commercial products. After hearing of Tuholske's experience, he wrote the Director of the Parke Davis & Company research laboratories, asking him to get in closer touch with Tracy, and urging him to make their product conform to Tracy's standards. As a result it was found that Parke Davis had been taking the nitrogen determinations (Kjeldahl method) before heating the toxins for sterilization, while Tracy had been taking them after sterilization. This one factor apparently made Tracy's product at least 10 per cent more potent. Other differences were also discovered.

This experience of Tuholske in treating the above case indicates many of the reasons why physicians become discouraged with this method: most of them used only the commercial product, whose weakness had not been appreciated fully even by Coley himself. The details of technic of administration as regards the best site, dosage, frequency and duration of treatment, adjusted to each type of neoplasm, and the age and condition of the patient, had not been properly studied or taught, yet good technic was as important as the need for potent products.

It is now apparent that in order that toxin therapy may produce the highest percentage of permanent cures, the technics of preparing and administering the toxins should be carefully studied, and there should be closer cooperation between the research bacteriologists and the pharmaceutical laboratories who prepare the material, and the physicians who administer it.

References: 41, 42, 77, 102.

CASE 24: Recurrent "small round cell sarcoma" of the gluteus maximus muscle, confirmed by microscopic examination after operation by Dr George E. Follansbee, in Cleveland, Ohio.

Previous History and Treatment Other than Toxin: Mrs D. M. W., age 23, of Bedford, Ohio. The patient's mother died of sarcoma originating in the calf of the leg at the age of 41, one year following onset. She was also treated by Follansbee, but received no prophylactic toxin therapy. Metastases developed in the neck, spine and sacrum, and six months after amputation she died. The patient's maternal aunt died of intra-abdominal cancer. A paternal aunt died of tuber-

culosis. The family history was otherwise negative except that three relatives were subject to hay fever. The patient had the usual diseases of childhood, many colds and severe attacks of tonsillitis but no hay fever, asthma, boils or skin eruptions—she had a very clear complexion always, even during adolescence. When she entered high school at 14 she was small and immature, weighing only 74 pounds. She stated that when she was about 16 she complained of her left leg because it was so sore and stiff after exercising. The family physician at that time was consulted and stated that “there was nothing wrong, that she imagined it” (77). The menses began at 16, and the flow was regular but profuse. The patient was married on February 11, 1914, at the age of 21. Her first child, a son, was born on October 9, 1915, with a double hair lip and cleft palate. The patient’s normal weight prior to this pregnancy was 125 pounds, her height 5 feet 2 inches. She stated that she had bruised the buttock about ten years previously, but had no trouble with it until onset, three years prior to admission, when a swelling developed in this region. For the next three years this lump slowly increased in size, and the motion in the hip-joint steadily diminished. After the birth of her child in October 1915, the patient did not regain her strength. She lost 15 pounds in weight and felt terribly tired. About January 4, 1916, a severe boring pain in the leg awoke the patient at night. She could hardly move the left hip enough to put on her shoes, and there was severe pain if the growth was touched, or on moving the joint. At this time she weighed 88 pounds, or 35 pounds less than she had prior to onset. On January 7, 1916, Follansbee removed the tumor which weighed about 24 ounces. He found it to be without a capsule of any kind, and bleeding was very free. When the dressings were removed at the end of 10 days there was a recurrence as large as an egg in the upper end of the scar. The patient was then referred to Dr William B. Coley (73).

Toxin Therapy: (Tracy XI). Injections were begun by Coley at Memorial Hospital on February 1, 1916, and were continued every other day for three weeks. The first injection was made directly into the tumor. Thereafter they were made in the region of the growth but not directly into the tumor tissue. Coley stated: “The tumor began to decrease in size after the third injection and continued gradually until no evidence of growth remained at the end of three weeks. The patient could lie on the affected side and move the left leg more freely than she had done for months” (73). She then returned to Cleveland and a week elapsed in which no injections were given. On March 1 an enlargement was noticed on the inner side of the thigh at about the level of the incision and apparently located in the adductor muscles. Follansbee injected $5\frac{1}{2}$ minims into this recurrent mass on that day, with about the usual reaction. Three days later this mass had increased to the size of a hen’s egg. It was very hard and quite tender. He then injected $6\frac{1}{2}$ minims directly into this mass with no reaction. The next day the growth was almost double in size. The growth became almost as large as a grape-

fruit and took about three months to absorb. The patient stated that "under continued treatment it burst, leaving a hole in my leg about the size of a dime which discharged for about four days and then closed up" (77). From March 16 to May 9 injections were made about twice weekly. At times the local reactions were very severe, causing a great deal of swelling and pain. At other times it was very slight and the general reaction was quite severe, with fever of 105° to 106° F. During May a rest period was given. (This was three months after injections were begun.) Coley received word from Follansbee on June 12, 1916, that the patient was entirely free from any indication of the disease and that she had gained weight and felt very well indeed. The patient wrote Coley at this time: "I am feeling splendid and have gained over ten pounds in about three weeks. My strength seems to come back so rapidly and with it a very good appetite" (41). Follansbee resumed treatment in June, using Tracy's filtrate, (Type XI F.). Two injections weekly were given, either in the gluteal muscles or sometimes in the muscles surrounding the site of the former growth, and they produced no reaction. They were continued until October 1, 1916, or a total duration of eight months. During the entire period of treatment the patient did not menstruate, although before and after treatment the periods were regular.

Clinical Course: The patient remained well and free from recurrence. She had three more children, all "bright and above average, and of rugged health". She was followed periodically by Coley until his death in 1936. Menopause began at the age of 45 in 1938 and was "difficult, with extreme exhaustion and severe flooding, lasting about six years". The patient was examined at Memorial Hospital by Dr Walker E. Swift, on January 27, 1943. He reported: "She has been in fine condition, no swelling of leg. No impaired function of hip or knee. No pain" (73). On April 19, 1944, she was presented at the Annual Meeting of the American Society for the Control of Cancer in Cleveland by Follansbee, as a 28-year survival. On April 12, 1947, the patient reported that she had been having some arthritis in her hands, elbows and joints, and that at times her thigh caused some discomfort, which subsided after resting in bed. She was otherwise in excellent health. During the following year she developed a persistent cough and lost 17 pounds. A chest x-ray revealed no evidence of disease. In January 1949 she developed a streptococcus infection of the throat, and erythema multiforme, being quite ill for seven weeks. She stated that "it seemed to affect the bad leg a good deal... (with) aches, pains, and extreme nervousness" (77). On November 26, 1950, she reported that in the preceding year she had not been too well, "nothing serious, but annoying. A severe bronchial cold which hospitalized me for six days revealed a sinus condition that had not been recognized, bad dizziness and trouble with my eye-sockets. Penicillin did not help me. Arthritis in my hands is annoying me too. I have to rest more... no loss of weight" (77). She reported on September 17, 1951, that she was very well and able to do all her own work. She added: "The

sinus and vertigo all cleared up and it has not been necessary to visit or call a doctor for a year" (77). Her weight increased in 1949 to 150 pounds, and this extra weight seemed to bother the leg a good deal. She then reduced to 138 pounds. At last observation in January 1953 she was well and free from recurrence, over 36 years after toxin therapy (77).

Note: This case seems to indicate the danger of suspending treatment for even a week during the early part of treatment, even if the tumor has apparently disappeared. It also encourages the persistent use of toxin therapy in recurrent tumors, even when at first the growth seems to be out of control.

