

**TESTICULAR CANCER
TREATED BY BACTERIAL TOXIN THERAPY
AS A MEANS OF ENHANCING HOST RESISTANCE**



End Results in 63 Determinate Cases

With Microscopic Confirmation of Diagnosis:

20 Operable (85% Successes) ; 26 Inoperable (35% Successes) ;

17 Terminal (6% Successes)



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**35% of the 26 inoperable cases in series B and C were successful.*

END RESULTS IN TESTICULAR CANCER TREATED BY BACTERIAL TOXIN THERAPY AS A MEANS OF ENHANCING HOST RESISTANCE

Testicular tumors are one of the most common forms of malignancy in men aged 20 to 35 years of age. They appear to be uncommon in the negro race. The methods of treatment in common use are surgical removal when possible, followed by irradiation, or when inoperable, irradiation alone. Few serious attempts have been made to enhance the natural resistance of patients with testicular cancer or other neoplasms.

However, impressive evidence is accumulating which indicates the importance of host resistance factors and we must now consider whether there is a place for adjuvant therapy designed to stimulate or protect the local and systemic resistance of patients so as to destroy incipient or inoperable metastases at the time of surgery and thus prevent recurrence or further spread of the disease in the highest possible percentage of cases.

For over 15 years we have been analyzing various factors which may favorably or deleteriously affect this natural resistance: when it is depressed or inactivated by carcinogens, irradiation, immunosuppressive drugs, corticosteroids or advanced age, cancer may develop and progress rapidly.

We found a considerable number of cancer patients who developed a complication which apparently favorably affected their resistance mechanisms so that their neoplasms decreased or disappeared. Bacterial infections, especially streptococcal and staphylococcal were associated with the largest number of such regressions.

A total of 223 determinate cases of cancer in which infection developed spontaneously or by inoculation have been abstracted in detail and analyzed. Cases which did not have microscopic confirmation of diagnosis or which were not followed for at least five years were excluded. Of these 223 cases 144 were traced 5 to 54 years after onset, 23 of them later died of their neoplasm.

It was on the basis of such observations that William B. Coley, M.D. developed his method of using heat-killed or filtered toxins of *Streptococcus pyogenes* and *Serratia marcescens* (then known as *Bacillus prodigiosus*). A total of 1065 determinate cases of cancer treated by these mixed toxins have been abstracted and analyzed. Of these, 479 were followed from 5 to 20 years after onset of their neoplasm, but 102 of them died more than five years after onset, and 46 subsequently developed an entirely different type of neoplasm 6 to 59 years after recovery from the first. Twenty-six of these second primaries proved fatal. A considerable number (110) are alive and well at the present time.

Possible Modes of Action of Bacterial Products on Resistance to Cancer:

Until recently physicians using toxin therapy were unaware of the fact that streptococci or their toxins are able to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. For example, Glynn and Holborrow found that four strains of streptococci and a strain of *Staphylococcus aureus*, when grown in agar media, gave rise to agar antibodies in antisera prepared against them. (32) Burky found that by combining staphylococcus with lens substance rabbits were sen-

sitized to lens and developed high precipitin titres to lens tissue. (7)

In order to stimulate this response the organisms do not need to be alive but the bacteria or their toxins must come into significant contact with the target tissue. This may be one reason why better results were achieved with toxin therapy when at least some of the injections were made in or near the tumor. In treating future cases it may be most effective to make the initial injections into the tumor following biopsy.

It is of interest to note that the majority of so called spontaneous regressions of cancer occurred in patients who developed streptococcal and staphylococcal infections rather than non-pyogenic infections such as malaria, syphilis or typhoid.

Havas has studied the effects of living hemolytic streptococci on ascites tumor cells (Sarcoma 37 and Krebs-2 carcinoma). Three of eight strains of *Streptococcus pyogenes* were highly effective against the tumor cells resulting in reduction of takes as well as reduction in tumor size. *Streptococcus lutea* and *faecalis* and *Serratia marcescens* were only partially effective in damaging tumor cells *in vitro*. The striking cytological changes produced by living streptococci on tumor cells were recorded by phase photomicroscopy. (36)

Christensen has studied the growth of Brown-Pearce carcinoma in rabbits treated with living or killed streptococci. None of the rabbits receiving injections of living streptococci developed metastases as compared with 50% of the untreated controls. Heat-killed cultures were not effective. (9)

A group of Japanese investigators began working with streptococcal toxins in 1955 and they appear to have produced an effective preparation. In a recent review Okamoto, et al, summarized the results obtained in their laboratories with hemolytic streptococcus toxins in experimental tumors. (63) They have achieved two distinct improvements in preparing their extracts: a) when suspended in Bernheimer's basal medium in contrast to simple media such as phosphate buffered saline, the tumor destructive properties of hemolytic streptococci were found to be resistant to heating at 45°C. for 30 minutes. This is of obvious importance since heat sterilization is used in making extracts for therapeutic use. b) preincubation of live cocci suspended in Bernheimer's basal medium containing penicillin yields a potent anticancer preparation which is 20 times more effective than live cocci suspended in NaCl without penicillin in inhibiting the growth of Ehrlich ascites carcinoma in mice. (63) Their preliminary clinical trials appear promising. Their reports indicate they were unaware of the end results which have been obtained with Coley toxins, judging from their comments on this subject. This may be due to the fact that so little has been published in recent years.

The availability or integrity of lymphoid tissues appear to be important for adequate resistance to malignancy. Two recent independent studies by Bierman (3) and McVay (49) on 1287 and 914 cases coming to autopsy suggest that a systemic and local protective effect is produced by the appendix on several types of malignancy. A number of surgeons are beginning to question the wisdom of routine radical lymph node dissections for cancer. Most of these have been related to breast cancer but Friedman and DiRienzo (31) recently stated in a report on testicular cancer that "there is growing evidence that omission of the retroperitoneal node dissection and employment of orchiectomy and irradiation yields higher survival rates" than are obtainable when lymphadenectomy is also performed in these cases.

Murphy and his associates at Rockefeller Institute were among the first to emphasize the importance of lymphoid tissues in resistance to cancer. (58) In this connection it is of interest that bacterial toxin therapy usually produces leukocytosis in cancer patients and often produces lymphoid hyperplasia in the regional nodes if injected intradermally, intramuscularly or intratumorally. Possibly toxin therapy may make the nodes more effective "strainers" of cancer cells.

The apparently beneficial effects of bacterial infections or their toxins may be due in part to the fever elicited for tumor cells are much more thermolabile than normal cells. (29, 30, 59, 62, 66) Analysis of end results in toxin treated cases according to the febrile reactions elicited showed the percentage of permanent successes was significantly higher in patients with reactions averaging 102°-104°F. This was especially evident in the inoperable cases. (66, Fig. 4, in monograph #3)

Adequately administered toxin therapy, if begun before the disease is terminal and the patient is unable to react, appears to stimulate the reticuloendothelial and hematopoietic tissues thus increasing the natural host resistance to the neoplasm and protecting the normal tissues against the deleterious effects of subsequent radiation or cytotoxic drugs. (1, 11, 29, 39, 41, 43, 64, 70). Other investigators have observed that preliminary treatment with bacterial toxins may potentiate the response of the tumor to subsequent radiation. (8, 60) Certain bacterial infections or their toxins may stimulate the synthesis or release of interferon or L-asparaginase, both of which are now being studied for apparent antitumor activity. (28,45)

Effect of Infections or Bacterial Toxins in Testicular Cancer:

Only one case of testicular cancer was found in which a concurrent infection developed, reported by Bolognino. (4) In this case two severe attacks of erysipelas in the region of the wound following incomplete removal of an extensive carcinoma of an ectopic testis, caused regression of the remains of the growth. The patient was traced well about two years after this infection and 4½ years after onset.

In reporting this and one other case of another type of cancer in which regression occurred following erysipelas, Bolognino stated that the early enthusiasm for "érysipèle salulaire" brought to light the first published cures of Busch and Bruns in Germany which led to the experimental inoculation with sterilized cultures by Coley, Lassar and Spronck. There followed an unjustified and continued opposition to toxin therapy. Bolognino pointed out that while the optimism of the first investigators might have been somewhat exaggerated, nevertheless one should consider that erysipelas infection is able to stop the fatal course of a malignant tumor. He added: "One can quickly be convinced that erysipelas infection possesses such a power by a glance through the literature, even if cases of complete cure are not too numerous, only because they have not been followed up for years. We still find many cases in which an erysipelas attack did not effect complete cure but only had a considerable influence on the size of the tumor, although later on it continued its unfortunate course. I mention among these the cases of Busch, Mosengeil, Hahn, Lussana, Nelaton,

Doleris, Stein, Dauchez, Powers and Dowd, Winslow, Neelsen, Richochon, Weichel, Kleeblatt, Eliot, Morris, Coley, Dandridge, Westbrook, de Gaetano and others." (4)

"It seems there are two factors which work together in the healing of malignant tumors through streptococcus infection. On the one hand the infection must be severe, on the other the tumor must not be too large." As regards the former, Bolognino stated: "We must remind the reader that Coley, by combining sterilized cultures of streptococcus with *Bacillus prodigiosus*, strengthened the potency of this microorganism. He took cultures of unusually severe erysipelas, maintained and intensified by passage through animals". (4)

"Consider the second factor (the size of the growth), one usually finds after incomplete surgical removal, before widespread metastases have developed, that the growth is not too extensive to regress completely under an erysipelas infection occurring at or near the site of the original growth." (4)

Bolognino's observations are sound and have been confirmed by the ex-

perience of other surgeons, such as Matagne (54, 55), Coley himself (14, 15, 16, 17, 18, 20, 21, 22), and more recently by the interesting experimental work of Martin (50, 51).

In attempting to evaluate the end results obtained in testicular cancer with bacterial toxin therapy, a review of the results obtained with conventional methods used in the same period may be helpful. Prior to 1915, the estimated five year survivals following surgery alone were about 10 to 15% (18, 38). Tanner (73) analyzed the end results following operation in 600 testicular cancer cases collected from the literature. Of the 465 which were traced, 377 (81%) had died of cancer, while only 25 (5½%) were known to be living and well four or more years after operation. He added: "Few neoplasms have a worse prognosis than those of the testicle." (73)

In recent years radiation, either alone or combined with surgery, has been advocated by the majority of surgeons or physicians and numerous reports describe the methods used and the results achieved. (31, 34, 42, 44, 74) Apparently with the exception of Cohn (10) these writers were unfamiliar with the results obtained by bacterial toxin therapy. For example, Pendergrass, et al (67) reported: "For several centuries neoplasms of the testis have been described in the medical literature, but until the advent of modern radiotherapy, the outlook for these patients was almost universally hopeless." The five year survival rates in their series of 43 patients were 42% for the entire series and 71% for the operable cases. Friedman and D. Rienzo (31) reported a five year survival rate of 28% in a series of 54 consecutive embryonal carcinoma of the testis treated at Walter Reed Army Hospital. (44% for the operable cases). Thompson et al (74) reported a 52% five year survival rate in 136 determinate cases seen in a 20 year period.

A few authors have called attention to the late effects of radiation given prophylactically to the retroperitoneal lymph nodes following orchiectomy for testicular neoplasms. (2, 5, 71) They stated that there is clinical evidence that even with much lower dosage levels than is usually given, the damage to normal bone within a radiated field may yield to fractures and in a few instances to fatal osteogenic sarcoma.

Radiation also destroys the spermatogenic function of the remaining normal testis, despite careful shielding. Since the majority of testicular cancer patients are in the age group of maximum sexual activity, this is a serious sequela.

In addition to damage and subsequent complications following radiation to bone cited above, Lewis (46) reported that of 85 cases seminoma testis, 10% had died of excessive radiation. Fourteen out of a series of 250 testicular cancers treated by over 2,000r had perforation of the stomach or bowel 18 to 24 months later. In concluding their report Spitz and Higinbotham stated: "The fact remains plain that prophylactic roentgen-ray therapy, directly or indirectly, was the cause of death in a number of cases of seminoma testis. Since seminoma is a radiosensitive tumor and since radiation complications, including osteogenic sarcoma, arise mainly in heavily irradiated tissues, it is suggested that prophylactic roentgen-ray therapy, if used at all in such cases, be limited to dosage levels that will not jeopardize the integrity of normal tissues within its beam." (71)

In recent years, a number of investigators have demonstrated that certain bacterial endotoxins afford significant protection against the lethal or deleterious effects of subsequent heavy radiation. (1, 11, 39, 70) None of the cases of testicular cancer which were successfully treated by both toxins and irradiation and were traced for long periods (up to 40 years) have developed any of the deleterious radiation effects described above. Cases treated by toxin therapy have no disturbance of sexual function. (The wife of one patient, Series A, case 7, conceived their first child during the first month of toxin therapy.)

