

END RESULTS IN LYMPHOSARCOMA TREATED BY TOXIN THERAPY
ALONE OR COMBINED WITH SURGERY AND/OR RADIATION
OR WITH CONCURRENT BACTERIAL INFECTION



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INTRODUCTION

In making this study of the temporary or permanent effects of concurrent bacterial infections or their toxins on lymphosarcoma, all microscopically proven cases known to have developed infection or to have received such therapy have been reviewed.

Bierman et al (3), Huth (70) and Pelner (106) reported a number of cases of leukemia in which concurrent infections produced complete or partial remissions. In none of these patients was there a permanent result. It is of interest to note that Everson and Cole (56) did not find any cases of spontaneous regression of lymphosarcoma in the world medical literature since 1900. (They found 176 cases of other types of malignant tumors with spontaneous regression.)

In our study a total of 16 cases were found with concurrent infection, three of whom were indeterminate as to end-result. Of the remaining 13, three recovered and remained well and free from further evidence of lymphosarcoma when last traced 8 to 40 years after regression had occurred. The type of infections in the determinate cases were as follows: Successes: one erysipelas, two extensive suppuration or wound infection and one otitis media. Failures: eight erysipelas, one severe wound infection, empyema and abscess over sacrum and one mixed streptococcal and staphylococcal peritonsillar abscess.

Among the 32 patients successfully treated by toxin therapy, five also developed infections, fever or other complications which may have favorably influenced their prognosis by stimulating host resistance and supplementing the toxin therapy: Three patients had varicella (Series C, cases 4, 31, 32); one had a hemolytic streptococcal lung infarct (case 29); one had repeated episodes of tonsillitis, an infected burn, an infected foot (case 31). One patient, in addition to varicella had febrile episodes during which the tumor decreased in size (case 32); one patient had two large abscesses in the groin, near tumor area (case 24).

In contrast to the apparent benefit of acute bacterial infections, the evidence suggests that upper respiratory viral infections may have a deleterious effect. In four of the toxin treated successes (Series B), onset or markedly increased growth rate occurred following grippe or influenza (cases 14, 22, 23 and 30). Among the failures (Series D), onset occurred after tonsillitis in Case 14, and three other patients were subject to tonsillitis (cases 16, 17 and 43). Case 38 was subject to colds and bronchitis, and onset occurred after grippe in Case 31.

A total of 94 microscopically proven lymphosarcoma cases were found who had received toxin therapy (Coley mixed toxins). Of these 86 were determinate as to end result; 32 (31%) were successfully treated and remained free from further evidence of their lymphosarcoma when last traced 5 to 66 years after onset; 54 were failures; eight were indeterminate as to end-result. (Two other cases in which toxins were given briefly for terminal lymphosarcoma with brain involvement have not been included).

Among the failures were several cases in which the disease appeared to be entirely destroyed, but recurred two to six years later. Dr. William B. Coley, in summing up his conclusions as to the use of toxin therapy in such cases stated: "The most important lesson to be learned from these recurrent cases, I believe, is that. . .the treatment was not kept up sufficiently long. I am convinced that it is better to continue the treatment longer than may be absolutely necessary in a certain number of cases than run the risk of recurrence by too short a course of treatment in certain other cases." (46)

In 1928 Coley reported 21 five-year survivals in malignant lymphomas, 18 of which were lymphosarcoma and three Hodgkins's disease. Toxins alone had been used in 16 of these cases; toxins and subsequent radiation in four and one case had received living cultures of *Streptococcus erysipelatis*.

In view of these results in a condition admittedly hopeless as regards permanent cure by either radiation or surgery, the question naturally arises, why have the toxins not been more widely used? Coley believed the principal reason was that a relatively greater amount of time and personal supervision was required on the part of the attending physician or surgeon for the administration of toxin therapy.

Recent analysis indicates that the variability or weakness of some of the toxin preparations, and the lack of knowledge regarding the optimum technic of administration (site, dosage, frequency and duration), were more important factors (92, 93). Another point, only recently apparent, is the importance of timing, i.e. as to when toxins should be begun in relation to other modalities used in a given case (101).

Radiation Protection Elicited by Microbial Products:

During the past decade there has been an increased interest in finding effective means of protection against the deleterious effects of irradiation as well as of potentiating the tumor's response to such treatment. Many investigators have attested to the effectiveness of various microbial products in protecting animals. Protection has been elicited by several organisms: *Brucella melitensis*, *Proteus morgani*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *S. typhosa*, *Streptococcus pyogenes*, *Serratia marcescens* mixed with *Streptococcus pyogenes* (Coley toxins), as well as by such products as dextran and zymosan. These studies include those of Ainsworth (1); Blondal; Donaldson et al. (53a); Hollcroft (69); Perkins; Ross; W.W. Smith (116); Strauch and Zweifach (137). Recently Ainsworth, and Cole and Dreyer have obtained excellent protection in mice with single injections of typhoid vaccine (88% survival) or of Coley toxins (100% survival) prior to 700 r of whole body irradiation; only 8% of the controls survived. (1, personal communication; 12)

This protection of the host induced by prior injections of bacterial toxins may be accompanied by enhancement of the response of the tumors to radiation, if the radiation is begun shortly after or during toxin therapy (or bacterial infection). (11; 101) This may be due to the febrile reactions and the hyperemia induced by injections in or near the tumors, as well as to stimulation of the reticuloendothelial and lymphoid tissues. Several investigators have noted that fever or heat may potentiate the effects of radiation (47, 48, 54) or improve the results in inoperable cancer patients (58, 73, 111, 114, 130, 131). Others have demonstrated their favorable effects on animal tumors (47, 48, 58, 104) or on tumor cells in tissue culture (76). Recently Gilchrist in reporting the potential effects of using electromagnetic heat in cancer patients noted: "Dr. Coley's vaccine is still under investigation and there are many cases of proved cures or long-term arrest of malignant growths which were treated in this way. An essential part of the treatment is a strong febrile reaction." (58)

Analysis of end-results in early, inoperable or generalized lymphosarcoma treated by toxin therapy, not unexpectedly indicates the advantage of beginning such treatment prior to radiation, and of giving the toxins somewhat aggressively, as regards site, dosage, frequency and duration of injections.

Factors Affecting Prognosis:

The following tables indicate factors which may affect prognosis in patients with lymphosarcoma treated by toxin therapy. Several histories suggest how narrow a margin may exist between dosage sufficient to cause complete or permanent regression (i.e. Series C, case 18, or Series D, case 47).

That permanent control may be achieved by persistent toxin therapy, even if the disease recurs or metastasis develops is shown by the few cases in which this was carried out: Series C, cases 8, 12, 19, 21, 22, 24 and 27.

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Cases such as Series C, cases 4, 17 and 29 suggest that even though no improvement is evident during the first three to six weeks of toxin therapy alone or combined with radiation, that a permanent result may occur.

TABLE 1 — Duration of Disease Prior to Toxins

<i>Total Cases</i>	<i>Interval</i>	<i>Successes</i>	<i>Failures</i>
3	0- 1 month	0 (0%)	3
5	1- 2 months	2 (40%)	3
27	2- 6 months	15 (56%)	12
15	6- 9 months	5 (33%)	10
13	9-18 months	4 (38%)	9
10	18-30 months	2 (20%)	8
8	30-60 months	1 (12.5%)	7
6	not recorded	3 (50%)	3

TABLE 2 —

End Results According to Extent of Disease when Toxins were begun.

<i>Total Cases</i>	<i>Stage of Disease</i>	<i>Successes</i>	<i>Failures</i>
1	operable, primary	0	1
3	operable, recurrent	1 (30%)	2
27	inoperable, primary	14 (52%)	13
22	inoperable, recurrent or local metastases	13 (59%)	9
16	inoperable, 2 or 3 areas of metastases	3 (19%)	13
18	generalized	1 (5.5%)	17

TABLE 3 — End Results According to Site of Primary

<i>Total Cases</i>	<i>Site</i>	<i>Successes</i>	<i>Failures</i>
40	head and neck	15 (37%)	25
19	groin, retroperitoneal	9 (47%)	10
4	intestines, mesentery	1 (25%)	3
10	axilla, chest wall	4 (40%)	6
3	supraclavicular	1 (33%)	2
3	back, leg, thigh	1 (33%)	2
2	bronchus	1 (50%)	1
2	more than one primary site	0	2
4	generalized	0	4

TABLE 4 — End Results According to Toxin Preparation Used

<i>Total Cases</i>	<i>Preparation</i>	<i>Successes</i>	<i>Failures</i>
16	Buxton V and VI	6 (38%)	10
1	Lister Institute VIII	0	1
2	Parke Davis IX	0	2
38	Tracy X & XI	18 (47%)	20
26	Parke Davis XII & XIII	7 (27%)	19
2	Sloan Kettering Institute XIV	1 (50%)	1
2	Johnston XV	0	2

The technic used at the time the Buxton products were available was more effective, i.e., injections in or near the tumor alone or combined with intramuscular injections, rather than intramuscular alone, using dosage sufficient to cause marked febrile reactions. Analysis of over 1000 cases of various types of neoplasms treated by Coley toxins indicates that Buxton VI and Tracy X and XI were all more potent than the other preparations available until very recently. (94, 95, 107, 108). An indication of their comparative potency in treatment of the same patient is clearly shown in certain cases such as Series C, Case 21, or Series D, Case 6. In the former case large doses of Parke Davis XII had absolutely no effect, but the first dose of Tracy XI caused a violent reaction (fever, chills and necrosis in the center of the tumor.) This case made Coley realize the serious difference in potency which existed. He then tried to get Parke Davis and Company to overcome this and thereafter their product (P.D. XIII) was more effective than those produced before (P.D. IX or P.D. XII). In the latter case it took 8 minims of Parke Davis IX to produce the same reactions as $\frac{1}{4}$ minim of Buxton VI.

TABLE 5 — End Results According to Type of Febrile Reaction Elicited

<i>Total Cases</i>	<i>Type of Reaction</i>	<i>Successes</i>	<i>Failures</i>
5	slight	0 (0%)	5
18	moderate	2 (11%)	16
31	more marked	15 (48%)	16
33	not recorded	15 (45%)	18

These figures are comparable to the results according to reactions elicited in sarcoma of soft tissues other than lymphomas. (96, Fig. 4, p. 10)

TABLE 6 — End Results According to Duration of Toxin Therapy

<i>Total Cases</i>	<i>Duration</i>	<i>Successes</i>	<i>Failures</i>
3	1 to 2 weeks	0 (0%)	3
9	2 to 4 weeks	0 (0%)	9
17	1 to 2 months	7 (41%)	10
13	2 to 4 months	7 (54%)	6
8	4 to 6 months	6 (75%)	2
11	6 to 12 months	7 (63%)	4
11	12 to 24 months	2 (18%)	9
5	over 24 months	1 (20%)	4
9	not recorded	2 (22%)	7

The highest percentage of permanent results occurred in the patients receiving 2 to 12 months' toxin therapy. Patients who received toxins for more than 12 months usually had two to eight courses of injections, often with long intervals of rest, whereas those receiving toxins for less than a year usually had more sustained treatment.

TABLE 7 — End Results According to Sex

<i>Total Cases</i>	<i>Sex</i>	<i>Successes</i>	<i>Failures</i>
65	male	21 (32%)	44
22	female	11 (50%)	11

It is of interest to note that 75% of these patients were males, and that the percentage of successes was significantly higher in females.

TABLE 8 — End Results According to Age

<i>Total Cases</i>	<i>Age Group</i>	<i>Successes</i>	<i>Failures</i>
7	under 10 years	3 (43%)	3
9	10 to 20 years	2 (22%)	7
18	20 to 30 years	10 (56%)	8
17	30 to 40 years	4 (24%)	13
14	40 to 50 years	4 (29%)	10
12	50 to 60 years	5 (42%)	7
7	over 60 years	3 (43%)	4
2	not recorded	1 (50%)	1

Successes occurred more often among young children and young adults and in patients over 50 years than among patients in the second, fourth and fifth decades. However, the numbers of cases in each group are probably too small to be really significant.

Period of Survival in Toxin Treated Cases:

Various authors have noted the rarity of prolonged survival in lymphosarcoma. Gellhorn's series contains no 10-year survivals among 239 lymphosarcomas (including reticulum cell sarcoma, lymphosarcoma and giant follicular lymphoblastoma). (58) It is therefore of interest to find that among the patients with these tumors who were successfully treated by toxin therapy alone or combined with surgery and/or radiation, 26 were traced 10 years or more, 17 for 20 years or more, 11 for 30 years or more, and 5 were traced from 40 to 67 years after onset.

Of the failures who ultimately died of their disease, there were seven patients who survived from 5 to 10 years and two who survived over 10 years after onset. The average survival rate among the failures was nearly three years.

Fifteen of the 32 successes died of other causes 5½ to 57 years after onset of their lymphosarcoma. The causes of death are given in Table 9.