References: 41, 73, 77.

CASE 25: Intra-abdominal carcinoma apparently primary in the ovary, with extensive metastases in the mesenteric glands, both the small and large intestines, the peritoneum and the liver. The pathologist reported: "Sections taken from the degenerated ovarian cyst and from different portions of the peritoneal cavity were examined microscopically and pronounced papillary adenocarcinoma" (5).

Previous History and Treatment Other than Toxin: G. V. W., female, age 29, stenographer, of Watertown, New York. The family history was negative and the patient had always been well, having had no serious illness. Onset, for two years prior to consulting Dr F. R. Calkins, she had noticed that her abdomen was increasing in size, but being a Christian Scientist, she had not consulted a physician. Calkins stated that when he first saw the patient she only weighed 80 pounds and the girth of her abdomen was over 40 inches. She had lost over 50 pounds in weight and had been unable to eat for two weeks. She had consulted another leading surgeon of northern New York state who refused to operate because of her weakened condition and because he regarded the condition as an advanced malignant case for which operation would afford no relief. Calkins was first consulted in June 1916, and physical examination at this time showed that the patient was decidedly cachectic in appearance, being very pale and exceedingly anemic. She had been confined to bed for over a month and the life expectancy was a matter of days. The abdomen was greatly distended, the abdominal wall not exceeding one-quarter inch in thickness. There were large blue veins radiating over the abdomen. The extremities were swollen, the heart and lungs normal. On June 29, 1916, Calkins operated under general anesthesia. A lower median incision was made and the abdomen explored. It was found that the tumor consisted of a very large multilobular ovarian cyst, which had undergone extensive malignant degeneration. The degenerative process had extended and involved the greater portion of the colon, and there were many places showing

metastases on the small intestines, the liver and the parietal peritoneum. The cyst was firmly adherent in many places to the intestines and to the parietal peritoneum, especially on the posterior surface. No hope was entertained of saving the patient's life, but it was thought that if she could survive the operation, temporary relief of her symptoms could be obtained by removal of the cyst. No attempt was made to remove large portions of the metastatic areas on the colon, the small intestine, the liver or the parietal peritoneum. The appendix, which was as large as a banana, was removed, and a pan-hysterectomy, double oophorectomy was performed. There was so much bleeding from the adhesions in the pelvis that the whole pelvic cavity was packed with three yard abdominal sponges and a drainage tube was inserted. The patient was returned to her room almost in a dying condition. Under heavy stimulation she rallied from the operation. She soon showed marked improvement, which continued without any complications.

Toxin Therapy: (Tracy XI). Injections were begun one week after this operation, and were given every other day. The patient was discharged from the hospital three weeks after operation, at which time she was able to be up and about and complained of no pain or discomfort. Apparently the remains of the growth regressed completely under continued treatment. The injections were given every day for nine months, and after a month's rest were resumed and given twice a week for another six months. Immediately after operation the patient weighed only 60 pounds. She gained weight steadily during toxin therapy.

Note: In describing his usual technic in administering the toxins Calkins stated that he used deep intramuscular injections in all his cases, usually in the gluteal region, occasionally the pectoral. He diluted with saline, or if this was not available, boiled water. The site of injection was massaged thoroughly and there was no induration at the point of injections, indicating thorough and rapid absorption. His initial dose was usually 0.3 cc., increased by 0.1 cc. each time until a profound reaction occurred, which was usually a week or two after the initial injection. There was usually a reaction within two hours, and the leukocytes would rise from 2,000 to 5,000. The appetite was usually nil on the day of the injection, and so they were given every other day at first. The patients who were in the hospital were usually given their injections in the forenoon, those in the office in the afternoon. Calkins added that the patients seemed to prefer the forenoon. There was usually some loss of weight (3 to 5 pounds) in the early part of the treatment, then a rapid gain. He usually prescribed iron in some form as a tonic. The duration of treatment was usually about six months to one year, with intervals of rest, decreasing the frequency of injections during the last six months.

Clinical Course: Calkins reported that $10\frac{1}{2}$ years after treatment the patient weighed 140 pounds, a gain of 80 pounds, and that she was in excellent general condition. She was last examined in December 1933, at which time she was per-

fectly well except for some hypertension, which did not prevent her working steadily as an accountant. She died at the age of 49 of a cerebral hemorrhage on March 21, 1936, over 20 years after onset of the ovarian cancer. There was never any recurrence or metastases. (See case 30, p. 89, which is similar.)

References: 5, 41, 77.

CASE 26: Osteogenic sarcoma of the tibia, with extensive inoperable metastases in the femoral, inguinal and iliac glands, confirmed by microscopic examination by Dr James Ewing and the Bone Sarcoma Registry Committee (2, Case No. 183). Ewing reported: "The tumor is composed of small spindle cells consisting chiefly of nuclei. They are very numerous, with no visible stroma. The cell masses are very compact. The tumor is quite malignant in structure." One of the metastatic glands was also examined by Ewing and pronounced "actively growing sarcoma" (73).

Previous History and Treatment Other than Toxin: C. S. S., male, age 39, of Haverford, Pennsylvania. The family history was negative for any form of malignancy, tuberculosis, diabetes or other familial disease, except for hay fever. The patient's general health had been very good, and he had practically never been ill except for the usual diseases of childhood and hay fever. He sustained a compound fracture of the right tibia ten years prior to onset, in an auto accident. For a number of years prior to onset the patient wore spats, and Dr William B. Coley thought there was a possibility that the top edge of the spats might have caused some irritation over the tibia. During the summer of 1914 the patient sustained a hard bump on the left leg in contact with a brass bed-post during a period of restlessness. Onset, early in 1917, a sensation of slight pain was felt in this area, but no swelling was evident until the latter part of March. On April 27, 1917, the patient was referred to Coley by Dr John S. Gibbon, of Philadelphia, with a history of a rapidly growing tumor of the shaft of the tibia of four weeks' duration. Gibbon and several other surgeons regarded it as a periosteal osteogenic sarcoma. Coley concurred with this diagnosis, but in order to confirm it a biopsy was made on April 27, 1917, and reported by Ewing as a highly malignant osteogenic sarcoma. It was decided to try conservative treatment for a while, instead of amputating immediately. Physical examination at this time revealed a marked swelling of the lower third of the left leg, apparently originating in the periosteum, and extending nearly around the leg. It began an inch above the internal malleolus and extended upwards five inches anteriorly, and $4\frac{1}{2}$ inches in the outside of the fibula. The swelling was most prominent over the inner and anterior part and was markedly tender on deep pressure. The skin was slightly discolored and there was marked local heat, the temperature being 99.5° F.

Toxin Therapy: (Tracy XI). Injections were begun by Coley on April 28, 1917, and were made daily at first and then four or five times weekly in doses sufficient to produce a febrile reaction of 102° to 104° F. The maximum dose was 7 minims, and the site was the buttocks. On May 1, the patient received 1,020 mc. of radon through 2 mm. lead filter, 10 cm. distant, applied to the inner aspect of the left leg for 12 hours. On May 23 the same amount was applied at a distance of 6 cm. over the external aspect of the limb for 12 hours. On May 26, the patient returned home where the toxins were continued by the family physician, Dr R. G. Gamble. On June 19 he was readmitted to Memorial Hospital for further radon therapy, receiving 1,200 mc. through a 2 mm. lead filter at 10 cm. distance over the internal aspect of the leg for 8½ hours, or a total of 42,720 mch. of radon from May 1 to June 20. The toxins were then continued at home during June and July, but in view of the fact that all evidence of the disease had disappeared, and the patient was in such fine physical condition, it was thought safe to discontinue the injections for four weeks during the extreme heat in August and early September.