Factors Affecting Prognosis in Toxin Therapy of Testicular Cancer:

The stage of the disease when toxins are begun, the type of toxin used, the technic of administration as regards site, dosage, frequency and duration of the injections, appear to be the most important factors influencing prognosis. Another is the most judicious timing of various combinations of treatment. For example, toxins are more effective if begun before or immediately after orchiectomy than if begun weeks or months later. Also, any treatment such as heavy radiation or cytotoxic chemotherapeutic agents, which is given prior to toxin therapy and which depresses or destroys the reticuloendothelial and lymphoid tissues, may limit the effectiveness of subsequent toxin therapy. As one would expect, a much higher percentage of permanent results may be obtained in the operable than in the more advanced cases.

Coley recognized the importance of beginning the injections in the earlier stages of the disease and in his first paper on testicular cancer he suggested administering toxins for two or three months post-operatively as a prophylactic to prevent recurrence. (13)

The type of toxin used and the technic of administration were of special significance in the first decade after Coley introduced the method (1893-1903). Nine different preparations of Coley toxins were available in that period, none of which was consistently potent, all being particularly weak and variable except for Buxton VI. (58, 59). It was not recognized that unless a technic was used that was sufficiently aggressive to compensate for the weakness of these products, it was not possible to produce permanent results in inoperable and advanced cases. (58) Two physicians did produce permanent results in inoperable cases in this period: Mabon (18, case VI, p. 58) and Robinson (18, case I, p. 57). In both cases injections were made in or near the recurrent or metastatic lesion, using the Buxton VI preparation and marked reactions were elicited. The growths disappeared and the patients remained free from further evidence of disease when last traced 15 years later. (18, 23)

The highest percentage as well as the largest number of successful results in various types of cancer treated by toxin therapy occurred between 1906 and 1916 in cases treated by the Tracy XI preparation. (58, 59) None of the cases of operable scrotal testicular cancer treated by this product following orchiectomy are known to have died of the disease. One was traced three years, the remainder from 8 to 57 years.

The results in the inoperable case treated by Robbins (18) in 1909, (see Series B, case 19) and the operable cases of Cohn, Kretschmer, Ochsner and Coley, after 1921, which all received the weaker commercial product (Parke Davis XIII), indicate that when an effective technic was used for a less potent preparation (higher dosage, more frequent or prolonged administration) permanent results could also be achieved with these weaker preparations.

Although Coley published six papers on testicular cancer from 1903 to 1923 (13, 15, 18, 19, 20, 21) in which he advocated the use of Coley toxins for these tumors, only 24 other surgeons appear to have used the method in testicular cancer. Nine administered toxins after surgery as a prophylactic against recurrence: Lukens, Porter, Lilienthal, Brickner, Kimball, Brennecke, Ochsner, Kretschmer and Cohn. Of these ten operable cases so treated by other surgeons, nine were traced well 7 to 42 years.

Inoperable or terminal cases were treated by Mabon, Nicholson, Robinson, Schoonover, Hertel (two cases), Shields, Lee, Grant, Taulbee, Swartzlander, Robbins, Cohn, Townsend, Foster, Root, Harmer and Coley.

Coley achieved only one permanently successful result in inoperable testicular cancer (Series B, case 5), while eight other surgeons produced apparent cures in inoperable cases, traced 21½ to 20 years later. Analysis of these cases indicates that Coley did not administer toxin therapy sufficiently

aggressively as regards site, dosage, frequency and duration in his unsuccessful cases. One terminal case of testicular cancer was successfully treated by another surgeon, none by Coley.

Seven surgeons published their results in some detail: Nicholson of St. Louis (61), Hertel of Copenhagen, Denmark (37), Shields of Cincinnati (69), Brickner of New York (6), Robbins of Detroit (68), Grant of Denver (33) and Cohn of New Orleans (10). Both Cohn's operable cases are alive and well in 1968, 40 and 43 years after onset.

As regards the effects of other forms of treatment given prior to toxin therapy, it was found that all the inoperable or terminal cases in which heavy or prolonged radiation was administered had died of cancer. Three of the operable cases also received one or two radium pack treatments and one received x-ray during toxin therapy. This irradiation was apparently well tolerated, possibly due to the protective effects of concurrent toxins. All four survived and were traced from 36 to 45 years later.

The detailed histories of all cases of testicular cancer which received toxin therapy were abstracted from the literature, Coley's records, hospital records or through personal communications with the patients, their physicians or relatives. A total of 81 cases of testicular cancer were treated by toxins, of which 21 inoperable or terminal cases were indeterminate (no microscopic confirmation of diagnosis, no detail as to treatment or no follow up) and were therefore excluded.

In the remaining 60 cases, the diagnosis was confirmed by microscopic examination by such pathologists as Drs. William H. Welch, Mandlebaum, Ewing, Broders and Clarence Cohn. Wherever possible, sections have been reviewed during the course of this study. The cases were grouped according to the stage of the disease when toxins were begun, the type of toxin used and chronologically according to the type of toxin used. There were 20 operable, 24 inoperable and 16 terminal cases. The immediate and final results are given below.

It is hoped that these data will encourage modern surgeons to utilize microbial products such as bacterial toxins of various types or fungal extracts (zymosan or hydroglucan) to stimulate the resistance of patients with testicular cancer and thus potentiate the response to surgery and radiation, enabling smaller dosage to be used and thus protecting the patient against deleterious sequelae of radiation which have occurred in the past. It should thus be possible to salvage a larger percentage of cases than has been possible in the past by surgery and/or radiation alone.

SERIES A, BRIEF ABSTRACTS: OPERABLE TESTICULAR CANCER
TREATED BY TOXIN THERAPY COMBINED WITH SURGERY: 17
SUCCESSSES, 3 FAILURES

Diagnosis was confirmed by microscopic examination in all 20 cases. Three other operable cases are known to have received Coley toxins after operation, but were excluded from statistics due to lack of detail; Robinson's (1901) had no follow up at all; Shields' (1910) had no microscopic confirmation of diagnosis although traced well three years after operation; Oliver's (1911) also is not definitely known to have had histologic confirmation. The following 20 operable cases are therefore an unselected series. It will be noted that failures occurred only when the toxins were given inadequately as regards site, dosage, frequency and duration of treatment. (Cases 2, 3, 16). Antecedent local trauma occurred prior to onset in 50% of these 20 cases. (Cases 2, 4, 6, 7, 8, 12, 13, 14, 19, 20). Radiation was also given in five cases. (Cases 14, 16, 18, 19, 20).

*Years Traced
After Onset*

THE FIRST FOUR CASES RECEIVED THE BUXTON VI MIXED UNFILTERED PREPARATION

1. (W.B. COLEY): G.J., age 27; teratoma rt. testis, rapid growth; onset April 1900; diseased testis size orange removed December 12, 1900; 2 days later toxins begun, probably given 2-3 mos.; no recurrence, alive and well 1903. (12, 18, 57). 3
2. (W.B. COLEY): G.W.M., age 42; recurrent teratoma lt. testis; onset 3 mos. after injury; October 8, 1903 1st operation, left orchiectomy; recurrence involving spermatic cord; February 5, 1904, 2nd operation; February 15, 1904, 13 injections toxins, no marked reactions; disease not controlled, death March 12, 1904. (18, 25) Died
3. (W.B. COLEY): I.N.R., age 35; teratoma rt. ectopic testis; onset February 1903; surgical removal July 24, 1904; toxins not begun until 6 wks. after operation, small doses, no reactions; recurrence; death within a year. (18, 25). Died
4. (W.B. COLEY & LUKENS): W.M.H., age 26; March 27, 1906; "large round cell sarcoma" rt. testis; rt. orchiectomy about 6 mos. after onset; toxins begun 4 wks. postoperatively, given several mos; no recurrence or metastases; in good health 25 yrs., then had gastric ulcers; died heart condition and Bright's disease, February 13, 1943. (18, 21, 60). 37½

THE FOLLOWING CASES RECEIVED TRACY XI MIXED UNFILTERED PREPARATION

5. (PORTER): E.L.F., age 42, December 10, 1907; cancer rt. testis; rt. orchiectomy 3 mos. after onset; toxins begun 3 wks. after operation, continued under Coley's direction, well 14 years.; then developed cancer in other testis; end-result unknown. (18, 21 p. 373). 14

6. (LILIENTHAL): G. P., age 51, December 5, 1908; cancer lt. ectopic testis (inguinosuperficial type) size closed fist, of rapid growth; toxins begun 2-3 days after operation, given 3-4 mos.; well and free from recurrence until 1915, acute appendicitis, death following appendectomy, no evidence malignancy. (18, 21, 60). 7
7. (W. B. COLEY): J.P.N.L., age 24; adenocarcinoma, Grade II, lt. testis; November 7, 1910 lt. orchiectomy at Mayo Clinic 11 wks. after onset; referred to Coley for toxins soon after operation; 26 doses in 2-3 mos.; no recurrence or metastases; had 3 children after treatment (oldest conceived during toxin therapy); alive and well 1968 except for severe arteriosclerotic heart disease (see detailed history below). (18, 21, 60) 58
8. (W.B. COLEY): T.H.M., age 28; malignant teratoma consisting of Grade IV carcinoma lt. testis; onset July 1910; 5 mos. later left orchiectomy at Mayo Clinic; referred to Coley for toxins immediately; begun December 1910, continued for nearly 12 mos. by family physician, febrile reactions to 104°F. maximum dose 42 minims; no recurrence; remained well until death following wk.'s illness (influenza) 1918. (18, 21, 55, 60). 8
9. (W.B. COLEY): Age 17, large cancer testis; diseased testis removed; toxins given postoperatively, summer 1911; no recurrence; alive and well 1923. (21, p. 385). 12
10. (W.B. COLEY): Adult; cancer testis; onset early October 1911; diseased testis removed at Mayo Clinic February 6, 1912; February 15, 1912, toxins given under Coley's direction postoperatively; no recurrence, last traced well and free from disease December 1914. (18, case 16). 3
11. (BRICKNER): C., age 40; "perithelial sarcoma, chiefly large round cells, pronounced evidence of malignancy"; onset March 1912; diseased testis removed April 26, 1912; toxins begun 4 days later, 20 doses in 7 wks., no recurrence, alive and well 1923. (6, 21, p. 385). 11
12. (KIMBALL): R.M.M., age 32; small round cell sarcoma; surgical removal 3 mos. after onset; toxins begun November 2, 1912 shortly after operation, continued several mos., some marked reactions; no recurrence, alive and well 1923. (18, 21, 23). 11½
13. (W.B. COLEY): R.H., age 20 mos.; twice recurrent embryonal carcinoma lt. testis, with transition to pseudo-sarcomatous structure, was Ewing's original diagnosis; he revised it in 1923 to "sarcoma of the round and spindle cell type"; growth size 2 fists removed by Coley at 3rd operation October 19, 1917; toxins begun next day, given 6 mos.; later small nodules again developed; excised, toxins resumed, given 18 mos.; no further recurrence; alive and well 1967 (see below for detailed history; 20, 21, 22, 23, 60). 50
14. (W.B. COLEY): P.L.G., age 24; embryonal carcinoma lt. testis; November 2, 1917, lt. orchiectomy, about 3 mos. after onset; February 12, 1918 toxins begun; given with intervals of rest for 17 mos.; also 2 radium packs; no recurrence; no illness of any consequence in next 36 yrs.; alive and well 1954, living in South Africa; lost to follow up thereafter. (21, 22, 60). 37

THE FOLLOWING 6 CASES RECEIVED THE COMMERCIAL PREPARATIONS (PARKE DAVIS XII AND XIII.