TABLE 9 — Causes of Death in Successfully Treated Cases

Total Cases	Causes of Death	Years after Onset	Age at Death
1	adenocarcinoma (#2)	57	82
1	carcinoma bladder (#24, also had mixed tumor parotid 24 yrs after onset — did not recur)	27	79
1	Hodgkin's disease (#15, developed 31 yrs after onset)	32	62
1	renal neoplasm (#12, also had emphysema, bronchiectasis, hypertension, arteriosclerosis)	48	81
8	cerebrovascular disease		
	3 coronary occlusions (#10, 20, 22)	32	90
		33	63
		51½	51½
	1 cerebral hemorrhage (#13)		
	generalized arteriosclerosis present prior to onset	5½	62
	3 cerebral hemorrhage — with arteriosclerosis (#19, 27, 30)	5	38
		28½	78
		21	84
	1 chronic myocarditis (#16, terminal intestinal obstruction — n.e.d at autopsy)	11	69
3	miscellaneous		
	1 lung abscess, non-tubercular (#23)	8	62
	1 drowning (#17)	15	?
	1 ruptured appendix (#20)	27	52

Alive and well in 1969:

Six of the successfully treated patients are living in 1969. These were treated in 1902, 1906, 1908, 1931, 1942 and 1948. Series C, case 4, treated in 1902 is of special interest since this patient developed several other types of tumors in the next 52 years: 1949, epidermoid carcinoma, basal type, in right temporal region, excised in 1949; multiple small leiomyoma and adenomyosis of the uterus, papillary cystadenoma of the ovary, panhysterectomy, 1950; epithelial cyst of the right pyriform sinus, excised 1951; lipoma on neck, excised 1953; benign hemangioma in the mediastinum 1953, excised 1954.

The remaining 11 patients in Series A were lost to follow-up from 5½ to 30 years after onset. Of these five were traced 10 to 30 years.

TABLE 10 — End Results According to Therapy

<i>Type of Treatment</i>	<i>Successes</i>	<i>Failures</i>
<i>Toxins Alone</i>	17 (61%)	11
Biopsy or exploratory incision	6 (#2, 7, 13, 21, 22, 23)	6 (#1, 3, 20, 22, 34, 35)
After failure of surgery (i.e. recurrence or metastases present, untreated)	11 (#1, 2, 6, 8, 10, 12, 17, 18, 19, 26)	5 (#2, 11, 16, 18, 19)
<i>Toxins Combined with Surgery</i>	5 (50%)	5
After apparently incomplete removal	5 (#9, 11, 14, 16, 25)	2 (#17, 21)
After complete excision of operable primary or recurrence	0	3 (#13, 36, 37)
<i>Toxins Combined with Radiation</i> (no sur- gery other than biopsy or exploratory incision)	5 (19%)	21
Toxins begun prior to radiation	4 (#25, 27, 29, 30)	6 (#25, 26, 29, 32, 40)
Toxins begun during radiation	1 (#32)	2 (#7, 28)
Toxins begun after radiation	0	13 (#30, 35, 39, 41, 42, 44, 45, 46, 48, 49, 51, 54, 55)
<i>Toxins Combined with Surgery and Radiation</i>	5 (22%)	18
(surgery incomplete in all but 1 case)		8 (#1, 6, 14, 23, 31, 38, 43)
Toxins begun prior to radiation	2 (#5, 24)	5 (#5, 8, 9, 12, 52)
Toxins begun during radiation	0	5 (#10, 15, 47, 50, 53)
Toxins begun after radiation	3 (#24, 28, 31)	

Discussion:

Some or all of the factors cited may have had a beneficial or deleterious effect on prognosis in lymphosarcoma treated by toxin therapy. It would appear that the most important were the stage and extent of the disease when toxins were begun, the timing and the amount of irradiation given, and the site, dosage, frequency and especially the duration of the toxin injections.

Analysis of end-results suggests that to be effective in the highest percentage of patients with lymphosarcoma, toxin therapy should begin two to six months after onset, and a reasonably potent preparation should be used. The optimum technic of administration from the experiences recorded here and from end-result studies of other types of tumors, appears to be injections in or near the tumor areas, alone or combined with intramuscular and/or intravenous injections. A few physicians have recently used intradermal injections with apparent success (100). Toxin therapy should be continued for at least two to six months, decreasing the frequency from about five weekly during the first three weeks to once weekly during the latter part of treatment. Several courses of one or two months over a period of 6 to 12 months may also be effective. Males may require more aggressive and persistent therapy than females. Dosage designed to elicit sharp febrile reactions and chills seems to be more effective than smaller doses, but further research is needed to determine if new purified non-pyrogenic toxin preparations may also prove effective.

Surgery Combined with Toxins: If surgery is to be used in these cases, it may be desirable to limit it to excision of a node, or exploratory plus biopsy for diagnostic purposes immediately prior to toxins; later after toxins have caused extensive necrosis, one may establish drainage of the necrotic tumor tissue (as in case 7, Series C). When nodules appear during toxin therapy, these may occasionally be removed and toxins continued (i.e. Series C, case 19). Case 1, Series A, suggests that removal of such a persistent or recurrent nodule may be decisive in effecting complete control of the disease. This child suffering from a very extensive inoperable lymphosarcoma involving the tonsil, buccal cavity, pharynx and tongue, had a truly spectacular "spontaneous regression" following a violent erysipelas infection. There remained two pea-sized nodules at the site of the biopsy incision. These appeared to be increasing in size when removed. The patient never had any further evidence of disease and was traced well 16 years after onset.

This case and a few others suggest that regression may be less prompt or complete in cicatricial tissues, or in irradiated tissues, probably due to decreased vascularity. Therefore such areas should be given local injections or in some cases they may be excised.

Regarding the advisability of using surgery in lymphosarcoma, Coley noted that in many of his cases operation, particularly incomplete removal, seemed to cause the tumors to grow more rapidly (see Series D, cases 3, 6, 10, 43); also cases 6 and 8 in Series B (Infection Failures). Recent work by many surgeons or investigators confirms the fact that surgical stress may decrease the natural resistance of patients or animals to their tumor. (6)

As regards the effects of physical trauma it is of interest to note that eight patients in the present study had severe physical trauma or strain at the site of the subsequent tumor just prior to onset of symptoms. One had two severe traumas shortly after onset. In each of these cases the growth rate was particularly rapid.

Successes, Series C, two patients: Case 8—struck in left groin by iron lever (was a blacksmith) a week later he noted a mass at the point of injury. Case 16—muscular strain in groin, just prior to onset. Failures, Series D: Five patients: Case 15—boy of 12, onset followed blow to chest and occurred at site

of injury. Case 16—severe trauma to neck two years prior to onset, at site of injury. Case 20, boy of 6, kicked in abdomen, onset shortly thereafter, at site of injury. Case 30, fell 18 feet, striking abdomen, onset 6 months later, at site of injury. Case 49, onset one month after severe trauma to abdomen in auto accident (struck by steering wheel, head-on collision). Case 51, child 6½, two severe traumas shortly after onset of vague symptoms (bumped several times by a ram against a tree, and a fall, striking back in right kidney region) onset severe pain and mass two weeks later. Case 53, repeatedly bumped her leg against corner of lower desk drawer for five years prior to onset, growth occurred in area of injuries. In most of these cases a latent tumor was probably present and the injury stimulated the growth rate very markedly.

Radiation: If radiation is also to be used in conjunction with toxin therapy, it should be started after a preliminary course of toxin injections. This will prevent radiation sickness and will allow more effective use of both agents. For an example of preliminary toxins with no radiation sickness, even though given over the abdominal region, see Series C, case 24. Examples of extreme radiation sickness in patients given radium treatments prior to toxins see Series D, cases 30, 33. Several histories suggest that preliminary toxins combined with subsequent radiation causes the neoplasm to respond more dramatically than if either agent is given alone. With a radiosensitive and toxin-sensitive tumor such as lymphosarcoma this may be dangerous, for absorption of large quantities of necrotic tumor cells too rapidly may overtax the reticuloendothelial and lymphoid tissues and may then be followed by reactivation of the disease. This is a special danger in patients who have already received radiation sufficient to affect these defensive tissues. When toxin treatment is given alone or with minimal radiation or when necrotic tumors are incised and drained this problem may be avoided.

Minot and Isaacs (89) and others have pointed out the dangers of large doses of radiation in the highly cellular cases. In a number of their cases there was very definite evidence that radiation had hastened the generalization of the disease. Coley stated that the weight of opinion was that radiation could be regarded only as palliative. At least two cases in this series suggest that wide generalization of the disease was induced by radiation: Series D, cases 4 and 7.

Table 9 indicates that 61% of the patients receiving toxins alone recovered permanently; 50% of those in which toxins and surgery were used survived. Only 19% of those in which toxins were combined with radiation survived and 22% in which all three modalities were used.

Suggested Procedures for Future Cases:

Since end-results suggest that toxin therapy alone or combined with minimal surgery and little or no radiation have produced the highest percentage of permanent results in lymphosarcoma, such therapy deserves to be more widely used now and in the future.

Mode of Action:

As to how toxin therapy or concurrent infection and fever may exert their beneficial effects on patients with lymphosarcoma, or other neoplasms, the following factors have been considered:

- a) Certain strains of bacteria or their toxins may increase the antigenicity of the tumor cells. (59)
- b) Streptococcal infections or their toxins may stimulate fibrinolysin production in patients. Administration of human fibrinolysin to rabbits diminishes the mortality and is highly effective in preventing the production of metastases by inoculation of V2 carcinoma or Brown Pearce carcinoma (61). In

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addition to this, streptodornase and streptokinase secreted by streptococci may facilitate the debridement of necrotic tumor during concurrent streptococcal infections. (123) It is believed that these enzymes are destroyed in the preparation of Coley toxins. One investigator has found that the use of Varidase with Coley toxins seemed to enhance their effectiveness.

c) The fever induced by bacterial toxins or acute infections is also believed to play a distinctive, beneficial role. Many authors over the past 100 years have observed the apparent benefit of fever or heat in cancer patients (73, 77, 106, 110, 114, 131). Doub and Crile have used heat to potentiate the effectiveness of radiation (47, 48, 54)

d) Adequately administered toxin therapy (if begun before the disease is terminal and the patient is unable to react) appears to stimulate the reticulo-endothelial and hematopoietic tissues, to produce leukocytosis and to stimulate antibody production. All of these effects appear to increase the patient's resistance to his tumor.

e) Recent studies have shown that preliminary administration of foreign protein or bacterial toxins (1, 12, 69, 116) protect mice against the deleterious effects of radiation. Several cases in this series of lymphosarcoma indicate that preliminary toxins decreased the radiation sickness and hematopoietic changes as well as the skin reactions.

f) A few investigators have observed that preliminary treatment with bacterial endotoxins may potentiate the effectiveness of subsequent radiation so that a smaller dose of radiation can be used and radio-resistant tumors can be treated in this way. (11, 100)

g) Surgical stress may markedly increase the incidence of tumors or metastases following transplantation in animals (6) or in patients. Several of the cases in the present study indicate this to be true. These findings suggest the need to begin toxin therapy prior to all surgery except biopsy, and to resume the injections immediately after such procedures.

h) Bacterial infections or their toxins may stimulate the synthesis or release of interferon or L-asparaginase both of which are now being studied for anti-tumor activity.

Summary: The many factors which may affect prognosis in lymphosarcoma treated by bacterial toxins alone or combined with surgery and radiation have been reviewed. These include the site and extent of the disease, the type of toxin used, the technic of administration (site, dosage, frequency and especially duration), the timing and dosage of radiation and the extent of surgery. Also the age and sex of the patient and the various complications, such as infections, inflammatory episodes or trauma.

The possible modes of action of bacterial toxins as regards protection against the deleterious effects of radiation or surgical stress are discussed.

Permanent results were obtained in 61% of the patients treated by toxins alone, 50% of those treated by surgery and toxins, 19% of those receiving toxins and radiation, and 22% of those receiving toxins, surgery and irradiation.

SERIES A: LYMPHOSARCOMA WITH ACUTE CONCURRENT INFECTIONS, SUCCESSES: TRACED WELL 8 TO 40 YEARS: 3 CASES.

The name in parenthesis following the case number refers to the physician, surgeon or hospital handling the case. The cases are listed chronologically. References are given at the end of each abstract. Detailed histories of these cases will be found immediately following these abstracts. (In three other patients with concurrent infections complete regression of their lymphosarcoma occurred but as these patients were not traced at all or for only one or two years they were excluded.)

Years Traced
After Onset

1. (BIEDERT): Female, aged 11; extensive, inoperable very vascular round cell sarcoma left tonsil, involving whole posterior half of buccal cavity, pharynx, left half of tongue (ulcerated mass), palate, nasopharynx, inner canthus of both eyes, both orbits, (right eye a mass of fungus growth), tissue over malar bone; onset 1882, tumor in left tonsil deeply infiltrating pharynx; marked temporary spontaneous regression; leaving small ulcerated fragment over left tonsil; disease then rapidly recurred, progressed as described; attacks of asphyxia, deglutition very difficult, finally impossible; intense dyspnea, condition almost moribund; tracheotomy November 14, 1884; placed in bed formerly occupied by erysipelas case; 3 days later *erysipelas developed at site of ulcerated mass over right eye, (with fever 40°C) infection lasted 6 days during which time tumor masses melted away in all directions, ulcers rapidly healed; appearance of face, mouth normal; respiration, deglutition, phonation all normal, appetite excellent; all extensive growths disappeared except for 2 pea-sized nodules in scar over left eye; these were excised; in good health, no further evidence of disease; date of last examination, April 1898.* (2, 5, 14, 56, 70, 91, 111, 119, 132). 16
2. (NEALE): J. McK., male, aged 28, lymphosarcoma of neck; operation June 1897, followed by extensive suppuration of wound; no further evidence of disease; traced well 1905. (29, case 6 infection series; 46) 8
3. (COHN): A.B., male, aged 4½; lymphosarcoma or reticulum cell sarcoma cervical nodes; onset at age 3, November 1928; tonsillectomy, February 1929; no effect; growth removed; *wound infection, febrile for some weeks later acute otitis media, mastoiditis; no further evidence of disease; had lymphocytosis, (50% lymphocytes) with normal white count 1930-1941; never ill; last traced very well, 1968.* (85, 100) 40

SERIES A, INFECTION SUCCESSES, SELECTED DETAILED HISTORIES

CASE 1: Extensive inoperable round cell sarcoma of the left tonsil, involving the posterior half of the pharynx, and the left half of the tongue, the palate, the nares, the nasopharynx, and the inner canthus of both eyes, confirmed by microscopic examination at the Haguenu Hospital, Strasbourg. The pathologist reported that the growth was very vascular, with "cells of medium size and nuclei in the process of mitosis."