Clinical Course: The patient returned to Coley for observation on September 25, 1917, stating that he had recently discovered a swelling in the left groin which was increasing in size. Physical examination showed the leg to be apparently normal, but there were several large glands in the left groin involving the femoral, inguinal and iliac regions, some of which were an inch or more in diameter. The largest was removed under ether anesthesia and Ewing pronounced it "actively growing sarcoma" (73). The prognosis seemed hopeless, but Coley decided to try the treatment a little longer.

Further Toxin Therapy: Injections of Coley's toxins were resumed. In addition the radon pack was applied over the glands in the groin on the following dates: October 1, 18,000 mch.; November 8 and 9, 17,000 mch.; and December 7, 12,000 mch. The toxins were continued for a period of 2½ years, with occasional intervals of rest. They were given at home by the family physician twice weekly, at first in the gluteal region, later in the deltoid, causing reactions lasting four or five hours. The dosage used was not sufficient to interfere with the patient's regular occupation and his general health remained perfect the entire time, except for one occasion, in December 1917, when his entire body became covered with blisters, apparently an allergic reaction. Injections were suspended for a time, and after this condition cleared up, they were resumed, using Tracy's filtrate (Type XI F.). In April 1918 the patient was presented at a conference at Memorial Hospital, at which time all evidence of the primary and metastatic growths had disappeared.

Clinical Course: The patient remained in excellent health, his only illness being several attacks of gout, none since 1937. He also dislocated the shoulder joint and "cracked this same arm again later". In the fall of 1945 he suffered two broken

ribs. He developed cellulitis in the left leg on four occasions, usually during the summer, requiring rest in bed and penicillin therapy. One of these attacks required five weeks in hospital. The first attack was in 1940, the next two in 1947 to 1948, and the fourth in the summer of 1950. Each time the infection cleared up entirely and did not disable the patient after it responded to treatment. He remained in excellent health when last traced in January, 1953, 37 years after onset (77).

Note: This case is one of many malignant bone tumors in which the limb as well as the patient's life was saved by Coley's method. However, it appears to be the only case of true osteogenic sarcoma in which Coley attempted to do this (the others being endothelial myeloma, reticulum cell sarcoma of bone, or fibrosarcoma). The case clearly indicates the danger of stopping the toxins too soon, even though the tumor seems to have disappeared completely. This case and many others in which treatment was resumed even when the prognosis looked hopeless due to metastases, should encourage surgeons now and in the future to resume treatment aggressively and persistently in order to salvage a larger number of such patients. (See Case 29 for another example.)

As to the role played by radiation in effecting the excellent result in this case, it should be noted that only two unequivocally proven cases of true osteogenic sarcoma appears to have been cured by radiation alone. Doub reported a case of osteogenic sarcoma of the clavicle with pathologic fracture which regressed completely following combined fever therapy and radiation, and which was followed for over 20 years, well and free from recurrence or metastases (49, 50).

References: 2, 33, 34, 35, 36, 41, 43, 73, 77.

Note: The following four cases received the commercial products prepared by Parke Davis and Company, and designated Parke Davis XII (available 1907 to 1915), and Parke Davis XIII (available 1915 to 1950). These were considerably weaker than Tracy's products.

CASE 27: Twice recurrent malignant melanoma of the back, with metastases in the axilla, confirmed by microscopic examinations after the first and second operations at Massachusetts General Hospital, Boston, Massachusetts. Whitney reported: "Large cells many of them containing black pigment with a little intercellular substance between and irregularly infiltrating the periphery." (72, W. S., 179016. 1911.)

Previous History and Treatment Other than Toxin: F. H. F., male, age 46, structural iron worker of Somerville, Massachusetts. The family history was negative for cancer or tuberculosis. The patient had always been well except for pneumonia 20 years previously. Onset, without known cause, a pigmented mole in

the scapular region began to swell early in June 1911. Five weeks later, or on July 14, 1911, Homans excised the growth with a two inch margin of normal skin. The patient was seen every two weeks thereafter and no recurrence was noted until October 22, when a small lump was seen on the outer aspect of the scar. Three days later the patient was admitted to Massachusetts General Hospital, and Cobb excised the recurrence. The patient was first seen by Dr Torr W. Harmer two weeks after this operation, at which time he had another recurrence $2\frac{1}{2}$ by 0.5 inches in diameter in the second cicatrix, and a palpable mass in the axilla the size of a pigeon's egg (58, 59, Case 17).

Toxin Therapy: (Parke Davis XII). Injections were begun by Harmer on November 15, 1911. No details are given as to the site, dosage or frequency of injections during the early treatment, which did not prevent another mass the size of an English walnut from appearing in the same scar. The two masses became confluent, but under continued toxin therapy they sloughed out entirely in one month, leaving a thin soft scar. Harmer stated: "During this time, however, a recurrence appeared in the upper scar, which became $3\frac{1}{2} \times 2 \times 1$ inch in diameter. This whole mass was entirely sloughed out by January 13, 1912" (58). A pigmented mass appeared in the right pectoral region early in January 1912. It ruptured in three weeks with local injections, but increased in size until it was 3×2 inches in diameter. There were several "erysipelatous" attacks when the whole pectoral region would be red, hot, tense and tender, Harmer stated. A second gland appeared in the axilla and another in the neck. The latter became the size of a cherry but disappeared in one month. The axillary masses became the size of a hen's and pigeon's egg during these erysipelatous attacks, but within a month decreased considerably and never became any larger until treatment was discontinued 11 months later. (The upper axillary mass, which was present when the patient was first seen by Harmer, was no larger and just as movable 26 months later.) The entire breast tumor sloughed out with cutaneous appearance of dark pigment by August 1913 and never recurred.

Harmer stated that one bluish black mass about $1\frac{1}{2}$ inches in diameter regressed under local injections to an apparently fibrous mass of dull red color about $\frac{3}{4}$ inch in diameter. During this period another pigmented mass was developing within a few inches of the former one. The second mass attained the size of a pigeon's egg during the time that the treated one was regressing. Both masses were then excised under ether anesthesia, with an elliptical area of skin, subcutaneous tissue and fascia about 6 by $2\frac{3}{4}$ inches in diameter. Fourteen sections were made from these two tumors. In reporting this case in 1914 Harmer showed characteristic portions of the treated tumor in Figs. 3 and 4, in marked contrast to Figs. 5 and 6, the untreated growth (58). By August 1913 the patient was in excellent condition with a good appetite and no evidence of internal metastases. The other masses had sloughed out, or been excised, as stated above. (Note: this

case received both Tracy's XI and Parke Davis XII, mostly the latter (108). No other case is known to have received as high dosage as this man was given.)

Clinical Course: The patient then disappeared on a "spree", returning 18 days later, haggard and weak.

Further Toxin Therapy: Injections were resumed, but the patient never regained his former tolerance for the toxins. He had been taking 40 or 50 minims at a dose prior to this spree, but when he returned 4 to 8 minims produced as severe reactions as he had formerly experienced only with the larger doses. New masses began to appear on the abdomen, arms, breast and back. This second course of toxin therapy lasted only from October 1, 1913 to January 26, 1914. The patient received a total of 195 injections over a period of 26 months, the maximum dose being 53 minims.