*Years Traced
After Onset*

15. (W.B. COLEY): D.E.B., age 27; lt. ectopic testis; (patient had had pulmonary tuberculosis 10 yrs. before, treated and cleared up in 3 yrs.); June 11, 1908, operation by Dr. John Murphy (Chicago) 10 days after onset abdominal pain; tumor size orange removed from lt. inguinal region; toxins begun by Coley 4 wks. later, given intermittently for 6 mos.; pulmonary tuberculosis reactivated (after being quiescent 7 yrs.) returned to Wyoming; well 2 yrs.; died March 1912 "pulmonary disease"; no autopsy. (21, 57). 31½
16. (BRENNECKE & W.B. COLEY): P.H.C., age 48; recurrent malignant teratoma rt. testis; April 5, 1921, rt. orchiectomy; soon after operation toxins intramuscularly in abdominal wall; small doses, little or no reactions; diffuse cellulitis, marked edema leg, thigh; condition improved temporarily, radium pack, x-ray therapy tried, no further improvement; death July 25, 1922. (23, 57, 60). Died
17. (OCHSNER): G.C., age 27; "mixed cell sarcoma" rt. testis; rt. orchiectomy May 28, 1924; June 16, 1924 toxins given twice a wk. for 13 mos., then once a mo. for 2 more yrs.; no recurrence; alive and in excellent health 1938. (60). 14
18. (COHN): J.B., age 28, June 1925; seminoma lt. testis; lt. orchiectomy; one radium pack; toxins for 2 yrs. (only once a week after 1st few mos.); no recurrence; alive and physically well (though hospitalized for mental disease since 1948) in 1968. (10, 23, 60). 43
19. (KRETSCHMER): L.W., age 32, surgeon; sarcoma rt. testis; rt. orchiectomy February 20, 1925, less than 2 mos. after onset; toxins begun about March 15, 1925; given i.m. by family physician concurrently with x-ray therapy to groins, back, abdomen (3000 to 3500 r); no recurrence or metastases, married, no children; still working daily 1968 at age 75. (23; 60). 43
20. (COHN): A.R., age 33; June 8, 1928; embryonal carcinoma rt. testis; rt. orchiectomy early in June 1928, one radium pack June 7, 1928; toxins June 8, 1928 every 48 hrs. for 3 mos.; no recurrence; alive and well 1968. (10, 23, 60). 40

SERIES A, OPERABLE, DETAILED HISTORIES

THE FOLLOWING TWO DETAILED HISTORIES, SELECTED AS REPRESENTATIVE OF THE OPERABLE SERIES, ARE GIVEN BELOW.

CASE 7: Adenocarcinoma, (grade II) of the left testis (not a seminoma nor apparently a teratoma), confirmed by microscopic examination by Dr. A. C. Broders, Pathologist at the Mayo Clinic, who reviewed the sections in 1944. The original diagnosis at the Mayo Clinic in 1910 was sarcoma of the testis. (21, Table I, case 6).

Previous History: J.P.N.L., male, age 24, of Yankton, South Dakota. The family and previous personal history were essentially negative. The patient was a farmer and had been in good health prior to onset. He was married on August 30, 1910. About August 23, 1910, ten weeks prior to his admission to the Mayo Clinic he bruised the left testicle on the seat of some agricultural machinery. There was some pain following this injury, which gradually increased in severity. The testis became swollen and very tender. The patient was admitted

to the Mayo Clinic on November 1, 1910. At this time the tumor measured about 14 by 10 cm.

Surgery: The left testis was removed by Beckman on November 7, 1910, and the patient was then referred to Dr. Wm. B. Coley for toxin therapy.

Toxin Therapy (Tracy XI) Injections of Coley toxins were begun soon after this operation, in the latter part of November 1910. They were continued after the patient's return home by the family physician, Dr. Embree, under Coley's direction, a total of 26 being given in a period of about three months.

Clinical Course: The patient made a complete recovery and remained in good health. There was never any recurrence. It is of interest to note that toxin therapy had no effect on the function of the other testis as the patient's wife had three children, the first conceived in January 1911, only a month after the toxins were begun. The second was born in 1913, the third in 1920, all healthy children. The patient reported in November 1950 that his health has been very good since 1910, and that he then weighed 200 pounds, his height being six feet one inch. He had a slight accident in September 1951, in which half of the distal joint of the left thumb was amputated. About 1960 he developed severe arteriosclerotic heart disease with intractable failure and persistent peripheral edema (2 plus often 4 plus). He had a mild myocardial infarction in December 1965. Gynecomastia was also evident. His physician advised him to lose weight because of his heart condition and his weight declined to 185 pounds upon dieting. In October 1967 he developed a pulmonary abscess attributed to pneumonia from which he recovered. He was last traced free from any evidence of his testicular cancer in April 1968, at the age of 82, over 57½ years after onset. (18, 21, 56.).

CASE 13: Twice recurrent embryonal carcinoma of the testis, with transition to pseudo-sarcomatous structure was Dr. James Ewing's pathologic diagnosis in 1917. He stated: "The specimen is a round solid soft tumor mass, 7 by 8 cm.; it fungates through the skin over an area 4 cm. wide . . . On section the tumor is smooth, translucent, hemorrhagic along the fungating edge. It is circumscribed by an indistinct capsule. No portions of the testis are visible in the single gross section. On microscopic examination the structure is composed of large and small groups of large polyhedral and spindle cells of indifferently embryonal type, consisting chiefly of hyperchromatic nuclei. These cell groups gave off into an abundant mucinous tissue of myxomatous type and every gradation from polyhedral to star-shaped cells may be followed. Some cell clusters surround blood vessels, which are not numerous. There are scanty small points of necrosis." (For microphoto see 20, Fig. 2, or 21, Fig. 1). In 1923 Dr. Ewing reviewed this case and stated that his diagnosis of "embryonal carcinoma" was an error and he regarded it as one of the very few cases of malignant disease of the testis in which he would make a diagnosis of sarcoma of the spindle and round cell type. (23, Fig. 1).

Previous History: R.H., male, age 20 months. The family history was negative for cancer or tuberculosis. The patient was born at full term, and was breast fed for about three months. He was perfectly well until onset in May 1917, when his mother first noticed a swelling of the left testis, at the site of a slight injury sustained by striking it against the side of the baby carriage a few months before. The swelling increased very rapidly and at the end of three weeks had reached the size of an orange. The skin was of purplish hue and covered with many veins.

Surgery: Three weeks later the testis was removed by Dr. Murphy and the wound closed. The pathologist report was "non-malignant." At the end of three weeks a local recurrence developed which grew with great rapidity, until in a few weeks it had reached the size of the primary growth. A second but ineffectual attempt was made to remove the recurrence.

Clinical Course: This was followed almost immediately by a second recurrence which grew with great rapidity and became fungating over the distal portion. No enlarged nodes were observed. The patient was referred to Dr. William B. Coley and admitted to Memorial Hospital on October 19, 1917. Physical examination at this time showed a large elliptical tumor about the size of two fists, occupying the entire left scrotum, the distal portion being greater in circumference than the proximal. The distal end was covered by a fungating mass with an extremely foul discharge. The mass was freely movable and did not extend up into the inguinal region. The cord was apparently not involved.

Further Surgery: The third operation was performed by Coley on October 19, 1917, under ether anaesthesia. He removed the entire tumor as far as the external ring. The cord was not enlarged and apparently was not involved. Enough healthy skin from the other side of the scrotum was found to close the wound. (For a photograph of the condition just prior to this operation see 20, Fig. 1).

Toxin Therapy: Injections were begun the day after this operation, on October 20, 1917, the initial dose being 1/10 minim, increasing daily by 1/8 minim to the point of producing a febrile reaction of 103°-104°F., with chills some of which lasted an hour. All the injections were made intramuscularly in the buttocks. During the first four months Tracy XI (unfiltered) product was used; after February 10, 1918 Tracy XI-F (filtrate) was used. The wound healed promptly, with the exception of the site of the drainage tubes. At the end of a month the child returned home where the injections were continued by the family physician, being given daily at first then every other day. Coley suggested that the treatment be kept up for a considerable period, but the child felt so well at the end of six months that the injections were discontinued.

Clinical Course: About 18 months later another nodule the size of a pea appeared in the region of the scar. This was removed and examined by Ewing, who reported that it was of the same structure as the one removed by Coley at the third operation.

Second Course of Toxin Therapy: Injections were then resumed and were kept up for about 18 months, at first every other day and later once a week. (60).

Clinical Course: There was no further recurrence. The boy's health was unusually good all during his childhood and adolescence. His mother reported that in 1924 the two other children had scarlet fever and were very ill for three weeks, but Robert had such a light case that he did not even go to bed. His mother added: "He never had any sickness take him very hard, where the other children would have scarlet fever, measles, etc. they would be very sick, and he would only have the same disease very mildly." (60).

The patient remained in excellent health and "never had to consult a physician," for about 40 years. His weight gradually increased to 205 pounds, his height being 5 feet, 11 inches. His father died in 1935 and the patient supported his mother and a sister thereafter. He was a metal worker. His mother died in 1964 at 82. The patient married at the age of 48 in 1963. In 1961 he developed slight cardiac symptoms when shoveling snow. An electrocardiogram in 1964 showed extensive damage. He was hospitalized for 3½ weeks. He remained under care for arteriosclerotic heart disease. He was put on a low calorie

diet and reduced to 195 pounds. He had anginal syndrome but remained ambulatory working full time. In September 1967 he felt fine. This was over 50 years after onset of the testicular cancer.

COMMENT: In regard to this case Coley stated in 1932: "The method of treatment employed in this case is one that I have used for many years and I believe it has given a larger number of five-year recoveries than any other method: i.e. immediate surgical removal of the testis and cord as soon as the diagnosis was made. The operation was immediately supplemented by prolonged prophylactic treatment with the toxins of erysipelas and *Bacillus prodigiosus* injected into the buttocks. This treatment was kept up by the family physician for a period of from three to six months. The initial dose of 0.5 minim was increased daily by 0.5 to 1 minim up to the point of producing a marked reaction (102°-103°F.). After this was obtained, an injection was given every other day, then one every three days and then once a week." (22) It is of interest to note that none of the 20 or more patients treated by orchiectomy and toxin therapy, appeared to have had any functional disturbance of the remaining testis, i.e. they married and they had normal, healthy children. Note the above patient's markedly increased resistance to infectious diseases of childhood. This may have been induced by the prolonged toxin therapy. (20, 21, 23, 57, 60).

5. (Coley): E.O.T., male, age 46; recurrent round cell sarcoma testis, enlargement iliac nodes, orchiectomy February 1906, 2½ mos. after onset; recurrence and node involvement evident in 4 wks; toxins (3 a week for 7 mos.), fairly good febrile reactions; recurrence and node involvement regressed, complete recovery, traced well 1914. (22; 35)

8

SERIES B: INOPERABLE TESTICULAR CANCER SUCCESSFULLY TREATED BY TOXIN THERAPY: 9 SUCCESSES

THE FIRST FIVE PATIENTS RECEIVED BUXTON VI PREPARATION OF COLEY TOXINS.

	Years Traced After Onset
1. (MABON): Adult, sarcoma testis; surgical removal 1890; metastases to tongue 4 yrs. later; further surgery refused; August 1894: injections toxins into tumor following biopsy (examined by W.H. Welch); severe reactions produced, <i>metastatic growth disappeared comparatively rapidly; no further evidence of disease</i> ; alive and well 1910, 20 yrs. after onset. (17, 18, 22, 23).	20
2. (NICHOLSON): E.P.L., age 54; recurrent inoperable spindle cell sarcoma testis; primary growth removed surgically, recurrence untreated; March 31, 1897, toxins given every other day, good febrile reactions, chills, <i>complete regression; well and free from disease</i> July 1899; not traced subsequently. (61).	2½
3. (ROBINSON): D.R., age 44; round cell sarcoma rt. testis, recurrent in lt. testis after rt. orchiectomy; another operation strongly advised but patient refused castration; 1898: toxins aggressively administered, mostly into scrotum; <i>complete regression, no further recurrence</i> ; well and free from disease 1913. (14, 17, 18, 21, 23).	16
4. (MATAGNE): Age about 60; round cell sarcoma rt. testis, inguinal node metastases; 1st operation: rt. orchiectomy and excision of involved nodes in rt. inguinal region; January 1902: toxins for 1 mo.; did not prevent recurrence in 3 mos.; toxins resumed, given another mo.; 2nd operation: lt. orchiectomy and excision of further lymph node metastases, histologically of extremely rapid growth; <i>no further evidence recurrence or metastases, in excellent health many years later</i> . (53, 54).	5 or more

THE NEXT THREE CASES RECEIVED TRACY XI OR XIF PREPARATION OF COLEY TOXINS.