Previous History: Female, aged 11. The family and previous personal histories were not recorded. The patient was first seen by Dr. William Biedert, Medical Director of the Haguenu Hospital in 1882, at which time she had a sarcoma of the left tonsil, the size of a hen's egg, infiltrating deeply into

the pharynx. She was referred to Dr. Lücke of Strasbourg for operation, but as he could not promise the child's mother that the operation would save her life, the woman declined to have it performed. Shortly thereafter, there was a marked "spontaneous regression". Examination by Biedert showed that most of the growth had indeed regressed, leaving a small ulcerated fragment over the left tonsil. The improvement was only temporary and the cause of this regression is not recorded. The patient was again seen by Biedert, at which time she was in a frightful condition. The growth had invaded the whole posterior half of the buccal cavity and the pharynx. The left half of the tongue was an ulcerated mass protruding through the lips. The disease had also invaded the nasopharynx, the nares, the tissue over the malar bone, and both orbits, the right eye being a mass fungous growth. For some weeks the child had many attacks of asphyxia, deglutition had become very difficult, and she seemed almost moribund. She was admitted to the Haguenau Hospital on November 13, 1884 in a hopeless condition, and was isolated because of the foul odor resulting from the ulcerating tumor. At this time there was intense dyspnea and she was unable to take any food at all. The following day a tracheotomy was performed during a severe attack of asphyxia. In order to have the child where she could be watched more carefully she was transferred to a bed which had been occupied by a case of erysipelas of long duration; the bed had been disinfected by a "spray".

Concurrent Infection: Three days later, on the afternoon of November 17, 1884, erysipelas developed at the site of the ulcerated portion of the growth over the right eye. The temperature rose to over 40°C. No attempt was made to limit the infection as Biedert felt it would perhaps put her out of her frightful misery more rapidly, and also because he wanted to see the effect of the infection upon the neoplasm. Biedert stated: "This effect was produced in a manner which surpassed our boldest hopes." The attack lasted six days, with a very high fever. During this time the tumor masses melted away in all directions, the ulcers rapidly healed.

Clinical Course: The appearance of the face, mouth, nares and eyes returned to normal. Only where the tumor had ulcerated through the skin and the mucous membrane of the pharynx was there cicatricial tissue evident. The tube was removed 13 days after tracheotomy. At this time respiration, deglutition and phonation were all normal. The child had an excellent appetite and three weeks after the infection developed she appeared to be in perfect health. There remained a little nodule the size of a pea in the cicatrix over the right eye which seemed to be increasing in size. This was removed and examined microscopically as stated above. Another nodule persisted in the scar over the nose, and this was excised a few days later. Biedert followed this case for at least two years.

The patient remained free from recurrence. She was seen by Drs. Galippe and Hallopeau at the Hôpital St. Louis in Paris, in Auriy 1898, because of an eczema of the forearm. This was 16 years after onset. During the interval she had been entirely well except for the stenosis due to the cicatrices at the sites of the extensive growths. Examination at the hospital showed a cicatrix occupying the internal angle of the right eye, and a similar but much smaller scar on the left side of the nose at the inner angle of the eye. The nose deviated to the left due to a vertical cicatrix 1½ cm. wide, the inferior maxilla was normal, but the superior maxilla and the roof of the mouth were markedly contracted, the latter being composed of blanched and cicatricial tissue. The teeth had been cramped by this lack of space and two large molars were seen

*Years Traced
After Onset*

inside the others on the left and right. Several teeth had already been extracted, due to having appeared inside the outer ones. The stenosis in the throat was marked, the aperture being so small that one could barely pass one's index finger. The scar tissue had contracted and caused the tongue to deviate markedly to the left. Biedert reported to Galippe that the patient had had a perfectly normal buccal cavity and pharynx prior to developing the sarcoma. The regression of the very far-advanced growth during the erysipelas infection had caused the deformities, due to extensive cicatricial tissue, and had also apparently somewhat arrested the development of the upper jaw and the roof of the mouth, resulting in the abnormal eruption of the teeth. (In the discussion which followed this paper, Moty stated that the eruption of the teeth in this patient was not very rare and might be due to the recent development of wisdom teeth. Fourmier agreed, and stated he did not believe the tumor had played a role in the abnormal dentition.)

In November, 1898 she was re-admitted to the Hôpital St. Louis for treatment of syphilis which she had contracted in the previous few months. She was thus traced over 16 years after onset, and 14 years after her very advanced sarcoma had regressed under the influence of a severe concurrent erysipelas infection. (This famous case was also cited by Bruns, 1887-1888; Weichel, 1889; Spronck, 1892; Coley, 1893; Delbet, 1895; Roncali, 1897; Moullin, 1898; Vidal, 1910; and others.)

References: 1, 5, 14, 56, 70, 90, 111, 128, 132.

✓ CASE 3: Operable lymphosarcoma of the cervical nodes, confirmed by microscopic examination by Dr. Alex Frazer of Bellevue Medical College. Dr. James Ewing also examined the section and reported: "It seems to be lymphosarcoma with rather large polynuclear cells of reticulum cell type, but the cells appear to form sheets, and there is a slight alveolar tendency. The exact nature of this process is somewhat uncertain. Other possibilities are lymphoepithelioma and metastatic carcinoma."

Previous History: A.B., male, aged 4½ years, of New York. The patient's paternal aunt died of carcinoma of the breast at Memorial Hospital. Otherwise the family history appeared to be negative for cancer, tuberculosis, diabetes or allergies. The child was born by normal delivery and had always been well except for measles and bronchial pneumonia at the age of five months. Onset, in November 1928, when the boy was three years old, the mother first noticed a lump in the right anterior cervical region. This increased until it was the size of a small hen's egg. Prior to onset the child had not had any trouble with his teeth nor any elevation of temperature.

Surgery: A physician was consulted in February 1929, who performed a tonsillectomy. This did not have any effect upon the growth. A month later Dr. Harry Cohn was consulted and he removed the growth.

Concurrent Infection: The child ran a temperature for some weeks after this operation, apparently because the wound became infected.

Clinical Course: The growth did not recur and the child had no further symptoms except fatigueability. He had no skin eruptions, no cough, no loss of weight. However, the mother was told that the condition was lymphosarcoma and for this reason he was brought to Memorial Hospital. Examination

SERIES A, INFECTION SUCCESSES, DETAILED HISTORIES

*Years Traced
After Onset*

on March 10, 1930 showed a well-developed child, well-nourished but rather pale with a scar in the right anterior cervical region. There were a few small submaxillary nodes on each side but no other adenopathy in the neck. The tip of the spleen was palpable. No treatment was given but the child was examined periodically at Memorial Hospital.

Second Infection: In April 1931 he developed a sudden sharp pain in the right ear. The condition proved to be otitis media. The ear drum was punctured and a small quantity of thick yellow pus was drained. At this time there was a chain of small lymph nodes on the right side of the neck just below the ear, averaging 3 to 4 mm. in diameter. During the next few weeks it was necessary to perform a mastoidectomy. The child made a good recovery.

Clinical Course: He was again seen by Dr. Lloyd Craver at Memorial Hospital on October 22, 1931, at which time there was no evidence of lymphadenopathy and the general condition was good. He was examined there periodically for another ten years. It was noted on February 15, 1941 that the only interesting constant finding had been the lymphocytosis which had run about 50 per cent lymphocytes with a normal white count in the previous 11 years. He was never ill except for an occasional cold after his recovery from the lymphosarcoma. He became a teacher and was married about 1948. His height in 1949 was 5 feet 11 inches, his weight being 193 pounds. In September 1961 he developed a left lower lobe pneumonia which responded adequately to home care. Early in May 1962 he suffered first and second degree burns of the face, chest and left arm. These healed adequately and he was discharged in good condition. His physician reported on May 29, 1962 that there have been no other significant illnesses and no indication of recurrence of his childhood lymphosarcoma. He was last traced in very good health in April 1969, 40 years after onset.

References: 85; 100.

SERIES B: FAILURES IN LYMPHOSARCOMA
WITH ACUTE CONCURRENT INFECTIONS:
10 CASES — 6 DIED OF CANCER — 4 DIED OF INFECTION

The name in parenthesis following the case number refers to the physician, surgeon or hospital handling the case. The cases are listed chronologically.

1. (BUSCH): Female, aged 28; very malignant lymphosarcoma left cervical region size of child's head, great pain, dyspnea, deglutition almost impossible; February 28, 1866 *developed erysipelas; immediate improvement, mass decreased 50% in week; right cervical nodes entirely disappeared*; 9 days after erysipelas developed patient collapsed and died; *post-mortem showed growth in left cervical region had regressed to size of apple, structure reduced to network of connective tissue containing large quantities of yellowish fluid; tumor cells had undergone fatty degeneration*; by injecting water into the growth it filled to former size. (9, 90, 92, 124)
2. (RICOCHON). Mme. F., aged 52; inoperable malignant lymphoma tonsil, neck, groin; onset, January 1884; cervical nodes became enormous, extending from spine to chin; almost complete obstruction throat, deglutition and respiration difficult; hearing affected; mass in groin size of fist; October 1884 *facial erysipelas*; no treatment given; *immediate regression*: in 6 days neck could be moved, deglutition easy, *hearing normal*; *tumors almost disappeared*; (nodes still palpable in neck, groin, but family considered her cured); recurrence 3 weeks later; tumors regained former size in 1 month, legs, hands, eyelids also became infiltrated; symptoms lymphatic leukemia; arsenic then given vigorously; no effect; sudden death, apparently due to brain involvement, April 1885, 16 mos. after onset. (90, 109)
3. (VERNEUIL): Young male adult; extensive lymphosarcoma neck, pressure seriously limited respiration; lymph nodes in other regions less markedly enlarged; irritating ointment applied to neck, excoriation; *severe erysipelas, causing death on 4th day; tumor had almost disappeared on 3rd day.* (128)
4. (KLEEBLATT): C.F., male, aged 54; recurrent lymphosarcoma tonsil and neck; growth size of child's head above scapular region; deglutition difficult due to tonsillar lesion; had recurred after extensive operation; patient almost moribund; March 3, 1888: *severe erysipelas developed spontaneously over neck, back, face; growths in tonsil completely disappeared, growth over scapula decreased from size of child's head to pigeon egg*; metastases developed 2 months later, left axilla, left carotid region; *erysipelas inoculations* (scarification on both sides); *well marked erysipelas developed involving trunk; metastatic growths almost disappeared*; recurrence again developed within a month; another inoculation failed to produce further infection; disease progressed, death November 18, 1888. (76)
5. (WYETH): Male, aged 60, 1891; far advanced lymphosarcoma neck, general condition poor; *severe erysipelas; death on 3rd day, no noticeable effect on tumor.* (136)
6. (SAUFHERING): Mrs. L. aged 58; very extensive inoperable round cell sarcoma neck, infiltrating behind sternocleidomastoid and sternum;

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

very little motion jaw; mastication impossible, deglutition difficult; incomplete removal, large vessels, nerves imbedded in tumor; tracheal, supraclavicular nodes and base of tongue also involved; May 1895, *mild attack erysipelas in region of wound; swelling of entire neck, breathing impaired; caused disintegration and liquefaction of tumor tissue*; condition improved during and following this infection; later given Coley toxins; curettage of large amounts of necrotic tissue under anesthesia, *showed necrosis of all tumor tissue had occurred*; fistula into trachea and esophagus, allowed food and air to escape into wound; condition declined rapidly after operation, died inanition August 11, 1895. (112)

7. (RICHARDSON): J.R., male, aged 6; recurrent lymphosarcoma primary in left cervical nodes; onset, April 1892; 1st operation October 7, 1892; local recurrence removed 1 year later; 3rd operation, June 1895; axillary metastases appeared soon after, grew rapidly during next year; large lobulated mass involving left axilla, scapula, overlying tissues; extensive dissection down to axillary vessels, too extensive for complete removal; 18 days later *severe infection developed in upper angle of wound, pleurisy, empyema, large abscess over sacrum, condition desperate; complete recovery*; well 18 months after infection, then developed mediastinal metastases; died suddenly August 20, 1898, 6 years after onset, 22 months after infection. (82, 95, pp. 24-25; 108)
8. HANSZEL): M.F., female, aged 4; recurrent inoperable round cell sarcoma tonsil with metastases at angle of jaw, submaxillary nodes; *peritonsillar abscess (Strep. pyogenes and Staph. pyogenes)*; perforation to external meatus; *tumor in throat became necrotic, disappeared*; hard, submaxillary node remained size of bean; 4 weeks later all symptoms recurred, protruding mass in soft palate and tonsil size of apple; incisional biopsy; thereafter tumor growth much more rapid, required tracheotomy; death, May 14, 1902; post-mortem revealed involvement of tongue, right atrium of Highmore, down to submaxillary fossa, main mass filled buccal cavity; *evidence of some fatty degeneration of tumor and anemia*. (62)
9. (KAPPES and KRASKE): Female, aged 64, extensive inoperable lymphosarcoma involving right axilla and supraclavicular fossa (each mass size of child's head), also involvement right cervical region (nodes size of walnuts); *erysipelas of right forearm lasting 4 weeks; in this period 2 largest masses in axilla and supraclavicular fossa regressed from size of child's head to size of small orange, cervical lymphadenopathy disappeared*; patient died 5 weeks after outbreak of erysipelas; *autopsy showed marked necrosis and regressive changes in tumor*. (75)
10. (WALDAPFEL): F.S., aged 51; inoperable lymphosarcoma right neck pushing right posterior pharynx forward; metastases in both supravascular regions, right axilla, left inguinal region; 1929: biopsy; radium to pharynx; *phlegmonous erysipelas infection, multiple abscesses (on right elbow, gluteal region, fibula and left upper arm)*; *cervical metastases softened somewhat*; patient died on 9th day of infection; *post-mortem showed pus-like degeneration of cervical tumors and of submaxillary metastases*. (129)

Note: See series D, case 24 for a patient in whom pneumonia developed late in the course of the disease after failure to control it by toxin therapy. This caused complete regression lasting a month.