Clinical Course: The disease was not controlled. Death occurred on February 26, 1914, with metastases in the spinal cord and abdomen (59).

Note: This case indicates the danger of suspending treatment too soon after visible masses have regressed in cases of malignant melanoma with metastases. It is also apparent that any factor which lowers the patient's general physical condition, such as large amounts of alcohol, or returning to hard physical labor too soon, or any other excessive activity, may throw the balance in favor of the neoplasm, making it difficult or impossible to regain control of the disease. It appears that a larger quantity of toxins aggressively and persistently administered may be necessary in order to produce results in cases where several metastatic masses are present. Compare this case with that of Greenwood (1911), where a better product was used and the toxins were begun for a recurrent malignant melanoma before metastases developed, and were continued persistently and aggressively for many months after the recurrence had disappeared. That patient remained well and free from further recurrence until his death from acute bronchitis, 14 years later. (See above, Case 17.)

References: 41, 58, 59, 72, 108.

CASE 28: Inoperable angiosarcoma of the mediastinum, confirmed by microscopic examination by Dr F. S. Mandlebaum, Pathologist of Mount Sinai Hospital. Dr James Ewing also examined the sections and reported: "Malignant cellular tumor of embryonal type, composed of many blood sinuses lined by two or more rows of tumor cells. Very delicate stroma." He regarded it as an extremely malignant form of tumor (67).

Previous History and Treatment Other than Toxin: P. H., female, age 22 months, of New York. The family history was negative for cancer, tuberculosis or

venereal infection. The maternal grandfather developed diabetes at the age of 60 or 65. There was no history of antecedent local trauma. The child had been normal at birth, weighing 9 pounds. She was breast fed for 10 months and she walked at 16 months. She had gained slowly in weight although there had been frequent green diarrheal stools. At the age of 5 months the mother noticed that the child's breathing was distinctly labored, but the family physician found nothing wrong with the lungs. For two months there was respiratory disturbance without cyanosis or other sign of deficient aeration. The child was pale and heart action was often rapid. At the age of eight months the mother noticed a "lump on the right shoulder blade" while bathing the child. She took her to the Babies Hospital, where a roentgenological examination was made. This was reported as showing "a large roughly quadrilateral, dense shadow in the lower part of the right chest, extending over the heart, also the left chest and down over the liver shadow. Right chest above this appears free from lung tissue. The right diaphragm appears free from lung tissue. The right chest is smaller than the left. The right bronchus is not seen. Probably congenital atelectasis." The mother refused to leave the baby but took her to Lebanon Hospital, where fluoroscopic examination was made, April 30, 1923. This revealed "a dense shadow, homogeneous in character, sharply circumscribed, ascending apparently from the lower mediastinum, and projecting to the right. The mass is the size of a small orange; its lower border projects slightly to the left of the median line and is overshadowed by the heart. The appearance is either that of a cyst or a neoplasm ascending from the mediastinum." A puncture was made which produced sterile, bloody, non-coagulating fluid. The Wassermann, blood, and urine examinations were all negative. An exploratory operation was suggested but refused by the child's mother, who took the patient home. At 20 months, tonsillitis developed and the child was taken to Beth David Hospital, where another roentgenological examination corroborated the former findings. On March 16, 1924, when the child was 21 months old, she suddenly stopped walking because of weakness of the right lower extremity, which became rapidly progressive. At first she was able to stand, but the right foot turned out and she fell on attempting to walk. She was first seen by Dr Alfred W. Pollak at this time, at the Hospital for Joint Diseases. He noted that the patient was a bright, well-nourished child, without fever or pain. There was great weakness of the lower extremities: total inability to stand because of paresis of both legs. There was a mass between the right scapula and the spine, with dullness on percussion. Breath sounds were exaggerated anteriorly. A blood examination was reported as follows: hemoglobin, 42 %; erythrocytes, 3,200,000; leukocytes, 14,000; polymorphonuclears, 42, small lymphocytes, 13; transitionals, 1; eosinophiles, 3. Urinalysis was negative. Roentgenological examination at this time was reported: "Cyst, lower right chest; pressure erosions, spine and rib, oesophagus is displaced anteriorly" (67, p. 616, 617, 618 for roentgenograms). Dr Howard Lilienthal was called in to see the case on April 12, 1924, a month after she had stopped walking. He

found both legs flaccid and obviously paralysed. There was a protruding subcutaneous mass covered with normal skin between the right scapula and the spine which was firmly elastic. The child's general condition was good. On April 15, 1924, Lilienthal operated, at Mount Sinai Hospital. He resected about $1\frac{1}{2}$ inches of a rib subperiosteally over the tumor. He then aspirated a minute quantity of thick bloody fluid. The posterior mediastinum was then opened and the capsule of the tumor exposed. This was incised so as to admit the index finger. The wall was tense and the tumor rudely spherical. A large part of the contents was removed with the finger, consisting of grayish-red, soft neoplastic tissue, the total amount removed being a little greater than the bulk of a golf ball. The oozing cavity was packed with iodoform gauze. The pleura was not entered. Lilienthal then suggested toxin therapy.

Toxin Therapy: (Parke Davis XIII). On April 25, or ten days after this operation, injections were begun by Pollak. The initial dose was $\frac{1}{25}$ of a minim, the site being the gluteal muscles. This was followed by a severe reaction. For 11 days the injections were given daily, increasing the dose to a maximum of $4\frac{1}{2}$ minims. The febrile reactions ranged as high as 106° F. Further injections were refused by the patient's mother, because of the severity of the reactions. Pollak's observations as to the effects of toxin therapy are of value: He stated that the intensity of the reactions had been very great, and added: "From the very first the healing of the operation wound was extraordinary, and after the third injection the progress of the healing was even ten-fold quicker than before, and after the reaction was over the child seemed to be better generally. The hemoglobin count was 42 % at the time of the operation and after the eleventh injection it went down to almost 30 %. Because of the violent reactions the mother requested that the injections be stopped, at least temporarily, and Dr Lilienthal thought this might be done without ill effect, and a transfusion be given. While the advisability of giving a transfusion was being considered, the improvement in the patient's condition became so marked that matters were allowed to stand as they were, and in a comparatively short time the child was up and around." She began to walk within three weeks from the first injection, relief being due apparently to decompression (67).

Intercurrent Infection: During the summer immediately following toxin therapy, the child developed a very severe case of pertussis, there being as many as 14 violent paroxysms in one afternoon. During this time roentgenograms were taken of the lungs to see if they were affected, but the picture was negative. A severe attack of measles, and then bronchitis followed the pertussis, but the child recovered without any ill effects. It is possible that the severe attack of pertussis, as well as the measles and bronchitis may have generated toxins which helped to continue the process of regression of the neoplasm. The possible effects of contagious diseases other than tuberculosis on malignant tumors in man have not

been seriously considered until rather recently. However, several investigators have reported the inhibitory effects of intercurrent contagious diseases on tumors in mice or rats (97). Bashford was one of the first to note that mice convalescent from contagious diseases are refractory to tumor transplants (53).