6. (HERTEL): Age 29, castration, 1904; inguinal node metastases a yr. later; involved nodes removed at 2nd operation; 2 yrs. later another extensive recurrence of lymph node metastases; Lennander's operation performed; infiltrating nodes extending upwards along iliac vessels; incomplete removal; January 1908: toxins given 2½ mos.; <i>remaining neoplastic tissue entirely disappeared; no further metastases</i> ; alive and well 1918, 14 yrs. after onset. (16, 18, 21, 23, 37).	14
7. (SHIELDS): Adult; recurrent cancer testis; primary growth removed; recurrence May 1911; toxins given for recurrence; " <i>absolutely positive clinical cure</i> "; no further recurrence May 1914, over 3 yrs. after onset. (18, 69).	3

13

8. (TAULBEE): Age 35; primary cancer testis removed February 1910; well 2½ yrs.; abdominal metastases, then supraclavicular node metastases; both masses increased rapidly in size; seen at Mayo Clinic, family physician told prognosis was grave, only hope being toxin therapy; May 24, 1914: toxins given steadily 1 yr.; *steady improvement, complete disappearance both metastatic masses; no further evidence of disease*; died suddenly myocarditis, September 25, 1916. (23, 25, 56, 60). 6½

THE FOLLOWING CASE RECEIVED THE COMMERCIAL PRODUCT, PARKE DAVIS XII

9. (ROBBINS): Male, age 55; large tumor rt. testis removed January 7, 1909; very rapid local recurrence; 2nd operation January 22, 1909; 2nd recurrence soon apparent; further surgery deemed inadvisable; February 1, 1909: toxins given in or near growth for 3 mos.; *very rapid complete regression; no further recurrence or metastases*; alive and well June, 1914 See complete history below for interesting detail as to histology and response to treatment. (18, 21, 23, 60, 68). 5

Note: In none of the above cases was there any mention of antecedent local trauma. The diagnosis was confirmed by microscopic examination in each case.

SERIES B, INOPERABLE SUCCESSES, DETAILED HISTORIES

DETAILED HISTORIES OF THE FOLLOWING THREE CASES IN SERIES B, INOPERABLE SUCCESSES ARE GIVEN HERE:

CASE 4: Round cell sarcoma of the right testis, with metastases to the left groin and recurrence in the left testis. The recurrence and metastases were of extremely rapid growth, the pathologist reported.

Previous History: V., male, age 60, of Brussels, Belgium. The family and early personal history are not recorded.

Surgery: The patient had two operations by Dr. Van Engelen, Chief of Service at the Hôpital St. Pierre in Brussels. The right testis was removed and several metastatic lymph nodes were excised from the groin.

Toxin Therapy (Buxton VI formula made by Matagne himself): Beginning in January 1902 injections were given for one month by Dr. J.H.J. Matagne, following the second operation, in order to prevent further metastases. The details of technic were not recorded in this case, but elsewhere Matagne stated that if a tumor was not accessible (or not present — i.e., after operation) he made subcutaneous injections, and that these required much larger doses than intratumoral injections. The first injection usually induced an erysipela-tous-like plaque which disappeared in a couple of days. For subcutaneous injections he began with a dose of 10 cg., which was rapidly increased to 15 and 20 cg. or more, so as to produce febrile reactions of 38°C. or more. He noted that febrile reactions were less common and less marked with the subcutaneous injections than when intratumoral injections were given.

Clinical Course: Three months later the patient had a recurrence in the left testis.

Further Toxin Therapy: Injections were resumed at once, in late May 1902, and were given for another month.

Further Surgery: The left testis was removed on June 27, 1902, together with further lymph node metastases in the groin. These were examined microscopically.

Clinical Course: The patient was presented before the Société Médico-Chirurgicale du Brabant early in 1905, with no evidence of further recurrence or abdominal metastases, in excellent general health. This was over three years after onset. In 1953 Matagne cited this case stating he had been traced well "many years." (55)

COMMENT: Matagne reiterated that the results with toxin therapy are less satisfactory when they are given postoperatively than when they are given before operation, citing, the above case and a case of mammary cancer (54). However, he said that two other cases in which the toxins were given following operation had remained free from recurrence, an osteosarcoma of the knee, and a sarcoma of the axilla.

It is of interest to note that in all the cases treated prior to operation, Matagne made intratumoral injections and caused marked febrile reactions and chills, while in patients given postoperative therapy the subcutaneous route was used, which elicited much less marked or regular reactions.

Matagne continued to use these toxins and in 1913 he wrote Coley that for the previous 18 years he had consistently used them prior to operation, and that this procedure had given him a "percentage of cures much higher than ordinary surgical treatment alone." (23) He appears to have been the only surgeon here or abroad to have advocated *pre-operative* treatment as a routine method. (54, 55).

CASE 5: Recurrent round cell sarcoma of the testis of extreme malignancy with enlargement of the deep iliac nodes, confirmed by microscopic examination.

Previous History: E.O.T., male, age 46. There was no family or previous personal history of tuberculosis or venereal disease. In December 1905 the patient developed a tumor of the testis, which increased rapidly in size.

Surgery: Orchiectomy was performed on February 25, 1906, about 2½ months after onset. Dr. William B. Coley was first consulted on March 23, 1906, at which time there was a small lump the size of a hazel nut in the groin, with enlargement of the deep iliac lymph nodes.

Toxin Therapy (Buxton VI): Injections were begun at once and were continued three times a week for seven months, fairly good febrile reactions being obtained. The recurrent tumors disappeared and the patient made a complete recovery.

Clinical Course: He was examined periodically by Coley until May 1914, eight years after treatment, at which time he remained well and free from further recurrence or metastases. (22, 35).

CASE 6: Twice-recurrent inoperable sarcoma of the testis, with metastases to the iliac and retroperitoneal lymph nodes confirmed by microscopic examination.

Previous History: Male, age 29. The family and early history were not recorded.

Surgery: Castration was performed in 1904 for sarcoma of the testis. A year later metastases were observed in the inguinal lymph nodes, which were removed. Two years later there was another extensive recurrence in the same

region. Lennander's operation was performed, which revealed infiltrated nodes extending upwards along the iliac vessels. These could not all be removed surgically. The expected femoral thrombosis did not occur.

Toxin Therapy (Tracy XI): In the hope of destroying the neoplastic tissue which was left behind, Hertel, of Copenhagen, Denmark, began injections of the toxins in January 1908, following this third operation. He gave doses of from 3 to 20 cgm. The wound healed within a month after the operation, and on March 20, 1908 the patient was discharged well, the involvement having entirely disappeared.

Clinical Course: He was presented before the Koege Medical Society in November 1908, without evidence of disease. He remained well and free from further recurrence when last traced ten years after treatment.

COMMENT: Hertel reported another case of inoperable recurrent tumor of the testis treated by the toxins and he stated that he considered the outcome highly encouraging for the use of this method and that he would feel obliged to use the toxins in all cases which came under his care. In commenting on Hertel's experience with toxin therapy, Coley stated in 1923: "If results like these, not only in my own series of cases but confirmed by other observers, can be obtained by the use of the toxins, it would seem more rational and logical to advise a thorough course of toxin treatment as a prophylactic immediately after operation (i.e. orchiectomy) rather than subjecting all cases to the grave operation of extensive dissection of the abdominal glands." (16, 18, 21, 23, 37).

CASE 9: Twice recurrent inoperable sarcoma of the testis, confirmed by microscopic examination after the operation on January 7, 1909 by Dr. Carl S. Oakman and one other pathologist. For detailed report see below.

Previous History: Male, age 55. The patient's wife had tuberculosis and two sons died of it. The patient's general health had been good. For 20 years he had noted an enlargement of the right testis. Whether this was due to hydrocele or not was unknown. About a year prior to consulting Dr. Frederick W. Robbins of Detroit, the tunica vaginalis was tapped and a large quantity of serum was withdrawn, leaving an infiltration in the testis or epididymis. Several times thereafter tapping was resorted to by Dr. Stanley G. Miner, the last time a few weeks before being referred to Robbins, when bloody fluid was obtained. Thereafter a very rapid increase in the size of the testis was noted. At examination, January 6, 1909, a smooth oval tumor was found in the right scrotal sac, 20 cm. long, from which a much thickened cord passed through the inguinal canal. The upper portion of the tumor seemed hard, the lower third elastic. A provisional diagnosis of sarcoma was made and immediate operation advised.

Concurrent Infection: At this time the temperature was 100°F. and the pulse 96, indicating probably septic absorption.

Surgery: On January 7, 1909, Robbins operated, removing the testis and cord high up in the ring. At the bottom of the sac there was an ounce of clear serum and a testis which on section looked quite normal, but the main body of the tumor seemed to have its origin and growth in the head of the epididymis. It was firm outside with about half an ounce of dirty necrotic fluid in the center. The pathologist reported: "Marked hyperplasia of muscular coats with plentiful round-cell infiltration, not malignant." The next day the temperature was 100.6°F and on January 11, it was 99.8°F. There was fullness in the region of the cord which Robbins thought was probably due to infection. An ice bag was applied. On January 14, 1909, he "worked a director down into the scrotum

which, while healing nicely on the surface, was not right." The temperature had gone down to normal, and Robbins considered that the condition might be due to a hematoma, but only a few drops of bloody fluid were evacuated.

On January 20, McGraw saw the patient in consultation. Robbins reported: "We felt that we had to deal with a very malignant neoplasm which, now only 13 days after the first operation, had developed a firm growth as large as one's fist, seemingly three large masses fused together, one growing from the stump of the cord and two masses from the side of the cleaned-out scrotal sac." On January 22, 1909 Robbins again operated, in the presence of Miner, at St. Mary's Hospital, removing the scrotal skin on the right side, freeing the cord well up within the abdominal ring and keeping well without the new growth. The pathologist reported: "Greater part of section shows a degenerative process. Small areas of large round sarcomatous cells are not infrequent. Vessel walls are malformed and thickened." The specimens were also submitted to Dr. Carl Oakman who reported: "There is very little tissue characteristic of testis in any part of specimen: a few sections show some faintly stained seminiferous tubules, but they are ill defined, atrophic and in the midst of necrotic tissue; the larger part of the specimen shows a diffuse growth, of mesoblastic type, very irregular in its disposition; the cellular elements are fusiform, and fibrillary or branching, with considerable intercellular matrix, giving it a myxomatous character. Several degenerating areas show pronounced mucoid deposit, staining deeply with hematoxylin. There are many aggregations of small round cells, especially around the blood vessels. The vascularity is not marked, and much of the blood supply is primitive in character. There are many areas of hemorrhage in all stages of retrogressive change. Occasional bundles of smooth muscle are seen, mostly rather hyaline in appearance. There is widespread necrosis, in all stages, as a result of pressure of deficient vascularity. The tumor appears to be of the myxosarcomatous variety." The report on the recurrent metastatic tumor in the groin was as follows: "The most conspicuous feature of the material is hemorrhagic and fibrinous exudate in various stages of degeneration. The small portions which show recognizable tissue consist of closely packed thin fusiform cells, arranged in interlacing bundles; these in some places resemble smooth muscle, and in others connective tissue; there is widespread necrosis and hyaline change, and poor blood supply, with numerous areas of pigmentation, evidently hematogenous. The excised portion includes a little striated muscle, which shows hyaline change and round cell infiltration. In the fleshier parts of the mass there are masses of round cells which appear sarcomatous in nature." The patient did well, the temperature remained normal, but on the fifth day there was an undoubted recurrence within the scrotum and canal. Robbins reported: "You could see the increase in size every day."

Toxin Therapy (Parke Davis XII): Believing that further surgical procedures would offer no hope of controlling the disease, Robbins began the injections of Coley's toxins on January 23, 1909. The initial dose was 0.25 minim injected near the swelling, which caused a slight febrile reaction six hours later (100°F.). Injections were continued daily in the vicinity of the growth, increasing the dose gradually to a maximum of 5 minims (while in the hospital). The first marked reaction occurred after the third dose (103.6°F.) and a chill lasting 24 minutes. The second marked reaction occurred on February 7, 1909 after a dose of 4 minims: (104°F., pulse 118, chill lasting 45 minutes). Robbins reported at this time: "For the last four days there has certainly been no increase in tumor growth and there is a well-marked feeling on the part of all observers that perhaps the growth is beginning to disappear." On February 11, a dose of 4 minims was injected into the tumor, causing a febrile reaction of 102°F. The next day the same intratumoral dose caused a reaction of 103.6°F. Robbins reported: "The patient gradually improved and left the hospital February 17.

At that time improvement was marked. The case was a spectacular one. The rapid growth of the tumor was so unusual and the melting away of the growth so marked that some of those watching the progress of the case were willing to doubt its malignancy. However, the final report of the pathologist, Dr. Carl Oakman, to whom the specimens were submitted, seemed to show conclusively that we have treated a case of sarcoma with the Coley fluid and that at the present writing the patient is perfectly well." The injections were continued after the patient left the hospital twice a week through April, a total duration of three months (about 42 injections). On April 5, 1909, Robbins reported to Dr. William B. Coley, and added: "He has gained 40 pounds, looks the picture of health and no sign of recurrence can be seen or felt. I have never seen so rapid a recurrence nor have we had here so marked an effect from the Coley fluid." He later stated that the regression was so rapid that "from day to day we were greatly astonished to see the tumor melting away."