CASE 1: Inoperable lymphosarcoma of the cervical nodes, confirmed by microscopic examination at post-mortem by Dr. Rindfleisch, a Berlin pathologist.

Previous History: Female, aged 38. The patient had been healthy prior to onset. In the late autumn of 1865 she developed a very rapidly growing tumor of the lymph nodes in the left cervical region which reached the size of a child's head in a very few weeks. Tincture of iodine and salves were applied, without result. Examination on admission on February 5, 1866 revealed that the whole left side of the neck, the nape of the neck and part of the cheek, were occupied by a hard tense hemispherical swelling which was almost immovable. It extended from the clavicle to the parotid. The left sternomastoid muscle and the great vessels were deeply imbedded in the growth, the larynx being pushed far to the right. The patient had become markedly emaciated in the few months since onset. There was great pain, dyspnea, and deglutition was almost impossible, as the teeth could scarcely be separated. She was given nourishment and injections of morphine. During the next few weeks the growth increased in size and the right cervical nodes also enlarged, to the size of a man's fist. The skin over the most protuberant portion of the growth on the left side broke down in several places, from which blood and serum drained. By February 26, 1866 the patient could no longer swallow, and was fed through a catheter.

Concurrent Infection: Three weeks after admission, on February 28, 1866 she developed facial erysipelas. It was noted that on the first day of the infection the growth was softer and that the patient could again open her mouth and swallow. The erysipelas caused much swelling of the face and eyelids. The attending physicians did not attribute the softening of the growth to the erysipelas however, believing that an abscess in the pharynx had burst, as there was an evil-smelling discharge of mucus containing what appeared to be pus from the mouth. The erysipelas subsided and the patient became stonger daily. The growths regressed very rapidly. By March 6, 1866 one week after the infection had developed, the larger mass in the left cervical region was reduced to half its former size and the nodes in the right side had entirely disappeared. Regression continued very rapidly. Two days later the patient suddenly collapsed and died a few hours later (March 9, 1866). At post-mortem examination it was found that the growth had regressed to the size of an apple and was fairly movable. There were no enlarged nodes on the right side. The structure of the tumor was reduced to a network of connective tissue containing large amounts of yellowish fluid in its meshes. The cells had undergone fatty degeneration and had broken down into a yellowish-white emulsion, containing numerous fat granules. By injecting water into the growth it could be filled out again to its former size. Absorption had apparently taken place through the lymphatics. Portions of the tumor that were still intact showed it to be a round cell sarcoma.

Comment: It would appear that in this case death was due to toxemia caused by absorbing such large amounts of necrotic tumor tissue, following very rapid regression of the growth, rather than to the direct effects of the erysipelas infection. This history suggests that in treating such extensive growths in the future, it may be necessary to establish free drainage in order to evacuate necrotic tissue and prevent such toxemia. The case was reported in full by Dr. Wilhelm Busch in 1866 and was cited by Fehleisen, Tillmans and Moullin as well as Coley.

References: 9, 90, 92, 124.

SERIES B, INFECTION FAILURES, DETAILED HISTORIES

CASE 2: Inoperable malignant lymphoma of the tonsil, neck and groin.

Previous History: Mme. F., aged 52, at Beugnon, France. The patient was the mother of five children. She had always been in good health until January 1884, when the cervical nodes became enlarged. These continued to increase in size until they were enormous, reaching in one great mass from the spine behind to the chin in front. The tonsils were enormous and there was a mass of enlarged nodes in the pharynx, almost completely obstructing the throat, which interfered seriously with deglutition and respiration. There was a mucous discharge from the nares and respiration was labored. The hearing was affected by the obstruction of the Eustacian tubes. There was also a mass in the groin, the size of a fist.

Concurrent Infection: In October 1884, an attack of erysipelas developed, from a nasal excoriation. It soon spread over both sides of the face. The temperature did not rise above 40°C. As soon as the erysipelas developed, the tumors began to regress. By the sixth day, they were very much smaller, the neck could be moved, and the pharynx was free so that deglutition was easy, and the hearing had returned to normal. Diminution continued until the tumors had almost disappeared: the nodes were still palpable in the neck and the groin, but were so small that the family considered the patient cured.

Clinical Course: Three weeks later they again began to grow and in one month they had regained their former size. The overlying skin became livid and discolored, the condition having the appearance of lymphosarcoma. The legs gradually became infiltrated, then the hands, and the eyelids, and there was evidence of lymphatic leukemia. Death occurred suddenly at the end of April 1885, apparently due to brain involvement. Ricochon stated that no treatment was given during the course of the erysipelas infection, but that a month afterwards arsenic was vigorously administered by mouth, and by injection into the tumors without any apparent effect.

References: 90,109.

CASE 4: Inoperable recurrent lymphosarcoma of the tonsil and neck confirmed by microscopic examination following the first operation at Professor V. Czerny's Clinic in Heidelberg, Germany.

Previous History: Carl F., male, aged 54. The patient was of very strong build, well nourished, robust, and of healthy appearance. He had never been ill except with "gastric fever" four years previously. He suffered from hemorrhoids. Examination in May 1887, showed a hard, flat swelling of the left tonsil, the size of an egg, still quite movable, and apparently not affecting the neighboring tissues. Liquids appeared to be more difficult to swallow than solid food. The cervical nodes were enlarged to the size of walnuts on the left side, also those on both sides of the larynx.

Surgery: The patient came to Czerny's Clinic where an operation was performed on May 12, 1887, consisting of curettage of the enlarged carotid nodes, excision of a submaxillary node, extraction of the second lower molar, partial resection of the lower jaw, and partial excision of the tonsil.

Clinical Course: A recurrence developed in the supraclavicular nodes in September 1887, and increased in size. Cod-liver oil was administered, also injections of Fowler's solution (arsenic), but the disease progressed, with involvement of the cervical nodes and a recurrence in the tonsil.

Concurrent Suppuration: After about 45 injections of Fowler's solution had been given, six abscesses developed in various places, one after another. These were incised and continued to suppurate for a long time. There was

decided local atrophy and a marked decrease in the patient's appetite and strength. Also some of the growths appeared to be increasing, especially behind the left ear, in the region of the mastoid process, where there was a mass the size of a hen's egg, and another above the scapula almost the size of a child's head. The recurrent growth in the tonsil gradually increased in size so that deglutition and respiration became increasingly more difficult. The larynx was markedly displaced to the right. With the laryngoscope one could observe under the tongue on the left side of the epiglottis tumors the size of hazel nuts and walnuts. The general condition had deteriorated. Deglutition became almost impossible and death was expected within a few days.

Concurrent Erysipelas: On March 7, 1888, an erysipelas infection developed from the lower abscess on the edge of the cervical tumors. The first symptom was a chill during the night, then a fever of 39.5° and a slight reddening the next day which extended across the chest where blue veins showed more distinctly than normally. During the next day the infection spread over the entire chest, back, neck and face, and the fever remained between 39.5° and 40.5° . By the second day there was ulceration, of bad odor, much stronger than before, and the swelling on the neck was softer to the touch. The erysipelas then spread over the left abdomen. By March 12, 1888, it was noted that the tumors of the neck and throat were considerably softer and smaller, as indicated by a careful physical and laryngoscopical examination. Eight days after the infection developed, erysipelas was still present. The ulceration was diminishing in some places, still profuse in others, but there was considerable diminution of swelling. The temperature was 39°C . By March 18, 1888 the infection remained only on the right thigh. It was noted that the tumor of the neck was hardly one-fourth its former size. Ulceration continued. The temperature returned to normal on March 21, 1888, two weeks after the erysipelas developed. The growth over the scapula, which had been almost the size of a child's head, had reduced to the size of a pigeon's egg, and there remained two tumors at the base of the tongue the size of hazel nuts. The recurrence in the left tonsil had regressed completely.

Clinical Course: The patient was allowed up out of bed on March 25, 1888 as the temperature was normal. About April 10, 1888, the little nodules at the base of the tongue were removed by electrocautery. The general condition gradually improved. However, on May 1, it was noted that the nodes in the left carotid region were swelling, and also a nodule was found in the left axilla. This rapidly increased to the size of a walnut. By May 20, 1888, these tumors had grown rapidly.

Induced Erysipelas Infection: On June 2, 1888, using cultures of *Streptococcus erysipelas* furnished by Fehleisen, inoculations were made on both sides by scarification. The following day a chill occurred and the temperature rose to 41°C . A well-marked erysipelas infection developed, involving the trunk. The former abscess opened and discharged, the tumors softened. By June 15, 1888 there was considerable diminution of the swelling on the left and complete regression of the one on the right side. Ulceration continued.

Clinical Course: Thereafter the growths continued to increase in size rapidly. The patient grew weaker. Death occurred on November 18, 1888, from collapse, following a hemorrhage from a vessel in the throat.

Reference: 76.

SERIES B, INFECTION FAILURES, DETAILED HISTORIES

CASE 6: Very extensive inoperable round cell sarcoma of the neck, confirmed by microscopic examination following incomplete operation by Dr. F.R. Zeit.

Previous History: Mrs. L., aged 58, a German. No details are given as to the family and previous personal history. The patient consulted Dr. Sauerhering of Wausau, Wisconsin on April 29, 1895. Examination revealed a large solid tumor extending from the angle of the lower jaw forward and downward closely to the bone, but not firmly attached, with processes extending downwards behind the sternocleidomastoid muscle and the sternum. The glenoid cavity was involved, allowing very limited motion of the lower jaw, it being impossible to separate the incisor teeth more than 1.5 cm. so mastication was impossible. As the patient and her family were clamoring for an operation, Sauerhering decided upon incomplete surgical intervention.

Surgery: On May 2, 1895, he operated. After removing the larger part of the mass, using the elevator to separate it from the maxilla, he found that the large vessels and nerves of the neck were embedded in the tumor, the trachea just beneath the cricoid cartilage being affected, a portion about 5 cm. long infiltrating down behind the sternum. The nodes in the supraclavicular space were involved as well as those at the base of the tongue, the latter causing painful deglutition. The cavity was packed with iodoform gauze and the skin drawn together and sutured.

Clinical Course: The post-operative course was uneventful. The patient was told to go home and wait until notified that Coley's toxins had been obtained, and then to return for treatment. She stated that after she returned home the progress was uneventful for several weeks.

Concurrent Infection: The parts then became very sensitive, began to swell and the color deepened and discharge developed. Her mental health had been affected by her inability to take sufficient nourishing food, as well as by the depression caused by her knowledge of the character of her growth. However, Sauerhering stated that she was a "very strong-minded woman, wanted to recover, and aided our efforts wherever she was able." At this time the entire side of the neck was swollen and enlarged, deglutition was very difficult and painful, breathing impaired and the patient could not separate the jaws as much as formerly. She returned on June 4, 1895, about five weeks after operation. At this time she presented a pitiable appearance. The entire surface over the site of the tumor was a dusky red, with very offensive discharge from the sinus. Sauerhering believed that the reddening and swelling was an attack of erysipelas. No details are given as to fever, or other systemic effects, except that "she began to improve" during and following this infection.

Toxin Therapy (Unknown formula of Coley Toxins prepared by Mulford, probably similar to Buxton VI): Injections were begun on June 14, 1895. The suggested dosage for this product was 3 to 5 minims, but as this was Sauerhering's first experience with toxins, he decided to be on the safe side and injected 1 minim as an initial dose (site not stated). This caused a very prompt and violent reaction, a chill lasting 1½ hours, followed by a febrile reaction of 105°F, pulse 140-150. Three days later a dose of 2 minims produced the same reaction but slightly less violent. The dose was increased rapidly to 5 minims, injections being given at intervals of 96 hours. Reactions became weaker, depression not so marked. The interval was then shortened to 48 hours, and injections continued until the discharge became so copious and foul-smelling that a second operation appeared necessary.

Further Surgery: On July 30, 1895, large amounts of necrotic tissue was curetted under anesthesia. It was found that necrosis of all the malignant

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

tissue had occurred, and a small opening had formed into the trachea and esophagus, allowing air and food to escape into the wound. The sharp spoon was used and while working in the neighborhood of the large vessels and nerves there was a sudden sharp convulsive movement and arrest of respiration, apparently due to scraping of the phrenic nerve.

Clinical Course: Following this operation there was rapid decline in her condition. She died of inanition on August 11, 1895.

In reporting this case, Sauerhering stated that though this was his only trial of toxin therapy, he admitted that "a great many circumstances entered into the case which would have been a drawback to any mode of treatment." He added: "notable is that fact that disintegration and liquifaction had begun to take place as substantiated by the foul, sanious discharge under the attack of erysipelas, before the injections were begun, thus illustrating . . . the intense action of the streptococcus of erysipelas on malignant growths." (112)

Comment: Compare this case with those in which toxin therapy was begun before such extensive incomplete surgical procedures, or continued steadily for a considerable period. Little or nothing is known of the potency of Mulford's preparation as it was not used in many cases. It is probable that injections were made in or near the tumor, judging by the type of reaction elicited.

Reference: 112.