Clinical Course: The patient's condition continued to improve and a series of x-ray pictures taken by Dr H. B. Philips showed the gradual regression of the tumor mass during the next two years. On September 19, 1926, Philips reported: "The irregularity in contour and diminution in size indicates a partial collapse of the tumor. There appears to be considerable regeneration of the posterior ribs, which previously showed marked pressure erosions, and considerable regeneration of the resected portion of the eighth rib has taken place." A month later roentgenological examination showed a normal chest. In February 1928 Dr Leopold Jaches examined the patient's chest and reported: "No evidence of abnormality in the lungs, diaphragm, heart and aorta. The eighth rib shows evidence of previous resection, but it has regenerated almost completely", (film No. 11,846). The patient remained in perfect health and was seen periodically by Pollak and Lilienthal during the next 21 years. She was presented at various medical meetings by Lilienthal, who on one of these occasions stated: "This is not the first time I have noted a continuance of the regression in cases of malignancy after the treatment with Coley's toxins had been discontinued. My experience with this form of therapy in a number of other instances has been so favorable that I would strongly recommend its use in inoperable sarcoma and also as a prophylactic postoperative treatment after surgical removal of operable tumors as well" (66). The patient reported in November 1949 that she had had a son, her first child, 3½ months previously and added: "The baby was a natural birth and I had a wonderful pregnancy." Her average weight in 1949 was 150 pounds. The patient was last traced in good health on January 1, 1953, or over 28 years after the toxins were begun. Her only complaint at this time was a low basal metabolism (minus 25) and that she was overweight (165 pounds), her height was 5 feet 3 inches (77).

Note: Pollak's observations of the apparently stimulating effect of the toxins on the rate of healing of the operative wound are of interest, as this effect was also reported by other surgeons using the method, and is apparent in many of Coley's cases, especially osteolytic bone tumors, where extensive areas of bone destroyed by the neoplasm completely regenerated following toxin therapy.

References: 53, 67, 76, 77, 97, 98.

CASE 29: Reticulum cell sarcoma of the tibia, recurrent after amputation, with metastases to bone and soft parts, confirmed by roentgenologic examinations by Dr Frank Liberson, and microscopic examinations by a number of pathologists including Dr Fred W. Stew-

art and Dr James Ewing of Memorial Hospital (Pathological report No. 5677). In 1926 the diagnosis of the Bone Sarcoma Registry was Ewing's tumor or endothelial myeloma; all the members of the Bone Registry Committee agreed that it was a highly malignant tumor (2, Case No. 1143).

Previous History and Treatment Other than Toxin: G. B., male, age 32 (in 1926), master mariner. The family history was negative as regards malignancy, tuberculosis, diabetes or venereal disease. The patient had always been in good health until he sustained an injury to the left leg over the tibia on February 25, 1918, while on a voyage to England. He was thrown against a hatch, and the bruise took six weeks to heal, after which the leg appeared normal. Thirteen months later, while again at sea, he began to have severe pain at the spot where the skin had been bruised, accompanied by swelling and fever. The pain, but not the swelling, temporarily disappeared in about a week, followed by recurrent attacks of pain every two or three weeks for a period of three months, during which time the patient was making a voyage from Australia to New York. Shortly after his return to New York he sought medical aid. A roentgenogram of the leg revealed osteomyelitis of the tibia, and an operation was performed at St. Joseph's Hospital, Paterson, New Jersey, on August 19, 1919. He was discharged on crutches, on November 23, 1919, still suffering pain. He remained at home for the next four months, but did not improve very fast. On March 31, 1920, he was admitted to the Marine Hospital at Stapleton, Staten Island. He remained four months during which time he received physiotherapy, which relieved the pain, and a tonsillectomy was performed. He went back to sea and then returned to the hospital for two weeks in March 1921, after which he again went back to sea. On March 3, 1924, he was readmitted to the Marine Hospital for a chronic appendicitis and bilateral inguinal hernia. He was discharged on March 28, 1924, still having occasional attacks of pain in the leg. Six weeks later he was readmitted and remained under treatment $4\frac{1}{2}$ months, or to September 25, 1924, receiving baking and ultra-violet rays to the affected leg. At the time of his discharge all pain had gone, there was no swelling and the condition appeared to be cured. However, an x-ray taken on October 2, 1924, showed marked cortical thickening and irregularity of the middle third, and marked periosteal roughening with bony projections, especially anteriorly. At this time the diagnosis was still regarded as osteomyelitis (6, Fig. 1, p. 189). On April 24, 1925, the patient noted a swelling of the tibia a little higher up than the site of the operation in 1919. He was readmitted to the Marine Hospital and operated upon in May 1925. Osteomyelitis was again found, with free pus in the marrow and a sequestrum of dead bone. Two weeks after this operation the bone began to swell and ache just below the knee. An x-ray taken on June 30, 1925 (6, Fig. 2, p. 190), showed marked decalcification of the upper third of the left tibia with only part of the skeleton of bone remaining in the

anterior upper third of the tibia, appearing like a bone dissolving under corrosive fluid. Shortly afterwards, injections of sodium iodide were begun, and given every third day intravenously, until a total of 50 grams had been given. Another x-ray, taken September 13, 1925 (6, Fig. 3, p. 191), shortly after the sodium iodide treatment, showed further advance of the erosion, with pathologic fracture at the junction of the upper and middle thirds of the tibia. (Coley stated that this picture was quite characteristic of endothelial myeloma.) On September 11, 1925, a piece of bone was removed which was reported as "Myelosarcoma, very cellular, with slight fibrosarcomatous structure." A mid-thigh amputation was performed on September 21, 1925. The wound healed in two weeks, but pain in the stump continued. A roentgenogram taken 60 days after the amputation showed the periosteum intact, the cortex and medulla sharply demarcated and no evidence of recurrence (6, Fig. 5, p. 194).

On December 12, a nodule was noted beneath the skin just above the umbilicus. A biopsy was made, and the growth reported to be metastatic. On January 5, 1926, examination revealed that the head of the femur-amputated stump had a tumor mass the size of a man's fist on its inner aspect, with an additional growth about the size of a lemon over its outer aspect. The skin of the stump appeared to be quite healthy. There was a mass in the left inguinal region which was about two inches long, one inch wide and two inches thick. There was a supra-umbilical mass which involved the skin about $\frac{3}{4}$ of an inch in diameter. The circumference of the stump was 19 inches.

Toxin Therapy: (Parke Davis XIII). Injections were begun by Christian and Palmer on January 5, 1926, the initial dose being $\frac{1}{4}$ minim. The dose was increased daily by $\frac{1}{2}$ minim until the patient was receiving $6\frac{1}{2}$ minims, all injections being given intramuscularly in the gluteal region, alternating sides. Palmer stated: "There is little local reaction at the site of the injection." He added that he gave a few of the first injections "directly into the tumor mass" (76, p. 347). In describing the effects of the treatment Palmer stated: "Each injection would be followed by a severe reaction. About an hour after the injections he would have a violent chill, lasting 10 to 15 minutes. Four to six hours later the temperature would be around 104° to 106° F., accompanied by sweating and restlessness. Then in 4 to 6 hours it would be normal again and the patient would feel fine (76, p. 348). Subsequent series of injections, after the patient had established tolerance for the toxins, did not produce such reactions even with large doses (see below). On January 22, 1926, or three weeks after the toxins were begun, the circumference of the stump had decreased two inches, the mass in the groin had disappeared, and the supra-umbilical mass was decidedly smaller, softer and lighter in color. The patient looked paler, apparently due to the effects of absorbing large quantities of necrotic tumor tissue. The dose was held at $6\frac{1}{2}$ minims from January 25 to February 2, after which it was increased by one minim daily to a maximum

of 18 minims given daily. The site at this time was the muscles of the buttocks, the shoulders and occasionally the lumbar region. On February 20, the injections were discontinued because of the extreme weakness of the patient. At this time the stump appeared to have taken on a new growth, associated with considerable edema on both the good leg and the stump.