Clinical Course: The patient remained well and free from recurrence in June 1914, over five years after treatment. Apparently Coley believed that this patient ultimately died of nephritis (18, p. 56-57). However, Robbins did not corroborate this when contacted in 1943 (60).

In discussing Hinman's paper on the radical surgical treatment of cancer of the testis, Robbins stated in 1914: "I wondered while I listened to Hinman's paper if he had entirely forgotten the work of Coley in connection with his toxins in these cases." (38) He then gave a brief outline of the case reported above and in conclusion stated: "We should not forget that there are such cases as I have had and as Coley has reported, which are wonderfully helped and probably cured by these injections." (18; 21; 23; 38, p. 2014-2015; 60; 68).

SERIES C: INOPERABLE TESTICULAR CANCER FAILURES: 17 CASES

THE FIRST THREE PATIENTS RECEIVED THE BUXTON VI PREPARATION

Period of Survival

1. (W. B. COLEY): C. M., age 28; rt. recurrent round cell sarcoma testis, onset 1 yr. after trauma; at 1st believed to be hydrocele; tapped without result; December 10, 1898; castration when tumor was $7\frac{1}{2}$ cm. in circumference; abdominal metastases apparent 4 mos. later; April 30, 1899: toxins in small doses, no chills or febrile reactions from 1st 15 doses, but abdominal growth decreased decidedly, general health improved; toxins continued intermittently for 6 mos.; shortly after injections were stopped growth increased, metastases to spine, death about 6 mos. later, over 2 yrs. after onset. (13, 18, 56). 2 yrs.
2. (W. B. COLEY): F. T. H., age 28; round cell sarcoma lt. testis; left orchiectomy 1 yr. after onset, well 2 yrs.; then "lumbago" due to metastases iliac region, severe pain, lt. leg greatly swollen for 7 mos.; July 16, 1900: 19 injections toxins in small doses in 1st 30 days little or no febrile reaction; marked improvement at first, later no effect; toxins given 5 mos.; death about 6 mos. after last injection, $5\frac{1}{2}$ yrs. after onset. (13, 18, 56). $5\frac{1}{2}$ yrs.
3. (W. B. COLEY): A. H., age 46; onset 1894, tumor of slow growth in rt. testis (12 yrs. duration); by 1903 testis was twice normal size and hard; developed lump in groin and nocturnal pain; operation June 4, 1904; testis and affected nodes removed; metastases 16 mos. later, entire rt. groin and abdomen involved; toxins for 12 days, no marked reactions; marked temporary improvement; 5 x-ray treatments also given; death March 31, 1907 about 9 mos. after last injection, 13 yrs. after onset. (18, 5, 60). 13 yrs.

THE NEXT SEVEN PATIENTS RECEIVED THE TRACY XI OR F PREPARATION

4. (SCHOONOVER): S. C., age 49; cancer left testis; left orchiectomy, July 1906; metastases in 2 mos. (groin, iliac, abdominal nodes); enormous swelling leg, thigh; edema decreased almost immediately after toxins were begun, almost disappeared in 11 mos.; about 200 doses toxins given in 15 mos.; disease later recurred; death July 1909, about 15 mos. after final injection, over 3 yrs. after onset. (18, 21). 3 yrs.
5. (HERTEL): Age 38, primary tumor of testis removed surgically; few mos. later extensive inoperable abdominal metastases present; 1908: toxins caused softening, fluctuation of nodules; patient weakened steadily, developed ileus, died; autopsy showed single retroperitoneal cyst; no trace of disease elsewhere. (11, 18, 37). over 1 yr.

6. (W. B. COLEY): S.S., age 48; large round cell sarcoma lt. testis; September 1909; lt. orchiectomy few mos. after onset; large retroperitoneal metastases lt. hypochondriac and lumbar regions, nodes in both groins also enlarged; marked weight loss, pain, general lassitude; February 1910; toxins given intramuscularly, gluteal region, continued 4 mos., 5-6 times wkly.; *steady, slow but complete regression metastatic growth size of fist*; further toxins in August (inguinal nodes were still enlarged); *no evidence disease September 1910*; as precaution against recurrence toxins resumed September 7, 1910—55 doses in buttocks in 107 days; *general health improved*; biopsy of inguinal node November 3, 1910, showed no evidence of malignancy; mo. after injections were stopped, pain, weakness, distension; large mass in lt. kidney region; toxins resumed January 23, 1911; 7 in 16 days, only moderate reactions; *tumor began to regress slowly*; patient was discharged from hospital February 10, 1911 for "disobeying rules"; *end result unknown: no death record found*. 1911-1946. (15, 16, 17, 56). unknown
7. (W. B. COLEY): W. E. G., age 32; cancer lt. testis; lt. orchiectomy July at Mayo Clinic, 6 mos after onset; 2-3 wks. later symptoms abdominal metastases apparent; mass size child's head; September 1916: toxins given briefly (no details), *little effect noted*; disease progressed rapidly, death 9 mos. after onset. (11, 16). 9 mos.
8. (W. B. COLEY): J. I. F., age 44; cancer rt. testis, rt. orchiectomy January 1911, 6 mos. after onset; laparotomy February 1913 (incomplete removal involved nodes); February 26, 1913: toxins intravenously small doses, mild reactions, *some slight temporary improvement*; disease progressed, death 3 yrs. after onset. (15, 56). 3 yrs.
9. (GRANT): L. W., age 37, onset April 1913; rt. ectopic testis; December 6, 1913, exploratory operation revealed enormous growth involving bladder, also metastatic enlargements at base of bladder, edema of lower extremities; prognosis regarded as about 90 days; 3 days later toxins begun; *little effect from 4 wks. of Parke Davis XII; marked decrease following use of Tracy XI; when dose or frequency was decreased, growth increased*; 14 x-ray treatments also given, causing fibrosis, hardening; remains of growth removed surgically; toxins continued by patient's wife; *complete recovery; gained 37 lbs., well 3 yrs.*; recurrence in gastrointestinal tract, causing obstruction; no further toxins, died over 5 yrs. after onset. (18, 23, 33, 75). 5 yrs.
10. (W. B. COLEY): D. M., age 19; recurrent embryonal carcinoma testis; onset followed severe trauma; December 20, 1916: diseased testis removal surgically in Detroit under local anesthesia; *some suppuration thereafter*; toxins begun 5 wks. after operation for retroperitoneal lymph node metastases (rt. axillary and cervical nodes also palpable); 18 small doses in 45 days intramuscularly; marked reactions; also 8 x-ray treatments begun during toxin therapy (severe radiation sickness at times); *no effect; except nodes slightly more movable at times*; death from inanition March 11, 1916, about 1 yr. after onset. (25, 56). 1 yr.
THE FOLLOWING SEVEN CASES RECEIVED THE COMMERCIAL PRODUCTS, PARKE DAVIS XII AND XIII.
11. (W. B. COLEY): S. C., age 38; cancer lt. testis; lt. orchiectomy July 1907, 13 mos. after onset; metastatic mass in abdomen 15 cm. in diam-

- eter; October 10, 1907: 30 injections toxins in 77 days intramuscularly remote from tumor area; reactions 101° to 104°F: *temporary improvement*; death 22 mos. after onset. (25, 56). 22 mos.
12. (HARMER): S. G., age 40; tumor involved lt. testis, epididymis, cord, infiltrating abdominal muscles; involved testis was 6-8 times normal size; September 9, 1910: incomplete removal 2-3 mos. after onset; September 13, 1910: toxins in O.P.D. for 3 wks.; *little or no reactions, no effect*; rapid recurrence, death about 6 mos. after onset. (25, 35, 75). 6 mos.
13. (W. B. COLEY): S. S. S., age 42; primary in rt. testis; rt. orchiectomy September 10, 1904; recurrent nodule excised March 1906; well 12 yrs.; then metastases involving deep nodes along spine; exploratory laparotomy, Mayo Clinic; x-ray, radium, considerable temporary regression, then increase in size; developed mass in lt. supraclavicular region July 22, 1919; 17 doses toxins in 1st mo. (Tracy XI), moderate reactions; also radium pack; *complete regression both metastatic masses*; further radium; further toxins, continued 3 yrs. (Parke Davis XIII); *in excellent health. No evidence of disease 1924*; life insurance examination negative except for slight albuminuria for which he went on rigid diet, liquids, no proteins, took "Stafford Water," strong purgatives, upset his digestion. Although no evidence of recurrence or further metastases were present, further radium therapy was given 1924-1926; symptoms recurred 1926; node in supraclavicular region, nodes in thoraco-lumbar juncture; toxins not resumed; disease not controlled by further radiation; *death 23 yrs. after onset, 8½ yrs. after toxins begun*. (21, 23, 56, 60). 23 yrs.
14. (ROOT): R. S., age 25; embryonal carcinoma rt. testis following injury March 1928; rt. orchiectomy June 23, 1923; recurrence in scrotum July 25, 1923; radium pack over R.L.Q.; August 26, 1923: toxins intramuscularly thrice wkly., *rarely any reaction; felt fairly well about 2 mos.*; then had 1 very severe reaction; toxins stopped for 3 wks.; metastases developed; death December 18, 1955, over 2½ yrs. after onset. (23, 56, 60). 2½ yrs.
15. (COHN): C. R., age 32; malignant teratoma lt. testis; lt. orchiectomy by another surgeon January 1925; metastases to lumbar lymph nodes, lost 25 lbs., nausea, vomiting, partial obstruction due to extrinsic pressure; October 21, 1925; exploratory laparotomy; 5400 mch. radium; November 2, 1925 toxins, no marked reactions; patient lived 2 yrs. with known metastases during which time apparently as a result of treatment he showed *marked regressions in the size of the mass*; at no time did he present edema or ascites; later sternoclavicular and mediastinal metastases, death over 2 yrs. after onset. (10). 2 yrs.
16. (GIFFEN & KAUFFMAN): C. W. M., age 29; malignant teratoma lt. testis; onset December 1927; castration May 1928; developed severe pain in abdomen; deep x-ray caused no improvement in pain; toxins intravenously every 2nd or 3rd day; *pain decreased, general condition improved, gained weight*; severe pain returned, not benefited further; death about 6 yrs. after onset. (23). 6 yrs.
17. (W. B. COLEY): D. F., age 34; inoperable metastatic carcinoma retroperitoneal nodes, primary in testis; onset December 1928; lt. orchiectomy and excision tumor in rt. epididymis, February 14, 1929; well until

shortly after tonsillectomy April 1, 1930; 16 radium pack treatments totaling 120,000 mch. October 1930; toxins intramuscularly and intravenously, some good reactions; *mass in left upper abdomen regressed, patient gained 20 lbs., remained in excellent condition 18 mos., then mediastinal metastases; further radium, 15,640 mch., 16 x-ray treatments, complete regression, appeared clinically free from disease July 1932; further radiation September 1932; disease no longer controlled, death 2½ yrs. after onset.* (23, 56, 60). 2½ yrs.

Note. The following cases had antecedent local trauma prior to onset: Cases 1 (fall on bicycle), 2 (much horse-back riding), 4 (14 years before) 10 (severe kick in groin), 13 and 14 (strain). Cases 3, 9, 10, 11, 14, 15 and 16 had x-ray or radium therapy before or during toxin therapy.

SERIES C, INOPERABLE FAILURES, DETAILED HISTORIES

DETAILED HISTORIES OF THE FOLLOWING THREE CASES APPEAR TO BE OF SPECIAL INTEREST.

CASE 6: Inoperable recurrent large round cell sarcoma of the left testis, confirmed by microscopic examination by Dr. F. S. Mandelbaum, Pathologist of Mount Sinai Hospital, New York.

Previous History: S. S., male, age 46, Russian laborer. The family history was negative, and there was no history of antecedent local trauma. Onset, in June 1909, the left testis became enlarged, hard and painful.

Surgery: The patient was operated upon at Mt. Sinai Hospital in September 1909, a left orchiectomy being performed by Berg.

Clinical Course: About six months later, he began having considerable intermittent pain in the left side of the abdomen and around the left kidney, which was worse at night. There was no pain on defecation or urination, nor was there any marked loss of weight but there was a feeling of general lassitude. The bowels were regular, but the appetite was poor, and "it was painful to overload the stomach." The pain gradually became more severe and subsequently a large tumor developed in the left hypochondriac and lumbar regions. The patient was referred to Dr. William B. Coley in May 1910, at which time the lymph nodes in both groins were enlarged. Palpation of the abdomen showed an indefinite mass about the size of a fist to the left and slightly below the umbilicus, apparently originating in the retroperitoneal lymph nodes.