CASE 7: Recurrent lymphosarcoma involving the left axilla, the left scapula, and the overlying tissues, confirmed by microscopic examination by Dr. W.F. Whitney, who reported: "A large lobulated mass, composed of glands and fibrous tissue, which had infiltrated the muscles. The mass was nearly the size of two fists. Microscopic examination showed the structure to be solid masses of small round cells, separated by relatively large areas of connective tissue. In places these could be seen following the course of blood vessels in the perivascular lymph spaces. Round celled sarcoma originating in the lymph glands." (108)

Previous History: J.R., male, aged 6 (in 1896) of Townsend, Massachusetts. The patient had always been well until onset, in April 1892, six months prior to the first operation, when lumps appeared in the left side of the neck, which rapidly increased in size. There were no other symptoms. Examination on admission to Massachusetts General Hospital on October 6, 1892, showed a well-nourished boy. On the left side of the neck were numerous enlarged nodes. They were movable, elastic, not knotted together, and not tender or fluctuating. There was no redness of the skin. A few small nodes could be felt on the other side of the neck, but none were abnormally enlarged in the axillae or groins. There was no leukocytosis or splenomegaly.

Surgery: On October 7, 1892, 16 of the left cervical nodes were removed. The diagnosis at this time was lymphadenoma. The patient was discharged well a week later.

Clinical Course: Fowler's solution was taken in 1 minim doses three times daily for a few months following his discharge.

Further Surgery: On October 2, 1893, a recurrent growth, which had appeared in the region of the scar, was removed surgically. The general health had been excellent. In June 1895, one small node behind the cicatrix was removed through a 3 cm. incision, and a large node was shelled out from the left submaxillary region. They were dark and looked malignant.

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

Clinical Course: The boy was discharged about a week after the operation. Soon after this small lumps were noted in the left axilla. These gradually increased in size, but were never painful. Their growth was rapid from December 1895 to October 1896. The child had been under the care of Dr. R.H. Fitz. He was generally well and active. He was readmitted to Massachusetts General Hospital on October 1, 1896. Physical examination at this time showed a boy of good development, but of pale color. A large mass was evident in the left axilla, extending to the border of the pectoralis major. It involved the tissues of the anterior and posterior surfaces of the scapula, as well as the scapula itself. Posteriorly, the skin over the tumor was adherent, raised and discolored. The growth evidently infiltrated directly from the scapular mass and was movable, firm and elastic. In the posterior triangle of the neck there was a movable well-defined tumor as large as an olive, and two as large as peas. A small hard mass was also perceptible just below the clavicle.

Further Surgery: On October 5, 1896, an extensive dissection was made of the axilla and of the scapular mass. The growth was found to infiltrate the border of the pectoralis major and the latismus dorsi. It was dissected away from these muscles, the incision being enlarged sufficiently by backward extension. The dissection was carried down to the axillary artery and vein and backward to the scapula. In front the tumor was less adherent, but behind it merged imperceptibly into the skin, which was hard, and on section porky. The induration and infiltration involved and surrounded the axillary vessels. Further dissection was abandoned, the pulse and respiration being too poor to warrant prolonging the operation. The posterior triangle of the neck was not touched. The post-operative course was uneventful, and the patient was allowed outdoors on the ninth day in a wheel chair.

Concurrent Infection: On October 21, 1896, the 18th post-operative day, the temperature rose to 103°F. A fluctuating spot at the upper angle of the wound was opened and about an ounce of pus was evacuated. Sulphonaphthol dressings were ordered for the whole wound, which had become septic. The temperature remained high. On November 1, 1896, the respiration became labored. The following day the patient was seen by Fitz, who found the left chest dull in the lower back with absence of respiration. The pulse was 180 to 200. It did not seem possible for the child to recover. However, the axillary wound slowly healed by granulation. The pleurisy was followed by empyema. This was finally opened freely. On November 7, 1896 fluid was aspirated from the chest below the scapula. The fluid was pale green (S.G. 1026), with considerable pus and mononuclear cells. The patient also had diarrhea. A second aspiration was done that evening, and a third on November 11, 1896, which showed more purulent fluid. By November 16, 1896, the temperature had dropped to normal, but the child showed progressive emaciation and weakness. He developed a marked kyphosis and asymmetry of the chest, with bulging of the left side. The chest was aspirated a fourth time (pus) and a fluctuating spot over the sacrum was also aspirated, and creamy pus evacuated. The child was discharged home on November 20, 1896, to be treated by the family physician. During his convalescence, the induration about the scapula disappeared and the remains of the inoperable recurrent lymphosarcoma slowly regressed.

Clinical Course: At the end of six months Dr. Maurice H. Richardson stated that he "visited the patient at his home in Townsend and found no sign whatever of the mass. The scapula rested in its normal position upon the thorax; the induration of the tissues had entirely disappeared, also the discoloration and infiltration of the skin. There was not the slightest evidence of any growth about the scapula."

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

The child was examined several times during the next two years. On one occasion Richardson detected one or two enlarged nodes in the right cervical region. He made a very careful examination of the boy on August 18, 1898, at which time he appeared to be in very good health. "The region formerly occupied by the axillary and scapular tumor was entirely free from even a suspicion of involvement. There was, however, an evident metastasis in the mediastinum. He died suddenly two days later." (108)

In presenting this case before the American Surgical Association in 1898, Richardson stated: "The case seems of interest in connection with the subject of disappearance of malignant tumors under the influence of a general toxemia, whether artificially or accidentally produced. The occasional cure of malignant disease by internal medication excites not only interest but incredulity. . . . Scepticism may be so extreme that carefully observed cases are thrown out for one reason or another though I cannot but think chiefly for the reason that they were successful." (108)

"As an illustrative example I would cite one of the most extraordinary cures of sarcoma that I have ever seen." (95, pp. 24-25). "In this case Dr. Garland and myself at the time of operation made the diagnosis of hopeless malignant disease of the abdominal wall. Dr. Whitney made a careful microscopic examination of the tumor and reported it as fibrosarcoma. After some months' treatment with Coley, the tumor, though as large as a child's head, disappeared." (The abdominal wall had been infiltrated to a thickness of at least 15 cm.)

In conclusion he stated: "If a cure by means other than surgical is, from the very fact of cure, declared sufficient proof of a mistaken diagnosis, there seems little use in presenting evidence. I am convinced, however, that a considerable number of tumors, pronounced malignant, disappear under local or systemic conditions which are artificially produced. The curative influence of micro-organisms upon malignant growths, whether during the course of an accidental wound infection or under the influence of deliberate toxins injection, is a hopeful indication of far-reaching possibilities for good." (108)

References: 82, 95, p. 24-25; 108

CASE 8: Recurrent inoperable round cell sarcoma of the tonsil with metastases at the angle of the jaw and in submaxillary nodes, confirmed by microscopic examination.

Previous History: M.F., female, aged 4. The family and early personal history were not recorded. Onset, four weeks prior to admission the patient developed a swelling on the right cheek at the angle of the jaw. This caused difficulty in eating because the throat seemed involved. The child started speaking through her nose. She was brought to the clinic on February 11, 1902. Examination revealed an enlarged node the size of a chestnut in the right submaxillary angle. The growth was movable and hard, also very painful to palpation. The right side of the soft palate and tonsil were reddened and protruding.

Surgery: The provisional diagnosis was peritonsillar abscess and an incision was made. No pus was found and there was little bleeding.

Concurrent Infection and Fever: The child then developed a slight fever and was admitted to the hospital on February 13, 1902. There was rapid increase in the swelling in the tonsil and right side of the soft palate. The node at the angle of the jaw also increased in size. The temperature ranged from 37.5°C. and 39.8°C. The physicians were now more than ever sure that the condition was due to an abscess. Further incisions were made and on

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

February 19, 1902 an evil smelling discharge developed which contained *Streptococcus pyogenes* and *Staphylococcus aureus*. On February 21 and 22, 1902, the temperature remained over 39°C., attaining 39.8°C. and at night there was a bloody pus-like discharge from the external right ear, with severe earache. The specialist found a perforation into the external auditory meatus, which discharged the same foul pus as the tumor in the throat. The middle ear was not involved. The peritonsillar abscess was believed to have extended to the external meatus of the ear. On February 23, 1902 the discharge was no longer so brown or so foul-smelling, but became yellowish-white and contained only streptococci. The swelling in the throat became smaller and the nodular swelling on the cheek was less painful. There was still some scanty pus-like discharge from the external meatus, where there was necrosis of the skin about 1.5 cm in diameter. The morning temperature was now only 37.5°C., the evening temperature 39°C. The child ate and drank with great appetite. By February 25, 1902 the tumor in the throat had "decayed" and there was no more discharge. The perforation in the external meatus was free from discharge and quite dry, the temperature normal. The child was discharged from the hospital on February 28, 1902 at which time examination revealed no further swelling in the throat. The hard node in the submaxillary region was still the size of a bean, and was only slightly painful. The skin of the cheeks and submaxillary region were now covered with little blisters which itched somewhat. The ear seemed to be entirely healed. At this time the diagnosis of peritonsillar abscess was considered certain.

Clinical Course: Four weeks later, or by March 24, 1902, all the former symptoms had recurred. The mother stated that the child had remained perfectly healthy for three weeks and then the symptoms rapidly recurred. The protruding mass in the soft palate and tonsil assumed more and more the aspect of a solid tumor. There was no fever.

Surgery: An exploratory operation was performed and no pus was found. (The former perforation in the ear had healed). The tumor in the throat became the size of an apple and a specimen was removed for microscopic examination and reported to be a round cell sarcoma. The tumor grew with much greater rapidity after the biopsy, so that by March 28, 1902 deglutition and breathing were impossible.

Clinical Course: The child had to be nourished by rectal feeding. A tracheotomy was then performed under local anesthesia. For a few days the child remained somewhat improved. Because of the size of the tumor she could no longer close her mouth, and she attempted to pull out the tumor mass, and thus caused severe hemorrhages. The disease progressed rapidly with marked loss of weight. Death occurred on May 14, 1902.

Post-mortem examination revealed a tumor mass in the mouth with a very rough and uneven surface filling the buccal cavity and involving the tongue. The right antrum of Highmore was almost completely filled with polypoid tumor masses, extending over to the right naris down to the submaxillary fossa. From the tumor in the buccal cavity a probe extended directly to the mass in the antrum of Highmore. There was some evidence of fatty degeneration of the tumor mass and anemia.

Reference: 62

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

CASE 9: Inoperable extensive lymphosarcoma of the right axilla, supraclavicular fossa and cervical region, confirmed by microscopic examination at autopsy by Professor Zeigler. The structure of the tumor was that of a so-called "hard lymphoma."

Previous History: Female, aged 64. The family and early personal history were not recorded, except that the patient was said to have had erysipelas repeatedly. Onset, in late March 1903, she developed a tumor of the right axilla. This increased very rapidly in size, especially during the summer of 1903. A similar tumor of rapid growth also appeared in the supraclavicular fossa. At examination by Professor Kraske on September 26, 1903, the tumor in the right axilla was the size of a child's head, the overlying skin was somewhat reddish, but movable. The growth in the supraclavicular fossa was approximately the same size. In the right cervical region at the angle of the jaw anterior to the sternocleidomastoid muscle, nodes the size of walnuts were palpable. There was no lymphadenopathy in the left groin, axilla or neck, nor in the right inguinal region.

Concurrent Erysipelas: The right forearm became a diffuse bluish-red with edematous swelling. The skin in this area was scaly with some fissuring. Kappes, in reporting the case, stated that "obviously this was an erysipelas taking its course." Physical examination was otherwise negative except for some cyanosis, some pulmonary emphysema and some splenomegaly. The large tumor in the axilla was incised "with negative results." A few days after admission to the clinic, a fresh erysipelas infection developed beginning in the cracks in the skin on the forearm, and this involved the entire forearm, lasting approximately four weeks. During this period the tumor in the axilla which had previously been the size of a child's head regressed to the size of a goose egg and the enlarged nodes the size of walnuts at the angle of the jaw disappeared. The consistency of the remaining tumor masses also changed; they shrank to coarse knotty tumors.

Clinical Course: The patient died five weeks after admission to the clinic, which was a little over four weeks after the first outbreak of erysipelas. Death was reported as due to "a catarrhal disease of the respiratory passages with hypostasis in the lower lobes of both lungs." Autopsy reported a tumor in the right axilla the size of a fist which was not clearly delimited. In the right supraclavicular region there was a tumor the size of a small orange. The overlying skin was freely movable. Transverse section showed the interior of both tumors were full of coarse connective tissue, poor in cell structure. The main mass of the tumors consisted of greyish yellow necrotic foci, mostly encapsulated in indurated connective tissue. Necrosis was most pronounced in the tumor of the supraclavicular fossa, whereas vascular invasion in that area was minor. Microscopic examination: At first sight the foci could be thought to be tubercular lymph nodes, but detailed examination excluded tuberculosis. The necrosis in the midst of the tumor tissue was interpreted as "beyond a doubt regressive changes to which the tumors had been subjected." Kappes stated that some of these changes were regarded as having occurred at an earlier period, possibly from the effects of some of the earlier attacks of erysipelas which the patient had had, but possibly were all due to the final erysipelas. There were necrotic areas which extended directly into the tumor masses without any borders of connective tissue. In individual spots these showed non-nucleated masses of cells which could not be stained. In other areas they showed only slightly stained cells containing shrunken nuclei. In other places there were amorphous crumbling masses of nuclei with intensely darkish black stain clearly showing pyknosis. All these were signs that the

SERIES B: INFECTION FAILURES, DETAILED HISTORIES

cells had died. "The occurrence of necrotic foci in the midst of the tumor, and the reaction of the formation of connective tissue poor in cells, changing soon to shrinkage, were understood to be probably due to the direct action of erysipelas cocci. These erysipelas cocci had migrated from the site of the infection in the forearm by way of the lymphatic system." (75) The considerable decrease in the size of the tumors was primarily due to resorption of the necrotic tissue and furthermore to the inflammatory condition to which the tumors had been subjected by the infection. The marked vascularization of individual parts of the tumors were regarded as probably an unsuccessful attempt of renewed proliferation or else tissues which, when in a state of inflammation, had become more vascular. This vascularization appeared to be in regression.