Clinical Course: A roentgenogram taken February 23, 1926 (6, Fig. 7, p. 195), showed the stump of the femur undergoing dissolution. There was hardly a skeleton of the cortex seen, with the bony substance, primarily the calcium, disseminated into the soft structure in all directions, as if transported by lymphatics and veins. By March 17, there were three small vesicles on the stump. The supra-umbilical growth had increased considerably, being the size of a large lemon.

Further Toxin Therapy: On March 27, 1926, 2 minims of the toxins were injected directly into the tumor mass on the stump. The dose was gradually increased each day until the patient was receiving 5 minims directly into the tumor. Each of these injections was followed by considerable febrile reaction. Apparently the injections were suspended during the next few months.

Clinical Course: On May 5, 1926, several small nodules were felt under the skin of the abdomen. During May and June the patient grew steadily worse with metastatic growths appearing in many parts of the body, including considerable involvement of the right clavicle, and multiple tumors in the scalp, cranial bones and cervical vertebrae. About this time the maximum growth in the tumor of the stump was attained, the circumference being 31 inches. The end of the stump had broken down over an area about five inches in diameter, from which there was a foul profuse ichorous discharge.

Third Course of Toxin Therapy: The injections were resumed on August 5, 1926, the initial dose being 2 minims, which was increased by one minim a day until the patient was receiving 17 minims daily. The dose was held at this point until September 4. The effect of this series of injections was a marked improvement: the edema of the good leg and the stump decreased very much and the stump almost healed by September 4. The supra-umbilical mass had practically disappeared as well as the clavicular tumor. The area in the scalp had regressed completely. After a two weeks' rest period the injections were resumed on September 19 and continued for three weeks. Palmer stated that the September—October series of injections (as well as the final course in 1927) were not followed by marked febrile reactions such as had occurred during the first and second series in 1926. He added: "Very rarely would there be a fever. (Sometimes one to two degrees.) The depression, however, was marked and more pronounced than in the earlier series. Within a few hours after a large dose he would begin to feel badly, but would have no chill or fever. He would feel 'all knocked out'—having no appetite, and feel restless and irritable. This would last about 10 hours, and

then he would feel better again. Of course, after several weeks of this reaction, he would lose considerable weight and get terribly weak so that we would have to discontinue the injections to allow him to recuperate. In the later series it never seemed that we reached the maximum of toleration. We could have given larger doses than 30 to 35 minims, but this seemed enough. The marked depression seemed to tell us when to stop. I should like to emphasize again the difference in the type of reaction when the sarcoma was still present and later when all evidences of sarcoma had disappeared" (76, p. 349). (Note that during the first series some of the injections were made into the tumor mass, apparently the stump tumors, and that this may have partly accounted for the difference in reaction noted by Palmer.)

Clinical Course: By November 22, the general condition of the patient was excellent, his weight being 147 pounds, or 30 pounds more than it had been the previous January. The stump was 17 inches in circumference, a decrease of 14 inches. The old discharging wound on the stump had healed although the skin was quite leathery, and underneath it was a tough fibrous mass believed to be scar tissue. The growths on the abdomen had regressed completely; just above the umbilicus there was an area of pigmentation of the skin $3\frac{1}{2}$ inches long by $2\frac{1}{2}$ inches wide corresponding to the site of the former metastatic growth. Areas of involvement in the scalp and skull could no longer be detected, although there remained some degree of thickening and roughening of the right clavicle. The patient was discharged from the Marine Hospital on December 5, 1926, apparently cured (6).

Final Course of Toxin Therapy: The case was reported to Dr William B. Coley and at his suggestion, as a precautionary measure, in order to prevent further recurrence or metastases, the patient was given two more courses of toxin injections in the spring and fall of 1927. Between February 23 and March 27, an injection was given every third day, beginning with 3 minims, the dose being doubled each time until 30 minims was given each time. The final course was given between October 23 and December 7, 1927, when the injections were given every third day in doses up to 30 minims.

Clinical Course: Christian and Palmer presented the case at a Memorial Hospital Bone Tumor Clinic in December 1927. On this occasion Coley stated: "I believe this is one of the most remarkable cases of malignant tumor of the long bones that has ever been published, and I am quite willing to admit that, had the patient been under my care, he would probably not have been alive today. In the first place, I am almost certain that I should not have continued the treatment after three months when not only no improvement had been noticed, but marked increase had taken place in the metastatic tumors and especially in the recurrent tumor of the stump. (An increase of from 17 to 31 inches.) In the second place I am quite

sure that I should not have dared increase the dose to such a large amount (30 minims). However, it was not until these large daily doses were given that the improvement continued until all the tumors had disappeared. I have learned more from this one case than from any other that I have personally treated, and I feel that many of the past failures might have resulted otherwise had larger doses and more frequent injections of the toxins been given" (6, p. 196).

The patient was presented before the New York Surgical Society by Coley on March 13, 1929, in the best of health; at this time he weighed 140 pounds, the stump was normal, and he was wearing an artificial limb (36). Since this time he has not used the limb, but gets about on crutches (76).

The patient was examined periodically by Coley for several years. He remained well and free from further recurrence or metastases when last traced on January 1, 1953. He had no illnesses other than an occasional cold in the 27 years following toxin therapy (77).

References: 2, 6, 35, 36, 37, 38, 73, 76, 77.

CASE 30: Very extensive bilateral papillary cyst adenocarcinoma of the ovaries, with metastases in the omentum and both broad ligaments, . . . apparently involving the liver, confirmed by microscopic examinations at St. Luke's Hospital, New Bedford, St. Ann's Hospital, Fall River, as well as by Dr Fred W. Stewart, of Memorial Hospital, New York, and Drs John E. McWhorter and D. A. De Santo, Pathologists at the Hospital for Special Surgery, New York, who reported on March 28, 1935:

"*Gross:* Specimen is a pelvic mass measuring $8 \times 4 \times 3$ inches. In the center of the mass is a uterus. This has been sectioned sagittally. The cervix shows healed scars. The uterine wall appears natural and the organ is normal in size and shape. In the right broad ligament is an irregularly shaped mass $4 \times 3 \times 3$ inches, which has been sectioned in several places. The mass consists of a multilocular cyst, some of the subdivisions of which contain gelatinous material and others papillary tumors having a racemose appearance. In the left broad ligament the mass is larger and measures $5 \times 4 \times 2$ inches. It is similar in structure to the tumor of the right, but is more solid, with several areas of central softening.

"*Microscopic:* Sections from the right and left ovaries show a fibrous cyst wall lined by tall columnar epithelium, thrown into complicated connective tissue. The cyst wall is infiltrated by daughter cysts, which in turn are lined by papillary ingrowths of epithelium. Many areas of the tumor show a mucinous degeneration. Sections from the cervix and uterus show sclerosis of the vessels, and are otherwise natural.

"*Diagnosis:* Bilateral papillary cyst adenocarcinoma of the ovary. Fibrosis uteri." (Note: In February, 1949, Dr Sophie Spitz of Memorial Hospital reviewed the sections on this case and also reported it was a papillary adenocarcinoma of the ovary.)