Toxin Therapy (Tracy XI): Injections were begun in February 1910, the initial dose being 0.5 minim. The dose was increased to the point of producing moderately severe reactions (102°-103°F.) which occurred following doses of 7 to 8 minims given intramuscularly in the gluteal region. There was gradual diminution in the size of the tumor under toxin therapy, which was continued five or six times a week for about four months. The patient was then allowed to go home for a few weeks. He was readmitted to Memorial Hospital on August 9, 1910. Physical examination showed that the intra-abdominal tumor had apparently entirely regressed, but the inguinal nodes on both sides were still enlarged. The injections were resumed on August 11, 1910 and during the next 14 days 12 were given intramuscularly in the buttocks, only one of which caused any marked reaction. (104°F. and a chill, on August 25). The dose was increased very slightly to a maximum of 3 minims. The patient was discharged on August 29, 1910. The general health improved and a careful

examination early in September showed no evidence of tumor in the abdomen. As a precaution against further recurrence the toxins were resumed on September 7, 1910, and during the next 107 days, 55 intramuscular injections were given in the buttocks, in doses ranging from 0.5 to 7 minims, using both the filtered and unfiltered preparations (Type XI and XI F). The final injection was given on December 23, 1910. On six occasions the temperature rose to 100°-101°F., the maximum being 102°F., on October 14, following a dose of 5 minims. However, the injections usually caused no reactions. There were moderate chills, lasting 10 to 30 minutes on ten occasions. The general health improved and a careful examination about November 1, 1910, revealed no evidence of tumor in the abdomen, although the inguinal nodes on both sides were still enlarged. On November 3, 1910, Coley removed two very small nodes on either side of the groin under anesthesia. These were examined by Dr. William C. Clark, who reported: "Simple hyperplasia, no trace of sarcoma." Under ether examination at this time, no trace of the abdominal tumor could be felt. On November 23, 1910, the patient was presented before the New York Surgical Society, at which time Coley stated it was the only case of a malignant tumor of the testis recurrent in the abdomen, in which he personally had observed a complete regression. He had, however, up to that time, had four cases of malignant tumors of the testis in which he had used toxins following simple orchietomy, as a means of preventing recurrence, and that those patients had remained well over three years, but that he had never cured a case by operation alone.

Clinical Course: The patient was discharged on December 27, 1910. He was readmitted on January 23, 1911, a month after the injections were stopped, because he felt weaker and had pain over the left kidney, and occasional cramps in the abdomen. There was no indigestion and no blood in the stools but there was constipation. He was fairly well nourished, weighing 123 pounds. Examination on readmission showed a "pot-bellied," distended abdomen, with dullness over the entire left side, and tympanites on the right side. There was a large mass in the region of the left kidney.

Final Course of Toxin Therapy: Injections were resumed on January 3, 1911, and during the next 16 days, seven were given in doses of 1 to 5 minims. These caused only two marked reactions, with chills lasting 20 and 30 minutes respectively. The tumor mass began to regress slowly.

Clinical Course: Unfortunately, the patient had to be discharged on February 10, 1911, "for disobeying the rules of the hospital." He was not traced subsequently. In an attempt to trace him in 1946, no record of death was found in the Bureau of Vital Statistics, 1911-1946. However, it seemed best to include him among the failures, since the disease was still present when he was lost to follow up. (15, 16, 17, 56).

CASE 9: Inoperable cancer of the right ectopic testis, confirmed by microscopic examination by Dr. R. C. Whitman, pathologist of the University of Colorado School of Medicine, who stated: "A typical round-cell sarcoma of the testis, . . . that is, certain portions show a typical sarcomatous structure while others have some appearance of the usual carcinoma." (For microphotos of these as well as the gross specimen, see 33).

Previous History: L. W., male, age 37, of Radcliff, Colorado. The patient was married, and was the foreman of a copper mine. He had always had a right undescended testis. This caused no discomfort or inconvenience until April 1913, when moderate discomfort developed in the lower abdomen with dull

pain and "gastric indigestion." He consulted Dr. W. W. Grant of Denver, Colorado, in November 1913, who found a large abdominal tumor extending above the umbilicus and filling the lower abdomen. The superficial veins of the abdomen were conspicuous. The growth appeared to have a fixed point in the pelvis and admitted of but slight motion laterally. More frequent micturition was believed due to pressure on the bladder. Grant made a diagnosis of cancer of the undescended testis.

Surgery: An exploratory operation was performed on December 6, 1913, at St. Luke's Hospital. A large, solid, vascular tumor was found, with few adhesions to the omentum or intestines. The cornu of the right fundus of the tumor revealed a nodule the size of a hickory nut. The bladder was pressed down and partially involved in the growth and could neither be seen nor felt. Posterior to the tumor there appeared to be about six nodules or enlarged lymph nodes connected with the growth at the base of the bladder. An aspirating needle was inserted into the middle of the tumor and no fluid was withdrawn. With pressure around the puncture a little grayish brain-like substance escaped. As the condition was inoperable the wound was closed. At this time there was edema of the lower extremities and the prognosis was regarded as about 90 days.

Toxin Therapy: (Parke Davis XII and Tracy XI) Grant wrote to Dr. Martha Tracy for the Tracy XI toxins, but as sometimes occurred, the supply was temporarily exhausted and the first bottle sent was the Parke Davis XII. (75) Injections were begun three days after the exploratory operation, on December 9, 1913, and were given three times a week, commencing with 0.5 minim and increasing the dose rapidly until a febrile reaction of 102°-103°F. was reached. They were given intramuscularly, chiefly in the loins or gluteal region. At the end of a month there was scarcely a perceptible change in the growth but there was no increase. However, at the end of seven weeks there was a manifest decrease in size. (33) Beginning about February 1, 1914, the Tracy XI product was used, the initial dose being 2 minims, increasing 2 minims at each injection. On February 4, 1914, Grant wrote to Coley that the growth had reduced one-half.

Radiations: In February 1914 the patient was also given a few x-ray treatments by Dr. S. B. Childs. On February 23, 1914, he returned home and resumed his duties at the copper mine.

Further Toxin Therapy: Grant taught the patient's wife to give the injections, and so they were continued steadily about three times a week in doses of 8 minims, with two intervals of rest, for 11 months. Grant stated: "It seems remarkable that even a naturally vigorous and healthy young man could work with hardly the loss of a day under such conditions but it was made possible in this way. He went off duty every afternoon at four o'clock, and as soon as he reached home his wife gave him the injection. Immediately he went to bed. Usually he had a chill followed promptly by a rise in temperature which not infrequently reached 104°F. and occasionally a little higher. In two hours the temperature began to decline at a rapid rate. He was then given a dose of quinine and liquid food. He slept very well the latter part of the night and by morning was ready for breakfast and work." (33) During the first 11 months of treatment the patient received more than 100 injections, the maximum dose being 18 minims. Grant added: "The toxins were continued faithfully and persistently because the growth was steadily diminishing in size and I hoped it would reach a point where it would be successfully removed." (33) Apparently in late March 1914 Coley advised reducing the dose to 8 minims, or just sufficient to produce a temperature of 101° to 102°F. (instead of

103° to 104°F.) Grant wrote on April 8, 1914: "Wouldn't the effect upon the tumor be more decided with the larger dose, and so long as the kidneys aren't affected wouldn't it be better to use the larger dose for a week or two at a time and then reduce it." (Grant appears to have been correct.) In a letter to Coley he stated: "In April 1914 the injections were discontinued for three weeks that I might observe the effect. I examined the patient at the beginning and at the end of this period and could not fail to observe, as did the patient and his wife, an increase in the size of the growth. The toxin was resumed and soon the tumor decreased in size. In August 1914 the toxin was again discontinued with intention of an early operation, the tumor being much smaller. In ten days the tumor was perceptibly larger. The patient came to Denver and I verified the fact. The toxins were immediately resumed with prompt arrest in the increase of the growth." (23)

"On September 24 the patient called me on the phone and stated that one leg was swelling. On October 30 he came to Denver. Both legs were involved from the thighs to the feet, due to lateral pressure of the tumor on the iliac vessels. The patient was put to bed and his legs bandaged. I now injected the toxins myself into the tumor to the depth of two inches. The reactions were much more severe and profound and I found it necessary to reduce the dose to 50 per cent of that usually given . . . showing a more rapid and more extensive distribution of the toxins into the system when injected into the tumor. This was continued twice a week for five weeks and during most of this time the patient was confined to bed on account of the weight and discomfort of his legs in walking. The swelling of the legs rapidly disappeared and the tumor slowly decreased in size." The febrile reactions at this time were 103°-104°F. The injections were continued until January 30, 1915, a total duration of 13 months for the first course of treatment, with intervals of rest.

Further Radiation: After December 6, 1914, he was given another series of x-ray treatments by Childs: "13 ordinary gas-tube treatments, and one Coolidge tube treatment in January 1915. Grant stated that during the year 1914 under toxin therapy the tumor appeared to become harder and more circumscribed on palpation. X-ray therapy appeared to have the same effect.

Surgery: On January 30, 1915 Grant removed the remains of the growth completely. He stated that it presented a different appearance from that at exploratory operation 13 months before. The tumor was still quite large, but was now quite uniform and regular in outline, filling almost the entire hypogastrium. The projecting nodular appearance at the fundus had disappeared. The adhesions which had formed since the previous operation had obliterated the peritoneum. The growth was surrounded by a thick capsule of connective and fibrous tissue, and adhesions to the omentum and colon were extensive, due Grant believed to the radiation. The bladder, though adherent, was not involved. Grant stated: "The inferior half of the transverse colon was buried by adhesions to the fundus of the tumor. Its safe dissection without damage to the intestine was the most difficult part of the operation. With the hand beneath the outer capsule I shelled out the tumor leaving the iliac vessels, on the right side especially, freely exposed. No lumbar glands were enlarged nor were any discovered about the base of the bladder. (These had apparently been involved 13 months before, prior to toxin therapy). The testicle was plainly observed in the center of the tumor, but soft and in a degenerated condition, while the rest of the growth had the usual consistency and appearance of encephaloid sarcoma. The large cavity left at the base and sides bled quite freely and it was necessary to pack it with gauze for 48 hours. Necessarily such a wound would heal slowly, and fortunately adhesive ileus did not occur." The postoperative course was uneventful. In five weeks the patient

was able to return to his work at the mine. Before he left Denver, Grant injected bismuth paste into the fistula to complete the healing. The patient slowly gained weight.

Further Toxin Therapy: Shortly after this operation the injections were resumed and were continued by the patient's wife two or three times a week, until June 24, 1915.

Concurrent Infection: In June 1915 the patient had a local infection of the fistula which still extended to the full depth of the wound. There was some temperature and headache and local swellings of the abdominal wall and the lymph nodes in the groin were slightly enlarged, suggesting metastases. The patient returned to Grant who washed out the paste and pus with a dilute solution of hydrogen peroxide. The temperature was normal in 36 hours. The wound was irrigated daily for ten days.

Further Radiation: A third brief course of x-ray therapy was given from June 29 to July 5, 1915, using the Coolidge tube.

Further Toxin Therapy: Improvement was continuous and the patient gained 37 pounds in two months. All local indications of the disease disappeared in a short time. Injections were continued through July 1915, a total of 18 months, with intervals of rest.

Clinical Course: Grant reported this case in 1916 and stated that the patient's health appeared to be normal. His weight was 175 pounds, a gain of 36 pounds, his height was 5 feet 6½ inches. He remained well until 1918, when metastases apparently developed in the gastro-intestinal tract causing obstruction. No further treatment was tried. Death occurred in the summer of 1918, over five years after onset.

COMMENT: In the letter in which he reported this patient's death to Coley, Dr. Leonard Freeman stated that he did not believe the toxins had had a fair trial in this case due to the fact that the patient did not live in Denver, and the injections were given "in a desultory manner." (23) In another letter Grant commented on "one very interesting phase of the case: the rapid growth as soon as the toxins were discontinued even for a short time." He believed that the only influence that resulted from the radiation in this case was "to produce some hardening and thickening of the tissues and capsule surrounding the growth." He added: "I feel confident that the profession has never given the treatment a fair trial, or more cases would probably have been reported cured." (23)

In analyzing this case it should be emphasized that for the first six weeks the much less potent commercial preparation (Parke Davis XII) was administered, without much improvement being noted, that sufficient radiation was used to produce marked tissue changes surrounding the tumor, and to apparently lessen the regenerative powers of the tissues, so that the fistula did not heal for a year. In spite of these factors, the result obtained was significant, as the patient lived five years instead of three months.

In treating such cases in the future, some of the initial injections should be made into the tumor or its immediate periphery combined with intravenous or interadermal injections. The dose should be pushed to the point of tolerance, and given daily or every other day in the first few weeks, in order to cause regression before the patient or the neoplastic cells become immune to the effects of the toxins. The danger of suspending injections too soon, even for brief periods is also indicated in this case.