Reference: 75.

SERIES C: LYMPHOSARCOMA SUCCESSFULLY TREATED BY TOXIN
THERAPY ALONE OR COMBINED WITH SURGERY AND/OR
RADIATION: 32 CASES

The name in parenthesis following the case number refers to the physician, surgeon or hospital handling the case. At the end of each abstract the bibliography references numbers are given. Cases are listed chronologically according to the type of toxin used. For a brief description of the formulae used in making the various preparations of Coley toxins and the comparative potency of these formulae see references 92 and 95.

*Years Traced
After Onset*

- ✓ 1. (CHAMBERLAIN): Mr. N., aged 25; recurrent inoperable rapidly growing small round cell sarcoma of the tonsil, involving pillars of fauces; onset, October 1894; primary growth considerably larger than hen's egg removed November 1, 1894; suspicious granulations noted 23 days later; entire base cauterized by electrocautery; rapidly growing recurrence filled space between pillars of pharynx, extending beyond; February 14, 1895: toxins (Buxton V, filtrates), mostly i.m. in arm or neck, 1 in tumor, duration 3 or 4 months, 17 to 35 minims every 3rd day; *marked local inflammatory reactions, some fever, chills; in 7 weeks recurrence practically disappeared*, patient gained 8 lbs., was able to continue working during treatment; *complete regression, no further recurrence or metastases*; traced well spring 1900. (10;46) 5½
2. (W. B. COLEY): E.J., female, aged 23; advanced intra-abdominal round cell sarcoma involving omentum, mesentery of small intestine, gall bladder; onset, May 1894; explored August 16, 1894, specimen removed; October 1, 1894: toxins (Buxton VI) every 48 hours alternately into abdominal wall and buttocks for over 4 months, slight febrile reactions, pain in tumor region; *rapid complete regression*; sinus curetted twice spring 1895, toxins resumed for 33 days, July 1895; third curettage sinus, September 1895; operated twice for gallstone 1898-1902, no evidence of tumor found; married, 1904; normal pregnancy, confinement 1905; well, though frail, nearly 30 years, then arteriosclerotic heart disease 1943, incomplete intestinal obstruction 1946, cholecystectomy 1937, adhesions freed; developed large carcinoma sigmoid colon 1951; explored July 2, 1952, revealed metastases to mesenteric nodes; died next day cardiac failure, aged 80. (18, case 9; 29, case 6; 42, case 30; 85; 88; 100.) 58
3. (RODMAN and COOMES): Mr. W., aged 20; three times recurrent inoperable lymphosarcoma tonsil and pharynx, 4 operations with prompt recurrence each time; toxins (Buxton VI) begun by Coomes 1897; *recurrent tumors entirely disappeared, no further evidence disease*; traced well 1912. (40, case 124 in Table); 42 (case 30 in Table of other men's cases); 46. 16
4. (STEINER): A.P., female, aged 26 months; recurrent inoperable small round cell sarcoma cervical, submaxillary, supraclavicular and axillary lymph nodes; onset, early January 1902; too extensive for removal, whole cervical region involved from mastoid to clavicle, also submaxillary, axillary nodes; biopsy taken; March 8, 1902 toxins (Buxton VI) in vicinity of tumors for 3 weeks, (no improvement noted); continued another 3 weeks with daily x-ray; contracted varicella; child sent home, apparently much worse; *within 2 weeks definite improvement seen*,

SERIES C, TOXIN TREATED SUCCESSES, ABSTRACTS

Years Traced
After Onset

continued steadily; all traces of tumors disappeared by absorption; no further evidence of disease; in excellent health: married, had 4 children; 1949, developed basal cell epidermoid carcinoma right temporal region, excised; 1950 uterine hemorrhages, D and C, then hysterectomy, oophorectomy (multiple small leiomyomata, adenomyosis uteri, papillary cyst adenoma ovary); November 1951, epithelial cyst of right pyriform sinus, excised December 13, 1951; December 1953, lipoma of neck, excised, shadow seen in mediastinum; early 1954, x-ray to mediastinal mass without effect; removed surgically 1954 (hemangioma, no evidence of malignancy); in excellent health thereafter, last traced very well 1969. (Note many types of neoplasms developing in this case.)
(34;40, case 6;42, case 3; 44; 65; 100)

67

5. (GLASS): M.S., male, aged 20; recurrent operable small round cell sarcoma neck; onset spring of 1905; mass 5 cm. in diameter removed surgically February 28, 1906; prompt recurrence, of rapid growth; recurrence and sublingual nodes removed March 1906; shortly thereafter toxins (Buxton VI) given daily at first, continued 1 year; few x-ray treatments, tonics also given; *no further evidence disease; in excellent health when last traced 1914.* (42, case 3, other men's cases; 46)

9

6. (W. B. COLEY & FAMILY PHYSICIAN): Mrs. J. G., aged 45, inoperable lymphosarcoma axilla; onset December 1905; incomplete removal March 1906 (adherent to axillary vein); March 26, 1906: toxins (Buxton VI) at first by Coley, then at home by family physician for several weeks; *remains of growth regressed completely; no further evidence disease; in excellent health, except for severe bronchitis summer 1907; last traced well 1915.* (42, case 19; 46; 65, case 42)

10

The following case had the Tracy X preparation:

7. (W. B. COLEY): A.L., Female, aged 11; inoperable round cell sarcoma right tonsil, nearly blocking pharynx and cervical nodes, bilateral; untreated; patient had congenital cleft palate, harelip; onset, early September 1906; November 9, 1906: toxins (Tracy X) given aggressively, febrile reactions 103°-105°F.; 80 to 90 in 5 months, almost all injections made in cervical tumors, none into tonsillar growth; *improvement evident in 2 or 3 weeks; complete regression of all tumor masses in 2 months; surgical drainage established for necrotic tumor tissue from neck, portion of tonsil removed, 2-3 weeks after beginning toxins, central portion necrotic, several drams necrotic tumor curetted; (microscopically, tumor cells much swollen, good deal of degenerated intercellular substance); no further evidence of disease; in excellent health except for rheumatic fever, 1930, subject to colds thereafter; ovarian cyst and gallstones removed 1933; chronic abscess right breast 1939 or 1940; in excellent health thereafter; last traced well April 1969.* (34; 40, case 4, p. 27; 42, case 13; 46; 85; 100)

62½

Next 17 cases received the Tracy XI preparation:

8. (W. B. COLEY): E.C.T.B., male, aged 21; recurrent inoperable small round cell sarcoma inguinal, iliac lymph nodes; onset January 1908, 1 week after local trauma; removed surgically 3 weeks after onset; prompt recurrence, inguinal, iliac nodes; March 26, 1908; toxins (Tracy XI), i.m. in buttocks, marked reactions, to 104°F.; 27 in 1 month, *causing almost complete disappearance of tumors; returned home, toxins con-*

SERIES C, TOXIN TREATED SUCCESSES, ABSTRACTS

Years Traced
After Onset

tinued irregularly that summer; further recurrence by October; toxins resumed by Coley, partly into groin tumor, partly i.m. in buttocks; 18 in 21 days, then continued at home by family physician for 6 months; *complete regression; no further evidence disease*; in perfect health until 1950, supra-orbital neuralgia; supra-orbital nerve avulsed November 1, 1950; and again in March 1955; neuralgia recurred fall 1957; no other complaints; somewhat addicted to alcohol; hospitalized fall 1968; alive and well April 1969, 61 years after onset. (40, case 17, p. 41; 42, case 26; 46; 47; 85; 95, case 13; 100)

61

9. (LILIENTHAL): B.S., male, aged 22, large lymphosarcoma ileocecal region, with many enlarged regional nodes; onset December 1907, cramps, emesis; December 7, 1908; growth resected, ileotransverse colostomy, nodes removed *in toto* but Lilienthal considered removal incomplete; w.b.c. 14,000 at time of operation; December 1907 toxins (Tracy XI) given post-operatively; *condition rapidly improved; complete recovery; no further evidence of disease*; in good health over 3 years, then developed pharyngeal symptoms, lost 18 lbs., mass removed at operation on August 5, 1912, (at first believed to be further lymphosarcoma, later examined by Klemperer and reported to show no lymphosarcoma); toxins resumed, again condition rapidly improved; in good health thereafter; presented by Lilienthal at N.Y. Surgical Society, February 26, 1936; not traced subsequently. (78; 100)

28

10. (W. B. COLEY AND FAMILY PHYSICIAN): F.N.W., male, aged 58; recurrent inoperable round cell sarcoma right cervical region; onset July 1906; growth size of small hen's egg incompletely removed, November 24, 1908; some evidence recurrence by December 21, 1908 when toxins were begun by Coley; continued at home, 82 in 7 months, 5 i.m. in pectorals, 2 in tumor, rest in buttocks i.m., (Tracy XI, XIF and Parke Davis XII) *no further evidence disease; general health perfect*; well until sudden death coronary thrombosis, June 19, 1938. (40, case 15; 42, case 4; 46; 85; 100)

32

11. (LIPSETT): P. K., male, aged 41; highly malignant inoperable small round cell sarcoma of submaxillary region; onset, April 1909, grew rapidly to size of hen's egg, very vascular, marked infiltration muscles, skin, also periosteum of lower maxilla; June 12, 1909; *incomplete removal, prognosis hopeless*; June 1909 (following operation) toxins (Tracy XI) given under Coley's direction, 4 a wk. at first, 56 in 1 year. (intervals of rest between courses); *shortly after toxins were begun remains of growth gradually softened, disappeared in 3 months; no further evidence disease*; last traced in good health 1923. (35; 40, case 5; 46).

14

12. (HARMER): L. P., female, aged 33; twice recurrent inoperable malignant lymphoma (small round cells and large lymphocytes) involving antrum, ethmoid, right superior maxilla, posterior septum and nasopharynx; onset, September 1909 during 5th week of 4th pregnancy; had "cold" for 2 weeks prior to 1st operation, March 3, 1910, ethmoid cells curetted, sphenoidal sinus opened, contained pus, was curetted, right superior maxilla removed; toxins (Tracy XI) begun March 10, 1910 (7 days post-operative), 14 i.m. in 21 days, very small doses, one moderate febrile reaction; confinement May 1910; became pregnant

29

again (without having any menses) 2 months later; immediate recurrence; 2nd operation August 6, 1910; specimen removed from outer septum; 3rd operation October 20, 1910, partial removal of septum for recurrent nodular growth; no toxins given; 5th child born April 3rd, 1911; considerable dull pain right side of face; May 11, 1911 4th operation attempted, abandoned as disease had extended to left side of face, nose, would have required resection of left superior maxilla as well; toxins resumed, given in vicinity of tumor, febrile reactions to 103°F. for 3 weeks; *recurrence completely disappeared*; developed pulmonary tuberculosis, but recovered 1914; 6th child born March 1914; (total of 9 children, 6 born after onset); no further evidence disease; in good health until cholecystitis, 1942, 1944; operation advised for single large calculus, but was not done; 1950 chronic bronchiectasis, emphysema, generalized arteriosclerosis, arthritis; bad fall, 1954; lung symptoms subsided; hypertension; recurrent pneumonia 1957; some evidence renal neoplasm August 1957; died November 5, 1957. (64, case 5; 65 case 1; 82; 100)

48

13. (W. B. COLEY): C. H. W., male, aged 56; inoperable rapidly growing round cell sarcoma tonsil and cervical nodes; onset, March 1910; untreated except for biopsy; May 26, 1910; toxins (Tracy XI), i.m., mostly in pectorals, fairly severe reactions from larger doses; *immediate softening cervical tumor, decrease in size evident in a week, disappeared in 4 weeks; tonsil tumor diminished more slowly, completely regressed in 2 or 3 months*; no recurrence; remained well except for cerebral arteriosclerosis, causing progressive dementia, death August 8, 1915, almost 5½ years after onset. (5; 37; 40, case 13, p. 36; 42, case 17.)