Previous History and Treatment Other than Toxin: Mrs G. L., female, age 38 (in 1933), of Pawtucket, Rhode Island. The family history was negative for

cancer, tuberculosis, or insanity. The patient's father died at 72 of uremia. The mother was living and well. The patient had had 9 brothers, 3 of whom died of unknown causes, and 7 sisters, 6 of whom had died. She had had whooping cough, measles and mumps as a child. The menses began at 11 and had been irregular before marriage, sometimes skipping three or four months. Since marriage there had been a regular 28-day cycle. There had been no dysmenorrhea but some leukorrhea since marriage. She had had one child. The patient was first seen by Dr Raymond E. Senecal in January 1933. She had lost 15 pounds in weight in the previous six months, felt easily tired, and had noticed a fullness in the lower abdomen, although the periods remained regular. On February 27, 1933, an exploratory laparotomy was performed at St. Luke's Hospital, New Bedford. The uterus, adnexa, and gastro-intestinal tract appeared not unlike those found in advanced cases of tubercular peritonitis. The organs were atrophied and so changed that they could scarcely be identified. The appendix was removed and also a gland on the omentum. The pathological diagnosis at this time was "omental implantations of cyst adenoma and chronic periappendicitis" (92). The patient was discharged from the hospital in an ambulance on March 9, 1933, after a stormy convalescence, following which she did not improve. Her abdomen became greatly distended and she presented a picture of general anasarca. She was sent to the country, where she took daily sun baths. Her condition progressed unfavorably. At this time the patient was in an extremely bad condition. Her weight had decreased to 69 pounds, a loss of 31 pounds, and rectal feeding was considered necessary. A roentgenologist was consulted but he regarded the prognosis as hopeless.

Toxin Therapy: Injections were begun by Senecal on September 3, 1933. The patient was given eight alternating doses of 8 and 16 minims each (0.5 and 1 cc.) intra-abdominally, on September 3, 4, 5, 6, 8, 10, 12, 17. The reactions at times were very severe, the temperature ranging between 101° and 104.8° F. In describing the results of the treatment, Senecal wrote: "From the beginning the progress of the case was miraculous. Her abdomen, which at first was distended to one and one-half times a full-term pregnancy, rapidly flattened down to normal: it decreased from 34½ inches to 25¾ inches in the first four weeks. Her appetite became voracious and she gained weight and strength" (41).

No toxins were given between September 17 and October 12. Another series of seven injections was given as follows: October 12, 27, 29, November 1, 6, 11; each injection produced a marked reaction, usually with a chill lasting half an hour. The dose for this second course was maintained at 0.5 cc. (about 8 minims).

The patient was discharged from the hospital on November 13, 1933, having received a total of 15 injections, the total dosage being about 144 minims (9.5 cc.). (It should be emphasized that this was much higher than that usually advised by Coley. Under the dosage prescribed in the Parke, Davis & Co. package, this

patient would probably have received about 20 minims during the first eight injections, whereas Senecal administered 96 minims in those first eight doses.)

During November only two injections a week were given, and early in November a mass appeared in the pelvis which was hard, nodular and easily palpable externally. Injections were made directly into this mass, but only one a week was given during December, January and February. The mass increased slowly in size. The total number of injections given in the six-month period between September 1933 and March 1934 was 36.

Second Operation: In March 1934 it was decided that the patient return to the hospital for further exploration. At this time the abdomen was flat and soft, but a mass was palpable in the lower quadrant which seemed somewhat fixed. There was no pain. The patient was given two blood transfusions, on March 28 and April 2, 1934, each time receiving 500 cc. of whole blood and 1,000 cc. of saline. The operation was performed on April 4, 1934 at St. Ann's Hospital, Fall River, under spinal anesthesia, and "consisted of hysterectomy, bilateral salpingo-oophorectomy with removal of all growths around the tumorous condition. At first the mass appeared inoperable and only a semblance of the fundus uteri was recognized. However, the whole tumor was finally freed" (41). The specimen was examined by several pathologists, as stated above, the diagnosis being adenocarcinoma of all the adnexa. The patient left the operating room in poor condition but made a good operative recovery (41).

Further Toxin Therapy: Injections were resumed about June 1, 1934, and were continued for about a year following this operation. At first they were given by Senecal, twice a week, but during the latter part of the treatment the patient administered them herself, the site being the thighs. She began to gain weight shortly after the toxins were resumed and this continued steadily so that by December 1934 she had gained 40 pounds. Senecal wrote to Coley in regard to this case in February 1935 and stated: "There is no doubt in my mind that this patient owes her life to Coley's fluid" (41).

Clinical Course: There was no further recurrence or metastases. The patient reported in July 1945 that she had had no illness of any kind in the 12 years since toxin therapy was begun, and that she weighed 130 pounds, a gain of 61 pounds since September 1933 (77). In June 1950 she consulted Dr Robert V. Lewis, of Providence, who reported: "Mrs L. came to me because she was having a sense of discomfort in her rectum when she sat down. On examination the recto-vaginal wall and the surrounding tissue were full of nodules about the size of grapes. They were freely movable, firm and nontender in themselves" (77). She weighed 114 pounds in July and 119 pounds in August. Laboratory studies showed the sedimentation rate and the Bohlen test were essentially negative. Dr Emery Porter, a surgeon, and Dr Russell Bray, a gastro-enterologist, were seen in consultation.

Bray found nothing in the rectum on proctoscopy and sigmoidoscopy. During the next four months Porter and Lewis followed these nodules in the recto-vaginal wall and there was absolutely no change. On October 28, 1950, Lewis reported: "It is our impression that these nodules are entirely inactive." She was again seen in mid-October, at which time she was in good physical condition and had no complaints. Lewis reported, on April 3, 1951, that the nodules in the recto-vaginal wall had enlarged during the previous three months, and that the vaginal mucosa at one point had been slightly eroded by one of the lesions. She had lost 10 pounds in weight, but the clinical findings were otherwise negative. There was no anemia. The patient was again seen by Porter, the surgeon who is following her, and he stated that the only feasible operation in her case would be an abdominal-perineal resection and removal of the recto-vaginal wall. He stated that these lesions are not amenable to less radical surgery (77). At this time Lewis suggested further toxin therapy which was administered at Memorial Hospital in late May 1951. The patient gained weight and strength. She remained in excellent health, weight 128 pounds, when last traced in January 1953, with no evidence of disease, 20 years after onset (77).

Note: This is another case which indicates the danger of decreasing the frequency of injections too soon, even if marked or apparently complete regression occurs during the first weeks of treatment. It is apparently the only case in which such large doses were injected intra-abdominally, and the results suggest that this route may be most effective when dealing with extensive intra-abdominal or intra-thoracic neoplasms.

References: 41, 73, 77, 91, 92.

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INDEX OF VARIOUS PREPARATIONS OF COLEY'S TOXINS USED 1891-1953

TYPE I. *Living cultures of streptococcus erysipclatis*, inoculated by Coley and others in order to induce an actual erysipclis infection. Coley's first attempt: April 3, 1891 (8, 9).

TYPE II. *Erysipclis Toxins*: November 1892. Prepared by Dr Alexander Lambert for Coley. Bouillon cultures of streptococcus erysipclatis were heated to 100° C. (some to 60° C.) and were injected into the tumor. Symptoms and reactions corresponded to those caused by living bouillon cultures, though less severe and of shorter duration. They were not effective in controlling the neoplasms, however. (Lassar (65), Répin (88), and Spronck (101) in Europe also tried erysipclis toxins sterilized by heat, with indifferent results.) However, all cases treated by Coley and others with these erysipclis toxins were terminal cases, perhaps not a fair test.