In the discussion which followed Grant's report on this case in 1916 Coley stated: "I believe the very remarkable result obtained by Dr. Grant was largely due to his perseverance in the administration of the treatment . . . The prog-

nosis of cancer of the testis in general is very bad, while that of cancer of the undescended testis is still worse. In view of the generally admitted hopelessness of malignant disease of the testis, there has been a strong tendency recently to advocate a very extensive and radical operation consisting of removal of all of the retroperitoneal and preaortic glands — a very grave operation. I hold the opinion that it is unwise to submit the patient to such a prolonged and grave operation when the chances of saving his life by the operation are outweighed by the chances of death from the operation. I would propose the following substitute: in primary cases as soon as the diagnosis has been made, I would advise the immediate removal of the testis and cord as high up as possible, through the Bassini incision for inguinal hernia. Second, I would advise a routine prophylactic treatment with the mixed toxins of erysipelas and *Bacillus prodigiosus*, the same to be carried out for a long period of time, at least six months, and in some cases a year. The treatment could easily be carried out by the family physician without interfering with the patient's ordinary occupation." (33, discussion).

Recent studies suggest that a brief preliminary course of toxin therapy prior to surgical removal as well as afterward may be preferable to only giving the injections postoperatively in operable cancer. The reason for this is that host immunity is best elicited by causing necrosis of at least some of the tumor and its absorption by the host. Matagne (54, 55) was the first surgeon to urge this procedure empirically. (18, 23, 33, 75)

CASE 11: Recurrent inoperable round cell sarcoma of the testis, with metastases in the supraclavicular and retroperitoneal regions, confirmed by microscopic examinations by Dr. Mallory, Professor of Pathology, Harvard Medical School, also by Professor Thompson, of St. Louis University and Dr. Councilman of Boston. (23)

Previous History: S.S.S., male, age 42, of Blytheville, Arkansas. As regards the family history, the patient's father developed round cell sarcoma of the chest wall in 1921 and died in July 1933.

Surgery: The patient was operated upon for cancer of the right testis by Dr. M. J. Seelig, of St. Louis, Missouri, on September 10, 1904, and a diagnosis of round cell sarcoma was made at the University Laboratory. In March 1906 a small, hard nodule was excised from the scrotum and sent to Councilman, of Boston, who pronounced it lymph node metastasis. (56)

Clinical Course: The patient remained well until 1918, when he had occasional attacks of cramps in the right groin. It was thought at first to be chronic appendicitis. He consulted the Mayo Clinic in May 1919.

Surgery: At exploratory operation a large tumor was found in the abdomen. The report stated: "Probably a recurring sarcoma involving the deep glands along the spine. This growth apparently not attached to any organ. The general condition is good."

Radiation: The patient was given x-ray and radium treatment at the Mayo Clinic, and the tumor subsided considerably.

Clinical Course: However, shortly after his return home it again began to increase in size, and the abdominal symptoms recurred. Another tumor developed in the supraclavicular region. The patient was referred to Dr. William B. Coley by Dr. Charles H. Mayo in July 1919. Physical examination at this time revealed a large tumor in the right lower abdomen, apparently retroperitoneal metastases. The left supraclavicular region was occupied by a firm, elastic tumor the size of an orange, apparently another metastatic growth.

(Coley stated that he had seen four cases of metastases in the left supraclavicular region from primary cancer of the testis, the explanation being that the thoracic duct, which drains the abdominal lymphatics empties into the left subclavian vein.)

Toxin Therapy (Tracy XI): The injections were begun by Coley at Memorial Hospital on July 22, 1919, and 17 were given intramuscularly in the next 29 days. The maximum febrile reaction was 103°F., the average being 99°-101°F. The dose was increased gradually from 0.5 to 5 minims. Two weeks after the toxins were begun, the growth in the neck was barely palpable, and the condition was much improved. In another two weeks there was no palpable evidence of the growth in this region and the tumor in the abdomen had also diminished appreciably.

Further Radiation: The patient was then given a massive dose of radium over the left abdomen, and the radium pack was also placed over the left supraclavicular growth, totalling 25,230 mch. (Note that no radiation was given until the toxins had been administered for four weeks.)

Further Toxin Therapy: The patient returned home on August 26, 1919 where the injections were continued by the family physician, Dr. John F. Sanders, during the autumn of 1919 every third day and later twice weekly, the dose being 4 minims. There was one severe reaction with a hard chill in early November, but thereafter little or no reaction or chill. The patient wrote on November 25, 1919: "Have tried to tell him (his doctor) that the dose should be increased to get a reaction, but do not seem to make any impression on him." (23) When the patient returned to New York on February 21, 1920, deep palpation failed to reveal any tumor mass in the abdomen or the supraclavicular region.

Further Radiation: However, Coley believed it wise to give the patient further radium therapy over the abdomen. He was given four radium pack treatments between February 22 and 25, 1920, totalling 22,000 mch.

Further Toxin Therapy: The toxins were continued and in March 1920 the dose was increased to 12 minims, which produced febrile reactions of 102° to 104°F. with occasional chills. (At this time the patient believed he was using the filtrate and had doubled the dosage.) During May the frequency was reduced to once a week, the dose being 8 or 9 minims, given into the buttocks, which produced only slight reactions, 99° to 100°F. On one occasion the patient's wife made the injection ("7 drops") and the febrile reaction was 103°F. 12 or 15 hours later. The toxins were continued, with intervals of rest, for a total period of about three years. The patient stated that the treatment did not interfere with his work as a cotton broker. He returned to Coley every six months during the first two years, and later once a year, and careful examinations failed to reveal any palpable evidence of tumor, either in the neck or the abdomen.

Viral Infection: Early in January 1921 an attack of grippe was followed by a pleuritic effusion which caused pain and much dyspnea. Four aspirations were required and from 1½ to 3½ quarts of chocolate-colored sterile fluid was withdrawn. This greatly relieved the patient. Roentgen-ray and fluoroscopic examination failed to reveal any evidence of pulmonary metastases.

Further Radiation: One radium pack treatment was given on March 5, 1921 (6,210 mch.) and another on September 2, 1921 (8,162 mch.). On January 31 and February 2, 1923, two x-ray treatments were given over the right chest, anterior and posterior.

Clinical Course: Coley again examined the patient on July 25, 1923 and found him in excellent health, with no evidence of disease. In April 1924 the patient was persuaded by a life insurance doctor to have an examination. At this time he wrote: "I was feeling better than I had felt for years, and had a clear complexion, and weighed more than ever. I told him that I had a sarcoma and that they would not accept me because of my record, and he told me that he would ignore that because he did not believe that I would be so well as I looked if I had ever had sarcoma." The examination was absolutely negative except for albumin and casts in the urine. Therefore, the patient cut out eggs and meat and drank "Stafford Water" and as a result thoroughly upset his digestion and bowels and developed severe cramps. He then took strong purgatives and later magnesia and cut down his food to a liquid diet; buttered toast, weak tea, and strained soups.

Further Radiation: X-rays taken in July 1942 showed no evidence or recurrence or metastases. However, as a precaution, on July 23, 1924 one radium pack treatment was given over the left upper quadrant (12,000 mch.). Another was given in November, 1924 (15,000 mch.) In May, July, August and December, 1925, further radium pack therapy was given, totaling 38,000 mch. In February, April and May 1926, 25,283 mch. of radium was given over the abdomen and left supraclavicular regions. In August and September 1926 eight x-ray treatments were given over the superior mediastinum and left supraclavicular regions.

Clinical Course: Early in October 1926 a crampy pain developed in the upper abdomen, which radiated to the back. It was not related to digestion and there was no vomiting. The pain was relieved by codeine. Examination at this time at Memorial Hospital showed a small, soft node in the left supraclavicular region. The lungs were essentially negative, except for diminished breath sounds and increased voice sounds on the right side. The abdomen was negative.

Further Radiation: During November 1926 two x-ray treatments were given to the posterior neck and upper dorsal spine. Roentgenological examination showed at this time a sharply defined shadow just within and through the right contour of the heart which might be due to enlarged nodes. The chest remained clear of pulmonary metastases. Further films indicated involved nodes at the thoracolumbar juncture. Those increased in size, despite further x-ray therapy during October and November 1926, and January, February, April and August 1927. The disease gradually progressed, causing death on December 12, 1927, 23 years after the primary tumor was removed surgically and eight years after the toxins were begun. No further toxin therapy was given after the summer of 1922. (57)

COMMENT: This case is of interest as an example of the dangers of using such heavy radiation "as a prophylactic" which may reactivate a quiescent neoplasm. Also the medication and dieting in 1924 seems to have markedly affected his general condition which had been excellent. (21, 23, 57, 60)

SERIES D: TERMINAL TESTICULAR CANCER: 1 SUCCESS, 16 FAILURES

Period of
Survival

THE FIRST FOUR PATIENTS RECEIVED THE BUXTON VI PREPARATION

1. (W. B. Coley): R. A. C., age 33; round cell sarcoma lt. testis; castration 2 mos. after onset; well 2 yrs.; extensive metastases (retroperitoneal nodes), mass filled whole left abdomen; November 26, 1895: toxins for 2 wks., *no apparent effect*, death shortly after toxins were stopped, about 3 yrs. after onset. (13, 18). 3 yrs.
2. (W. B. Coley): G.S., age 29; lt. testis (malignant melanoma); lt. orchiectomy 4 mos. after onset; rapid recurrence; 4 operations; last 2 by Coley; October 3, 1897: toxins given after 4th incomplete operation for 2-3 wks., *without apparent effect*. Death 16 mos. after onset. (13, 18). 16 mos.
3. (W. B. Coley): A. W., age 35; lt. testis; lt. orchiectomy, July 24, 1902, 2 yrs. after onset (testis weight 3 lbs. — hard as stone); rapid recurrence in groin removed October 1, 1902; again rapid recurrence, metastases involving entire pubic and inguinal regions, ulcerated, foul discharge; November 28, 1902: toxins into tumor area, 13 small doses, no marked reactions; also 16 x-ray treatments; *foul odor almost disappeared, some slight regression*; no further improvement; discharged January 23, 1903. End result unknown. (13, 18, 57). unknown
4. (W. B. Coley): S. W. B., age 42; rt. ectopic testis; surgical removal 3 mos. after onset; multiple abdominal tumors few wks. later; growth size cocoon removed at 2nd operation, October 1906; shortly after multiple retroperitoneal and mesenteric node metastases; cachexia, in desperate condition; November 20, 1906: toxins given for short time, *no apparent effect*; death few mos. later, about 1 yr. after onset. (18) 1 yr.

THE FOLLOWING NINE PATIENTS RECEIVED TRACY X OR XI PREPARATION:

5. (W. B. Coley): H. W. B., age 30; lt. ectopic testis; surgical removal 8 mos. after onset (had lost 20 lbs.); recurrence lt. groin 18 mos. later, metastases inguinal, iliac nodes; December 1906: toxins 6 wks., combined with x-ray therapy; *no apparent improvement*; death 2 mos. later, 39 mos. after onset. (18, 23) 3 yrs.
6. (W. B. Coley): T. S. S., age 34; cancer lt. testis, lt. orchiectomy 3 mos. after onset; extensive abdominal metastases, severe pains, rapid weight loss, condition poor, spleen greatly enlarged; October 21, 1909: toxin injections in buttocks, *no marked reactions*, no effect; death 13 mos. after onset. (18, 57) 13 mos.
7. (W. B. Coley & Sumpter): J. R. S., age 33; bilateral ectopic testes, castration June 1905 by Wyeth; well 2 yrs.; then recurrent attacks

abdominal colic; by 1912 pain very severe, large inoperable retroperitoneal mass; emaciation; prognosis hopeless; May 5, 1912: toxins for 7 mos, *marked temporary improvement, gained weight, mass decreased*; when toxins stopped December 1912, disease progressed rapidly, death in 4 wks., 7½ yrs. after onset. (18, 23) 7½ yrs.