5½

14. (W. B. COLEY and family physician): P. J. B., male, aged 67; inoperable large round cell sarcoma of left axilla; onset, early 1908, stationary almost 2 yrs., rapid growth after grippe, early December 1910; appetite poor, some weight loss; February 2, 1911, incomplete removal (extended beneath clavicle); February 13, 1911; toxins (Tracy XI) 2 to 4 a week. i.m. in pectorals, continued at home by family physician, exact duration not recorded but was at least 2 or 3 months; *remains of growth, extending beneath clavicle, regressed completely*; recurrence September 1913 beneath pectoralis major, attached to subclavian vein; excision; toxins resumed, as prophylactic; *no further evidence disease*; in good health 1915, not traced thereafter. (42, case 23; 85, Book 63, III #18103, 1911; 100)

over 7

15. (HOGUET AND STANTON): C. F. R., male, aged 29; inoperable lymphosarcoma axillary region (primary in groin); onset, summer 1909; mass in groin excised early 1910, Fowler's solution given; some loss of weight, metastases involving right axillary nodes apparently incompletely removed August 8, 1911; toxins (Tracy XI) August 23, 1911, daily i.m., in pectorals, alternating right and left, later 3 or 4 a week for 5 or 6 months; *regained lost weight, no evidence of disease, in excellent health 1911-1939* except for colds, herniotomy; was strong, athletic; summer 1939, splenomegaly; splenectomy, November 1939; Boerk's sarcoid; brief respiratory infection spring 1940; otherwise normal health until summer 1940 then developed Hodgkin's disease, transfusions, x-ray, vitamins; biopsy, sternal marrow puncture; no further toxins given, disease progressed rapidly, death August 15, 1941. (40, p. 118; 42, case 5, Table of axillary cases; 100; 126)

32

SERIES C, TOXIN TREATED SUCCESSES, ABSTRACTS

Years Traced
After Onset

- ✓ 16. (JACOBY): W. S., male aged 58; inoperable small round cell sarcoma left inguinal nodes; strain in region of groin just prior to onset, March 1912; steady rapid growth; incomplete removal April 25, 1912, flap sloughed, large granulating surface; May 1912: toxins (Tracy XI), daily for 9 weeks; good febrile reactions; *wound healed rapidly, remains of growth disappeared*; no recurrence, died May 21, 1923, chronic myocarditis, arteriosclerosis. (42, case 2, other surgeons' cases; 100). 11
- ✓ 17. (TRITCH): Mrs. J. B. M., female, aged 62; twice recurrent lymphosarcoma inguinal, iliac nodes; onset, prior to September 1911; at 1st. operation, September 28, 1911, femoral vein involved, obliterated, with resultant gangrene in its tract; local recurrence, 2nd operation; 3 months later again recurrence above Poupart's ligament; October 10, 1912: toxins (Tracy XI), for 3 or 4 months; *no improvement in 1st 3 weeks, then gradual decrease in size, during most of later treatment only given once weekly in office; complete regression, no further recurrence; alive and well 1918.* (40, case 66 in Table, p. 159; 42, case 16 in Table other surgeons' cases; 46; 100) 7
- ✓ 18. (FOWLER AND W. B. COLEY): Dr. P. V., male, adult; recurrent inoperable rapidly growing round cell sarcoma of submental and cervical nodes; onset, early 1913; soon after onset lesion in submental region biopsied; removed surgically several days later; recurred in 4 weeks, rapidly extended from mastoid to clavicle (size of fist), considered inoperable; April 10, 1913: toxins (Tracy XI) begun by Fowler; given daily i.m., dose increased rapidly; *immediate regression, softening, opened spontaneously, discharged necrotic tumor tissue; dosage diminished, immediate rapid increase in size, 15 lb. weight loss; dose then increased, toxins given more aggressively by Coley, i.m., in pectorals; rapid decrease in cervical and submental tumors; toxins continued by Fowler, daily or every 2 days; complete regression, gained weight; toxins continued about 6 mos.; no further evidence disease; in good health thereafter; died from drowning.* (Detailed history deserves study.) (40, case 12, p. 36; 42, case 7; 46; 85, case #20450; 95, case 21, p. 61; 100) 15
- ✓ 19. (W. B. COLEY AND SHORES): H. W., male, aged 33; recurrent inoperable lymphosarcoma of the submaxillary and cervical nodes; onset, early 1913; excision; recurrence under sternomastoid; excision; diffuse swelling in 1 week; no attempt at further removal for fear of injuring facial nerve; toxins, (Tracy XI) June 5, 1913, at first no febrile reactions, and 3 small recurrent nodules appeared in cicatrix, grew slowly until 1st febrile reaction obtained; thereafter toxins thrice weekly by Shores; *submaxillary mass disappeared, other remained stationary; 3rd operation, October 7, 1913; Coley removed 3 growths about carotids, wound fulgurated; toxins resumed thrice weekly, 150 in 12 months, with intervals of rest; complete recovery, no further evidence of disease; well until death, cerebral hemorrhage.* (40, case 11; 42, case 9) over 5
- ✓ 20. (HARMER): A. A. K., male, aged 25; rapidly growing recurrent malignant lymphoma, of groin and pelvis; onset, March 1913; stationary in size at first, then gradually increased until February 1914, when growth was very rapid, constant pain; growth size of croquet ball incompletely removed March 8, 1914, involved nodes extending far into pelvis not touched; x-ray, 10 minutes daily for 4 wks.; growth recurred rapidly during radiation, filled Scarpa's triangle, extending above Poupart's

SERIES C, TOXIN TREATED SUCCESSES, ABSTRACTS

Years Traced
After Onset

ligament into pelvis (9 x 15 cm.); April 9, 1914: toxins (Tracy XI) into growth every 2 or 3 days, up to 11 minims; *at first marked decrease in size, softening, then increase; finally under continued toxin therapy given about 10 mos. growth ruptured, discharged necrotic tumor tissue, regressed completely*; no further recurrence; in good health until sudden death, 1940 from "overdose epsom salts taken for abdominal discomfort," (apparently due to ruptured appendix). 65; 82, case # 194236; 100)

27

21. (TUHOLSKE): M. B., male, aged 30, inoperable round cell sarcoma of right pharynx and nasopharynx, causing almost complete obstruction of airway; tracheotomy considered necessary, but toxins tried first; (date of onset not recorded); toxins (Parke Davis XII) May 1915, *no effect even in massive doses i.m., remote from tumor; 1st dose Tracy XI caused violent reaction, chills, high fever, necrosis in center of tumor; complete regression in 6 weeks; left hospital in perfect health; few months later recurrence in other side of pharynx, abducens nerve paralysis (apparent brain involvement); toxins resumed fall 1915, daily i.m. in arms for a week, no reaction, no effect on tumor; then given in thighs, abdominal wall alternately, marked reactions, rapid complete regression except for nerve paralysis; toxins stopped last week of January 1916; patient began to vomit January 25, 1916, very drowsy, delirious, in coma 3½ weeks, fed by proctoclysis, hypodermoclysis; weight reduced to 89 lbs.; regained consciousness, began to improve, gained 28 lbs. in 7 weeks, complete regression, speech and sight normal, nerve paralysis gone; no further evidence of disease; in good health except for symptoms of eunuchism which were apparent as he came out of coma March 1916; in good health 26 years, then mild hypertension, 1942; slight hemiplegia, 1945; moderate arteriosclerosis, 1946; died coronary occlusion, arteriosclerotic heart disease November 23, 1948, at 63. (46; 95, case 23; 100)*

33

22. (HOLLINGSWORTH): F. M., male, aged 40; inoperable reticulum cell sarcoma, primary on back involving right cervical and abdominal nodes, involving over half of abdominal cavity; onset, fall 1916, tumor on back following grippe; December 1916 general weakness, loss of weight (20-25 lbs. in 6 mos.); spring 1917, primary tumor excised, 3 or 4 months later node enlarged in right cervical region; by June 1917 extensive involvement of abdominal and cervical nodes; considered inoperable after biopsy at Mayo Clinic, where toxins were advised as only hope; July 9, 1917: toxins (Tracy XI) 9 in 1 month, *large doses, very severe reactions; marked regression*; then declined further injections; went to St. Louis, exploratory laparotomy, tumor incised, sewed up; improved; patient decided to resume toxins August 3, 1918; given intramuscularly at intervals for 5 years, maximum dose 53 minims; *complete regression, regained health, resumed arduous job*; in good health until sudden attack angina pectoris June 17, 1928, died next day of 2nd attack. (46; 100; 126)

11½

23. (LILIENTHAL): H. C. P., male, physician aged 54; lymphangiosarcoma of bronchus; onset, following influenza and pneumonia, December 1918; persistent cough April 1919, evening temperature to 104°F., considered to be lung abscess until biopsy at bronchoscopy July 1919 revealed neoplasm; lost 17 lbs. in few months preceding toxin therapy; July 9, 1919: toxins (Tracy XI) begun by patient himself (a physician) under

Lilienthal's direction, mostly in abdominal wall, later in pectorals, caused severe pain, marked induration at sites of injection; *in 4 weeks cough ceased; in 8 weeks, chest x-rays showed marked improvement*; then after intense coughing for 2 days expectorated very thick greenish pus, some staphylococci and diplococci presumably catarrhalis were present but no tubercle bacilli, no bits of lung or neoplasm were found in the sputum; toxins given 13 months; *gained 30 pounds during treatment* following initial 5 lb. weight loss in 1st week; fluoroscope showed area to be smaller; April 1920, hemoptysis during severe exertion; few others treated by pneumothorax with improvement; resumed his medical practice, cholecystectomy October 1924; again examined by Lilienthal October 1925, who found him "extremely well," died lung abscess, non-tubercular, April 13, 1927. (5; 46; 77; 126)

8

24. (GRAHAM & W. B. COLEY): MRS. F. B. H., female, aged 41, twice recurrent lymphosarcoma of the groin (small round cells); onset 1915, lumps in groin, at site of previous removal of non-malignant grapefruit-sized mass; these were excised; recurred 4 years later; 2 masses size of lemons removed at 3rd operation; again recurred; toxins (Tracy XI) begun July 9, 1919 following 4th operation, 16 in 16 days i.m., mild reactions, did not prevent another recurrence, December 1919; *toxins resumed, caused tumor to decrease while being given, but growth increased when injections were stopped*; toxins resumed April 14, 1920, when recurrence was 4 cm. in diameter, 1-12 minims i.m., febrile reactions to 104°F.; 5 radium packs given between April 30 and December 3, 1920 (no radiation sickness); *developed 2 large abscesses in groin at sites of injection; gained weight, much better general condition, mass regressed*; later patient gave herself the injections in deltoid regions or thighs; total duration 2 years; final radium treatment January 1922; *no further recurrence*; well next 20 yrs. then diabetes mellitus, controlled by diet; developed tumor left parotid gland, excised 1942, grade I malignancy, adenomatous structure; 1947, congestive heart failure; carried on digitalis, diet and insulin; hematuria, August 1949, papillary transitional carcinoma of bladder, grade I excised August 17, 1949, base fulgurated; recurrence thoroughly fulgurated November 1949; chronic cystitis, further heart disease; urinary symptoms worse 1953, liver enlarged, nodular; died general intra-abdominal metastases from her bladder carcinoma, September 19, 1953. (Note multiple primaries in this case). (46; 85)

38

The next 7 cases received Parke Davis XII or XIII preparation of Coley toxins.

25. (OGHSNER): MRS. V. H., aged 17; inoperable small round cell sarcoma right axilla; onset, early February 1910, pain in right shoulder, swelling in right axilla, of rapid growth; mass size of grapefruit incompletely removed March 10, 1910; toxins (Parke Davis XII) in deltoid muscles, marked reactions, given 6 mos.; *remains of growth regressed; no recurrence*; had 3 children; in excellent health 1946; not traced subsequently. (100)
26. (SPENCER): Corp. N. M., male, aged 26; twice recurrent inoperable lymphosarcoma of left cervical nodes; onset, early 1911 while in British Army; swelling in left neck, enlarged slowly; soft rounded tumor beneath sternomastoid excised March 6, 1912; very rapid recurrence; left side of neck filled with masses of enlarged nodes; March 29, 1912, in-

36

SERIES C, TOXIN TREATED SUCCESSES, ABSTRACTS

Years Traced
After Onset

complete removal; again very rapid recurrence; toxins (Parke Davis XII) begun April 6, 1912, given into tumor; *cessation of growth in 7 days, steady regression, even after toxins were temporarily stopped*; 3 courses injections given; 1st 16 doses totalling 76 minims; 2nd 14 doses totalling 140 minims, 3rd 15 doses totalling 150 minims, *almost all given in or near tumor; complete regression in 5 weeks*; toxins continued for 12 weeks; no further recurrence; rejoined army unit when toxins were stopped; *in perfect health thereafter*; entirely well when last seen 1923. (40, p. 139; 46; 117; 118)

12

27. (RICHTER): Mrs. M. M., female, aged 50; inoperable malignant lymphoma of retroperitoneal nodes; onset December 1931; early 1932 much gas, backache, abdomen very large; exploratory operation, February 18, 1932, disclosed soft, solid, immovable retroperitoneal tumor protruding through root of mesentery size of large melon; specimen removed, tumor very friable, vascular, entirely inoperable; 2 x-ray treatments; toxins (Parke Davis XIII) March 14, 1932, given daily i.m., marked reactions and chills (to 103.6°F.; *complete regression in 3 weeks*; few weeks later nodular tumor again became palpable throughout abdomen; 1 more x-ray treatment (1062 r.); April 1932; toxins resumed May 19, 1932, 11 more in 4 months.; x-ray given August 1932 to abdomen (1062 r.); during 1933-34 lymphadenopathy noted in groins, axillae, cervical or retroperitoneal nodes at each examination and further small doses x-ray given to some of these areas; *after 1935 remained free from further evidence of disease*; however, x-ray therapy was given to left axilla October 1939 (388 r.) and to mediastinum, January-February 1940 (2752 r.) and to left axilla (800 r.); in good health until 1950-1951, then cholecystitis; requiring cholecystectomy September 1951 (no evidence of the lymphosarcoma); in very good health until January 1960; cerebral hemorrhage, partial paralysis; gradual symptoms intestinal obstruction, required exploratory laparotomy; died July 1960, aged 78; autopsy showed no evidence of lymphosarcoma. (46; 100)

28½

28. (GOOSMAN): H. P. J., male, aged 33; recurrent inoperable lymphosarcoma supraclavicular, cervical, axillary nodes (bilateral) and mediastinum; good deal of emotional and economic stress prior to onset, summer 1931, left supraclavicular lymph nodes enlarged; September 1931; surgical removal; October 2, 1931; x-ray (11 in 17 days); January 1932; shadow in mediastinum, recurrence supraclavicular region, left axillary nodes also involved; April 25, 1932; toxins (Parke Davis XIII) i.m. and i.v. every 48 hours for 6 months, *very marked reactions, fever, nausea, some diarrhea; regression axillary, mediastinal and other lymphadenopathy, complete except for a few slight nodes in axilla*; latter given 500 r x-ray; further toxins, *reactions to 103°F.*, total duration, 20 months; *complete regression*; during early part of treatment lost 30 lbs. then regained normal weight and strength; no further evidence of disease, in good health except for symptoms of gastric ulcer 1951, due to stress; x-ray revealed diaphragmatic hernia, possible ulcer, short esophagus; ulcer diet for 6 weeks; no further gastric trouble; fell, tearing ligaments of shoulder 1955; shingles, 1965; coronary, April 1966; also mild diabetes; in good health April 1969. (46; 84; 100)