TYPE III. *Erysipclis Toxins*: Early December 1892. Prepared by Lambert for Coley. Living bouillon cultures of streptococcus erysipclatis were sterilized by passing through a Kitasato filter; (not subjected to heat). These also proved too weak to control the far-advanced cases in which they were tried (11).

TYPE IV. *Mixed filtered Toxins*: December 1892 to May 1894. Prepared by Lambert. The first *mixed* filtered toxins. A filtrate containing the soluble toxic products of streptococcus erysipclatis obtained from a fatal case, was added to a filtrate containing the soluble toxic products of bacillus prodigiousus. These were not subjected to heat, but were preserved in glass-stoppered bottles by the addition of thymol. They were mixed only at the time of use (12).

TYPE V. (*Buxton's*) *Mixed filtered Toxins*: Early in 1894. Prepared by Dr B. N. Buxton, at the Loomis Laboratory of Cornell Medical School. Cultures of streptococcus erysipclatis and bacillus prodigiousus were grown together in the same broth, the first being grown alone for ten days, and then the

bacillus prodigiosus added and the two grown together for ten days, and then filtered through a Kitasato filter. These appeared to be more potent than those grown separately as in Type IV (12).

TYPE VI. (*Buxton's Mixed unfiltered Toxins*: June 1894 to late 1907. Prepared by Buxton. The first mixed *unfiltered* toxins. The cultures were grown together as in Type V, but instead of being filtered they were sterilized by heating for one hour at 50° to 60° C. The first erysipelas cultures were obtained from a fatal case (12). From 1896 to 1899 the virulence was maintained by frequent passage through rabbits. After 1899 the virulence was maintained by passage through eggs as well as rabbits, and the preparation was sterilized twice by heating for about one hour each time. Thymol was used as a preservative (41). (It appears that Type VI was not as effective from 1899 to 1906 as it was from 1894 to 1899.)

TYPE VII. *Coley's Mixed Serum*: 1894. Prepared by Buxton and Dr William H. Park. Erysipelas and prodigiosus serum, prepared in the same way as diphtheria antitoxin. Few cases were treated by this product, as it appeared to be less effective than Buxton's Type VI.

TYPE VIII. *Mixed Toxins, filtered and unfiltered*: 1894—1943. Prepared by the Laboratories of the Lister Institute of Preventive Medicine, London. From 1894 to 1907 the formulae used were probably Buxton's IV, V, and VI, principally VI. After 1906 the formulae used were Tracy's XI and XI F. Very few histories of cases treated with these preparations are available, and we have therefore included them all as Type VIII. The existing evidence indicates that these products were less potent than Buxton's and Tracy's (41).

TYPE IX. *Mixed unfiltered Toxins*: 1899—1906. The mixed unfiltered toxins of streptococcus erysipclatis and bacillus prodigiosus, as prepared by Parke Davis & Co. The first commercial product; weak and variable, although the same formula was used as for Buxton's VI. When dosage was increased to compensate for weakness, successful results were obtained in a number of cases.

TYPE X. *Mixed unfiltered Toxins*: March 1906 to the end of 1907. Prepared by Dr Martha Tracy under grants from the Huntington Cancer Research Fund. The mixed unfiltered toxins of streptococcus (obtained from a fatal case of septicemia) and bacillus prodigiosus. The two organisms were grown separately and heated to 75° C. for one hour (15° higher than Type VI). The amount of prodigiosus was 5 mg. per cc. of the mixed toxins, determined by Kjeldahl's method of nitrogen determination. After mixing and bottling the toxins were again sterilized for two hours at 75° C. These were the most powerful of all, according to Coley (21). They proved to be too toxic, due to large amount of bacillus prodigiosus.

TYPE XI. (*Tracy*) *Mixed unfiltered Toxins*: Late 1907 to 1922. The mixed unfiltered toxins of streptococcus erysipelas and bacillus prodigiosus, made under grants from the Huntington Cancer Research Fund of Memorial Hospital, using the same formula as Type X, except that the amount of prodigiosus was reduced one-half, to 2.5 mg. per cc. of toxin. This product appears to have been used in the largest number of successful results (78). NOTE: From July 1, 1920 until 1922, Tracy's XI was prepared by Dr Morton Kahn for the Huntington Cancer Research Fund. His only modification was the use of the single cell method to insure purity of cultures (41).

TYPE XI F. (*Tracy*) *Mixed filtered Toxins*: Tracy also prepared *filtered* toxins. The exact formula has not been found, but probably was similar to XI, using filtration instead of heat for sterilization. Patients did not appear to become immune to this preparation as they did to the unfiltered, and occasionally tolerance to the filtrate actually appeared to decrease.

TYPE XII. (*Parke Davis*) *Mixed unfiltered Toxins*: 1906 to June 1915. Prepared by Parke Davis and Company. The mixed unfiltered toxins of streptococcus and bacillus prodigiosus. Original cultures of the latter obtained from Tracy, 12/29/06. Similar to Tracy's XI, except that nitrogen determinations were inadvertently made before the first sterilization until 1915. Also the chromogenicity of the bacillus prodigiosus varied considerably as it was not specified in the formula sent to Parke Davis by Tracy. For these and other undetermined reasons Type XII was much weaker than Tracy XI.

TYPE XII F. (*Parke Davis*) *Filtrates*: A small quantity of filtered toxins was prepared in this period by Parke Davis. The exact formula is not recorded but was probably similar to XII, using filtration instead of heat for sterilization.

TYPE XIII. (*Parke Davis*) *Mixed, unfiltered toxins*: Prepared from May 1915 to 1951. Similar to Parke Davis XII, except that chromogenic cultures of prodigiosus were specified, and that nitrogen determinations were taken after the first sterilization. A fresh culture of streptococcus was obtained from the Mayo Clinic in January 1922, isolated from a case of erysipelas (hemolytic streptococcus No. 01024). Although this product was more potent than Type XII, it is now known that the active toxins and enzymes of streptococci are more thermolabile than those of bacillus prodigiosus, and therefore it would appear that heating these organisms for $2\frac{1}{2}$ hours must have destroyed much of the streptococcus toxins. This product is no longer being made by Parke Davis and Company.

TYPE XIV. (*Sloan-Kettering*) *Mixed unfiltered toxins*: Beginning in February 1946, Dr C. C. Stock's laboratory at Sloan-Kettering Institute, New York, has prepared the Coley toxins, following Tracy's Type XI formula, with

certain modifications. New strains of streptococcus and of Bacillus prodigiosus have been tried, and the sterilization temperature has been reduced to 58° F. This product appears to be less toxic, and larger dosage is required to elicit febrile reactions by the intramuscular route, than was formerly needed with Tracy XI or Parke Davis XIII prior to 1943. Some of the variables are now being studied in an effort to produce stable, potent products.

This was available until 1955 when suddenly without warning to those who were using it, including the Bone Tumor Service at Memorial Hospital (Dr. Bradley L. Coley and Dr. Norman Higinbotham) the Director, Dr. C. P. Rhoades ordered Dr. Stock to stop making it, even though several patients were under treatment at the time.

Dr. Rhoades had written to Parke, Davis & Co. in 1951 and told them to stop making the Coley Toxins since Sloan-Kettering was taking it over.

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