8. (Lee): S. C., age 44; ectopic testis; intra-abdominal metastases involving almost all important viscera (mesentery, omentum, lower half left kidney); April 9, 1913: toxins daily at first, *good reactions; pain ceased, marked decrease in size, softening; improvement in general condition*; 60 injections in 5½ mos.; later condition declined rapidly, death December 4, 1913, 8 mos. after toxins begun. (18, 23, 75) 8 mos.
9. (W. B. Coley): A. H., age 55; lt. ectopic testis; 1st operation early 1911; large tumor removed; well about 16 mos. then pain, dyspnea, of increasing severity; 2nd operation December 1912; temporary relief; pain returned, lost 15-20 lbs., blood in stools and urine; prognosis hopeless; July 3, 1912: 13 doses toxins in buttocks in 15 days, 2 moderate reactions, 1 chill; *little apparent effect*; rapidly worse, death few wks. later, over 3 yrs. after onset. (18, 56) 3 yrs.
10. (W. B. Coley): C.F.P., age 52; right testis, right orchiectomy February 1914; 2 months later pain, resistance over right hypochondrium, extensive abdominal metastases, deeply jaundiced, clay-colored stools; some edema legs; November 22, 1914: toxins (4 doses intramuscularly); mild febrile reactions; *no effect*; death about a year after onset. (16, 33) 1 yr.
11. (Swartzlander): C. H., male, age 51; terminal cancer lt. testis; extensive abdominal metastases in kidney region, intestinal obstruction, extreme cachexia; onset, early in 1914; lt. orchiectomy, inguinal node dissection June 20, 1914; abdominal metastases some mos. later, lost wt. and strength; intestinal obstruction; exploratory laparotomy revealed metastases involving lt. kidney; prognosis hopeless; Mayo Clinic advised toxins; 30 lb. wt. loss, terrible emaciation, marked loss of strength in lt. leg, almost moribund when toxins begun; May 21, 1915, given daily at first in rapidly increasing doses for 7 mos., marked reactions; *steady improvement in general condition, growth ceased then regressed completely, gained 40 lbs.*; in excellent health until sudden death in 3 days from pneumonia, March 3, 1937, 23 yrs. after onset. (23, 33, 60) 23 yrs.
12. (W. B. Coley): C. J.S., age 31; teratoma rt. testis, after injury; rt. orchiectomy about 2 mos. after onset; metastases to epigastrium, pain, swelling; October 23, 1916: toxins daily, intramuscularly, dosage increased to 16 minims; radium packs October 29, 1916; *tumor no longer palpable* November 6, 1916; toxins continued 3 mos. (only 6 given in third month); total of 9 radium packs given, final one on March 24, 1917; disease recurred January 17 as soon as frequency of toxins decreased; partially controlled by radiation until March; then progressed rapidly; death 3 yrs. after onset. (16, 33) 3 yrs.
13. (Townsend): L. N., age 38; lt. testis Grade 4 cancer, seminoma type; onset after several injuries; lt. orchiectomy and excision of nodes in groin August 1916, about 9 mos. after onset; second operation June 1917, more nodes in groin removed; metastases to inguinal, retroperi-

toneal nodes; seen at Mayo Clinic, prognosis hopeless; October 15, 1917: toxins intramuscularly (daily); *marked improvement in first 6 wks.*; later disease no longer controlled; death nearly 4 yrs. after onset. (16, 33) 4 yrs.

THE FOLLOWING FOUR PATIENTS RECEIVED THE PARKE DAVIS
XII AND XIII PREPARATIONS

*Period of
Survival*

14. (*W. B. Coley*): C. F. B., age 25; cancer rt. testis, orchiectomy 6 wks. after onset; extensive metastases 13 mos. later; three large masses filling abdomen, inguinal nodes also enlarged; pain interfered with walking; January 1, 1908; toxins, small doses for 5½ wks.; *no marked reactions, no effect*; death from metastases to liver and spleen, March 6, 1908, about 2¼ yrs. after onset. (18, 35) 2¼ yrs.
15. (*W. B. Coley*): M. K., age 22; lt. testis, metastasis lt. groin; latter removed, patient too weak at operation to have testicular mass removed; lost 12 lbs.; anemic; mass 30 cm. in diameter; September 1, 1911: toxins, 15 doses in 19 days, no marked febrile reactions, (painful indurations in buttocks); *little or no effect*; death 3 mos. after onset. (18, 35) 3 mos.
16. (*W. B. Coley*): M. J. F., age 28; cancer rt. testis, rt. orchiectomy 3 mos. after onset; metastasis lt. supraclavicular nodes, 2 yrs. later; incomplete excision; apparent pulmonary metastases; radium treatment (Kelly, Baltimore, no effect); supraclavicular metastasis recurred; December 28, 1914: toxins, 24 in 27 days, in lt. pectoral muscles; supraclavicular mass dissected free, wound fulgurated; *pulmonary involvement regressed* (as seen in x-rays); death almost 3 yrs. after onset, from extension into throat of supraclavicular involvement. (12, 16, 23, 35) 3 yrs.
17. (*Potter*): Adult; rt. ectopic testis; surgical removal March 26, 1920; well 16 mos.: then metastases attached to spine, backache, pain, irregular hard mass; extreme edema both legs; August 15, 1921: toxins daily or every 2 days; after 2 wks. *pain and edema all subsided; gained weight; growth regressed until barely palpable; end result unknown.* (18) unknown

NOTE: There was a history of antecedent local trauma in cases 2, 12 and 13. Radiation was administered in cases 3, 11, 15.

The following case is the only terminal case of cancer of the testis to recover completely and to remain free from further recurrence or metastases. (Traced until death 23 years later from pneumonia). The detailed history appears of special interest.

CASE 11: *Diagnosis:* Cancer of the testis, recurrent in the kidney, confirmed by microscopic examination after removal of the primary growth. The recurrence was not examined microscopically, but at operation the macroscopic findings rendered the diagnosis "undoubted." (23, 60).

Previous History: C. H., male, age 51, a farmer, of Oyen, Alberta, Canada. The family history was apparently negative for malignancy. The patient had been married 20 years and had two children, 24 and 20. Onset, early in 1914 he developed a tumor of the left testis.

Surgery: This was removed together with the inguinal nodes by Gershaw of Medicine Hat, Alberta, on June 20, 1914.

Clinical Course: Some months later an abdominal metastasis developed, with constipation, loss of strength and weight. The patient consulted Dr. Harry C. Swartzlander, who referred him to Patterson, of Saskatoon, for operation in April 1915. The patient had been unable to have a bowel movement for one week prior to this, due to pressure from the growth.

Further Surgery: An exploratory laparotomy revealed an inoperable malignant growth of the left kidney, extensively involving the abdominal aorta. Patterson thought it best not to touch the growth, and after loosening the bowel in the vicinity of the tumor, closed the wound.

Clinical Course: The symptoms of intestinal obstruction were relieved by the operation, but the prognosis was regarded as hopeless. The patient then went to the Mayo Clinic and consulted the Mayo brothers who agreed with the diagnosis and advised Coley toxins. Physical examination at this time revealed the abdomen was tense and rigid. The patient had lost 30 pounds in weight and was terribly emaciated, with marked loss of strength in the left lower extremity. Swartzlander believed that he was almost moribund.

Toxin Therapy (Tracy XI): Injections were begun at once by Swartzlander and were made subcutaneously, the initial dose being half a minim on May 31, 1915, increasing daily by half a minim. After the first few injections the dose was rapidly increased. Swartzlander wrote on July 12, 1915, that he was giving 15 drops and that every fifth dose produced a chill, which the patient believed were becoming progressively more severe. The general condition continued to improve and he gained two pounds a week all during the treatment. By August 1 the dose was 22 minims daily and Swartzlander reported: "Mr. H. has picked up wonderfully and gained strength and weight steadily. When I first saw him he was quite cachectic. . . . The tumor is still fairly large and palpable through the abdomen and visible as it pushes out the anterior wall. It is not growing appreciably." The injections were continued, increasing the dose daily by half a drop. By October 1, 1915 the daily dose was 31 drops. At that time the patient started having very severe chills and it was necessary to give the injections at two day intervals, instead of daily. He weighed 185 pounds at this time and felt fine. All symptoms had disappeared and there was no further sign of obstruction, although the swelling had not entirely disappeared. Injections were made into the pectoral region during the latter part of the treatment and when a severe chill occurred the pain in the side of the breast which was injected was quite severe. Injections were continued seven months, until January 1916, during which time four or five bottles of the toxins were used.

Clinical Course: The patient continued to gain weight and strength. He was examined at the Mayo Clinic, February 3, 1916, at which time he had gained 40 pounds in weight. His constipation had gradually subsided. He stated at this time that he had been well until one month before, and since then had had "distress and fullness" in the abdomen. Examination showed the abdomen was distended and full and rather tense, and that there was free fluid but no palpable mass. Proctoscopic examination was negative. The patient was seen periodically by Swartzlander. He made a complete recovery and remained in excellent health. There was no further recurrence. He remained well until February 27, 1937, when he had a severe attack of pneumonia. Death occurred three days later, on March 3, 1937, at the age of 73 (lacking 8 days). This was 23 years after onset. (60)

Comment: In this case the toxins were more aggressively and persistently administered without radiation than in any other testis case. The result obtained

indicates that even when the disease is very far advanced, it may be permanently controlled if the patient is given steady, aggressive treatment. This case somewhat resembles that of Grant (see above Series C, Inoperable Failures, Case 9), but in that case toxin therapy was given less steadily and in smaller doses, combined with radiation. The immediate result was less satisfactory and the patient ultimately died of the disease. (23, 33, 60).

It is now apparent that to be effective in the largest percentage of cases toxin therapy should be begun earlier in the course of the disease, without preliminary heavy radiation.

The 16 other terminal cases of testicular cancer in which toxins were used are presented in the brief abstracts. It will be noted that in many only a few injections were given with little or no effect being observed. In cases such as 7, 8, 12, 13, 16, 17 where injections were given more frequently and for a longer period, marked temporary benefit was apparent even in this most unpromising group of cases.

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Goodwin of Los Angeles reported a case of metastatic testicular cancer with regression following a severe wound infection:

"... a young man who had a testis tumor an embryonal carcinoma: when I explored him, I found a metastasis as big as my fist over the vena cava, which I took out and really didn't try to take out all the rest of his lymph nodes because I thought it was futile. He then disappeared and I thought he was dead, but during the immediate postoperative period he developed a very, very severe wound infection with staphylococcus and drained the wound infection for a long time. About five years later he showed up for a follow-up examination. I was astonished to see him still alive. It could be, of course, that I got the only metastasis that there was but it seemed to me highly unlikely, and I always thought that the episode of infection that he had may have had something to do with it." (Letter to H.C. Nauts 6/7/1973.)

ADDENDUM: Testicular Cancer, #7 Monograph, Kakizoe & Ogawa.

DIAGNOSIS: Pure seminoma of the left testis, confirmed by microscopic examination following orchiectomy in 1968. In 1972 recurrence on the stump of the spermatic cord and metastases to both lungs. Microscopic examination of the recurrence showed seminoma with a few embryonal components.

PREVIOUS HISTORY: Male, age 38, of Tokyo, Japan. The family and previous personal history were noncontributory. Onset, in mid-June 1968 the patient developed a painless mass in the left scrotum which increased in size insidiously. He was first seen in the Department of Urology at the University of Tokyo on September 20, 1968, three months after onset. Palpation revealed a hard non-tender round mass in the left scrotum. Physical examination was otherwise negative. Laboratory examinations and chest films and IVP were within normal limits.

SURGERY: On September 24, 1968 a left orchiectomy was performed. The mass was 6 x 4.5 x 4 cm. in size.

RADIATION: A total tumor dose of 2500 rad of tele-cobalt treatment was given over the abdominal paraortic and left inguinal regions.

CLINICAL COURSE: For the next three years and six months the patient was asymptomatic. On May 9, 1972 he returned complaining of a left groin mass of one month's duration. Neither breast enlargement or change in libido was noted. A hard fixed mass measuring 3.5 x 3.0 cm. was palpated subcutaneously in the left inguinal region. Chest films revealed three round well defined shadows in both lung fields.

FURTHER SURGERY: On May 25, 1972 the inguinal mass on the spermatic cord was removed. It was adherent to the surrounding tissues.

CLINICAL COURSE: Chest films taken June 1, 1972 revealed a marked increase in the size and number of the pulmonary metastases in both lung fields. The largest was 3 cm. in diameter; there were six in all.

FURTHER RADIATION: Telecobalt therapy was again given over the left inguinal region, 4200 rad being given.

CONCURRENT INFECTION: Radiation then had to be discontinued because of a deep purulent skin ulcer which persisted.

CLINICAL COURSE: The patient remained well and chest films taken July 14, 1972 showed that the six metastatic lesions had completely disappeared. (1, Fig. 5) All laboratory data at this time were within normal limits. He remained well 17 months after his second surgery, although the purulent skin ulcer was still present. The patient finally died of brain metastases in 1981, approximately seven years after the regression of pulmonary metastases. Autopsy was not performed.

REFERENCE: T. Kakizoe & A. Ogawa: Spontaneous regression of pulmonary metastases from testicular cancer: a case report. Cancer 34: 761-764. 1974 and Cancer Research Institute correspondence.