37½

29. (PLAUT): J. P. G., male, aged 23; large recurrent inoperable lymphosarcoma right submaxillary region; onset early January 1942, increased

to size of baseball in less than 2 weeks, patient of very nervous temperament; admitted for perforated peptic ulcer, January 27, 1942, 3 weeks after onset; emergency operation: pre-pyloric gastric ulcer plicated; 12 days later *pulmonary infarct from embolus (hemolytic streptococci)*, fever to 103°F.-104°F.; large tumor entirely disappeared in 2 days; recurred 2 weeks later; no operation attempted, other than incisional biopsy; April 1, 1942: toxins (Parke Davis XIII and special preparation made by them using Buxton VI formula), 17 i.m. and i.v. in less than a month; reactions to 105.8°F. from i.v.; no immediate benefit noted; deep x-ray then given (6 to 8); recurrence disappeared, no further evidence disease; in good health except for obesity and further gastric symptoms, finally requiring partial gastrectomy 1952; weight then decreased from 246 to 185 lbs; June 10, 1966, sudden retinal hemorrhage caused permanent blindness right eye; in very good health April 1969. (100)

over 27

30. (REMBERT): Mrs. R. Q. B., female, aged 63, inoperable retroperitoneal lymphosarcoma; onset during 1942, gradual weight loss; December 1942 during attack of influenza, abdominal mass first noted, also slight bloody stools; rapid increase in size: By February 1943 extended from region of spleen, dipping over pelvic brim; February 10, 1943, exploratory laparotomy, no attempt at removal, biopsy taken; toxins (Parke Davis XIII) begun 3 days later, 17 daily in arm, thereafter once weekly, total duration about 2 months; reactions very mild at first, later marked, to 103°F.; x-ray begun after 1 week of toxins alone, given same day as toxins, 28 in all; had abdominal hemorrhage early May; hospitalized 6 weeks; vitamin therapy; growth regressed completely, gained 30 lbs.; in excellent condition except for a bad gallbladder; cerebral accident, June 1962, residual speech difficulty; died cerebral hemorrhage November 1963, (100)

21

31. (WEHRLY): S. E., female, aged 14 mos.; inoperable giant follicular lymphoblastoma of left axilla and inguinal regions, with possible skeletal and pulmonary metastases; had bad tonsils and continued respiratory infections since birth, also poor home conditions; onset, February 3, 1948, began to drag right leg; that week left forearm was burned, became infected; had huge infected tonsils, nasopharyngitis, fever to 104°F. for 4 weeks, prior to March 4, 1948, when first seen; destructive lesions in proximal and distal right femur (thought to be metastatic); March 14, 1948, measles; March 19, 1948, tumors 3 cm. and 1.5 cm. in diameter excised from left axillary region; post-operative fever to 102°F.; chest films April 27, 1948 revealed mass in hilus of left lung; x-ray (left axilla, 1208 r.), mediastinum (1725 r.), epigastric region (275 r.) delivered in 33 days; in middle of this cycle developed varicella, fever to 103°-104°F.; early August developed conjunctivitis; August 18, 1948; toxins (Parke Davis XIII), 15 in 22 days (7 i.m., 8 i.v.), moderate reactions; between September 16 and October 20, 1948, x-ray to femoral lesions (3075 r.); proximal lesion small, distal lesion disappeared by October 13, 1948; complete regression, no further evidence of disease, but continued to be subject to tonsillitis and 1955 had infection of right foot with right inguinal lymphadenopathy; tonsillectomy January 1956, general condition improved thereafter; November 1956 herpes zoster; traced well May 1964, lost to follow up thereafter. (100)

over 16 yrs.

The following case received Sloan Kettering XIV preparation.

32. (MEMORIAL HOSPITAL): J. M, male, aged 3; inoperable lymphosarcoma 10 cm. in diameter, right parotid region and regional lymph nodes; onset late September 1946; biopsy November 18, 1946, otherwise untreated; toxins (S. K. I. XIV) begun December 7, 1946, 25 i.v. in 50 days during which 10 x-ray treatments also given (200 r.); febrile reactions averaged 102°-104°F.; regression apparent 1 wk. after toxins begun, large mass completely disappeared in 3 wks.; February 20, 1947 3 x 4 cm. recurrence present in center of radiation field; nasopharyngitis March 2, 1947 caused 5-day postponement of operation scheduled for next day; in this interval the recurrence decreased to 2 x 3 cm.; excised March 7, 1947; considered edema of neck at operative site, penicillin given; x-ray (2500 r.) March 17, 1947; further nasopharyngitis March 31, 1947; given sulfamerazine; January 1948, varicella; impetigo of face, hands; symptom-free as regards neoplasm but a severe behavior problem; poliomyelitis fall 1949, causing partial paralysis lower extremity requiring long leg brace; severe scabies fall 1951; also persistent eosinophilia and severe emotional and behavior problems; finally overcame these; married 1965 daughter born 1966; no recurrence of lymphosarcoma, in good health September 1967. (85; 100)

SERIES C, TOXIN TREATED SUCCESSES
SELECTED DETAILED HISTORIES

CASE 1: Recurrent inoperable small round cell sarcoma of the tonsil, of rapid growth, involving the pillars of the pharynx, confirmed by microscopic examination of the primary growth, by Dr. Gray of the Army Medical Museum, Washington. (For microphotos, see 10, p. 291)

Previous History: Mr. N., male, aged 25, married, born in Arkansas, living in Washington, D.C., a type compositor. The family history was negative for cancer or tuberculosis. The patient's previous health had been very good, his only illnesses having been measles and pertussis in childhood. He was six feet tall, weighed 198 pounds, had been married 2½ years and had one child. On October 25, 1894 while eating chestnuts, a piece became lodged between the growth (the existence of which the patient had no knowledge) and the pharynx. The irritation occasioned by this caused him to seek medical advice. Examination on October 28, 1894 showed a growth on the right tonsil, considerably larger than a hen's egg, extending into the uvula, which was pushed over almost to the left side and which extended downward about 4 cm. below the tonsil, being somewhat pyramidal in shape, with the apex downward and to the left, leaving a space for breathing about the size of a pencil. The apex of the growth was somewhat mulberry in color and appearance, with indication of early ulceration.

Surgery: The probable dangerous nature of the growth was explained to the patient and an operation was performed on November 1, 1894, less than a week after its existence was first discovered. The operation was performed under cocaine. The only difficulties experienced were due to the hemorrhage and the tendency of the growth to fall into the pharynx, causing gagging and stoppage of air. This was obviated by passing silk through the apex of the growth and elevating it, while the base was being detached. The base, extending about 2 cm. internal to the pillar of the pharynx, and involving it, was thoroughly curetted. The surgeons believed the growth had been completely removed. As a few suspicious granulations were noted by the 23rd day, Dr. Frank T. Chamberlain of Washington, D.C. cauterized the entire base deeply with electrocautery.

Clinical Course: The patient progressed favorably and the wound healed. However, there was evidence of recurrence in late January 1895, about two months after operation. By February 14, 1895 the recurrent growth had increased so rapidly that it filled the space between the pillars of the pharynx and extended outside this area, the greatest growth appearing at the lower part of the previous site.

Toxin Therapy (Buxton V, filtrates): Injections of Coley toxins were begun by Chamberlain on February 14, 1895, the initial dose being 17 minims injected into the right arm. (This was about 30 times the usual initial dose). The site of injection became sore and there was a slight chill but no febrile reaction. The next day there was a chilly sensation and general aching of the body, moderate headache, restlessness and sleeplessness. The site of injection became very red, swollen for about 30 cm. in circumference and extremely sore. On February 16, the arm was much better and the patient was able to go to work (type setting). A second injection was given on February 17, three days after the first. This caused the arm to become very sore and red over an area 20 cm. in circumference. The throat was less swollen externally and internally. There was increased redness about the pillars and beginning ulceration of the upper right side under the anterior pillar, covered with what appeared to be

SERIES C, TOXIN TREATED SUCCESSES, DETAILED HISTORIES

yellow pus. The patient stated very positively that the throat was much better than it had been a week before. On February 19, 1895 the throat was less inflamed, but the ulcer was rapidly increasing in depth. A third injection was given that night at 7 p.m. On February 20, the ulcer was $1\frac{1}{2}$ cm. deep, triangular in shape. It was treated by application of cupri sulphatis 50 percent and wash of hydrogen peroxide. On February 23 and 25, 1895, the toxins were injected into the left arm as the soreness produced in the right arm interfered with his work. On February 27, 1895, 27 minims were injected in the neck over the site of the tumor. This caused a febrile reaction of 1°F. , a heavy chill, and general soreness of the limbs, with decided shooting pains and an aching sensation at the site of the tumor. On March 4, 7, 11, 14, 21 and 24, 1895 further injections, apparently in the neck, gave similar results, except that the reactions were less as regards incapacitating the patient from attending to business, although the throat appeared more inflamed, if possible, the day after the injections, and the reactions at the site of injection seemed to decrease. The injection on March 31, 1895 was given in the arm, a dose of 35 minims. Only one injection was made directly into the tumor, as the patient was "fearful of the consequences" from what he had seen of the reactions in the arm and neck. This injection (17 minims) was made on April 4, 1895. Chamberlain stated that approximately a third of this was probably lost owing to the sudden gagging caused by the irritation of the needle, but two hours later there was a decided chill and febrile reaction. The patient was presented before the Medical and Surgical Society of the District of Columbia on April 8, 1895. Chamberlain stated in presenting him: "As regards the results of the foregoing, I will leave you to judge, as you have the patient before you. He has gained eight pounds in weight, and although I consider it necessary to keep up the treatment for some time to come, I think you will concur with me in saying he is nine-tenths on his way to recovery—My own results in this case . . . would indicate a trial of this treatment, at least in inoperable cases, under which this would have been classed at the time of first injection." The exact duration of treatment is not recorded. The growth regressed completely.

Clinical Course: There was no further recurrence. The patient remained well when last traced $51\frac{1}{2}$ years after onset. Dr. J. D. Southard of Fort Smith, Arkansas, wrote Dr. William B. Coley in regard to this case on June 2, 1900: "A former patient of mine treated by Dr. Frank T. Chamberlain of Washington, D.C., in 1894 and 1895, the nature of the growth being small round cell sarcoma of the tonsil, was entirely cured, the toxins being administered after efforts at removal with the knife had been made and the growth had returned." He added: "I understand you introduced the remedy and I believe it to be a very valuable one in suitable cases."

References: 10, 46.

CASE 2: Inoperable intra-abdominal round cell sarcoma, involving the omentum, the mesentery of the small intestine and the gall bladder, confirmed by microscopic examination by Dr. F. Schwyzer, pathologist of the Lenox Hill Hospital, New York.

Previous History: Miss E. J., female, aged 23, born in Switzerland. The patient had always been well until onset, in May 1894, when she first noticed pain in the right hypochondriac region. It was intermittent, but became more and more frequent as well as more severe. The general health deteriorated until by August 1894 the patient was confined to bed and a "hardness" was noticed in the right side.

Surgery: An exploratory operation was performed by Dr. Willy Meyer at Lenox Hill Hospital on August 16, 1894. A solid tumor was found, appar-

SERIES C, TOXIN TREATED SUCCESSES, DETAILED HISTORIES

ently springing from the mesentery of the small intestine and attached to the gall bladder. It was clearly inoperable and no attempt was made to remove it, as such an operation would have required resection of a portion of the large as well as the small intestine, and a portion of the liver as well as the omentum. A specimen was removed for microscopic examination.

Clinical Course: The patient was then referred to Dr. William B. Coley and was admitted to Memorial Hospital on October 1, 1894. Palpation at this time revealed an intra-abdominal mass beneath the cicatrix in the right hypochondrium, about 10 cm. in diameter. The tumor was hard and fixed. There remained a sinus in the center of the incision, discharging a thin viscid fluid, possibly bile. The patient weighed 140 pounds and was five feet five inches tall.

Toxin Therapy (Buxton VI): Injections were begun by Coley on October 1, 1894, six weeks after the exploratory laparotomy. They were given alternately into the abdominal wall and the buttocks, and were kept up every other day with occasional intervals of rest until February 7, 1895, a little over four months. The febrile reactions were mild, the maximum being 100.4°F. Apparently the injections produced pain in the tumor region. The growth rapidly regressed, and by February it was reduced to little more than a slight induration. The general condition was good.

Clinical Course: The patient was readmitted to Memorial Hospital on April 16, 1895, in order to attempt to close the sinus. She had been losing strength and had had intermittent pain in the abdomen, especially when the sinus became blocked up. Examination at this time revealed a small tumor the size of an English walnut below the liver, which was freely movable. At the end of the sinus was some "jelly-like material", looking like necrotic sarcoma tissue.

Surgery: The sinus persisted although it was curetted on April 24 and May 19, 1895, each time being packed with iodoform gauze.

Further Toxin Therapy: Injections were resumed by Coley on July 16, 1895, and were continued for 33 days, skipping a few days. The maximum febrile reaction was 100.4°F.

Further Surgery: A third curettage of the sinus was made on September 11, 1895. The incision extended down to the peritoneum. Coley palpated the region and stated that no tumor could be felt. The patient was discharged on October 12, 1895, the sinus still persisting. She was readmitted on February 18, 1896, when she began to feel weaker and entirely unable to work. She had gained ten pounds in the four months since her discharge, but the sinus had opened and closed every few days, and when closed caused much pain, referred to all parts of the body. She stated that her menstrual periods had become more profuse and painful, lasting seven days instead of four as formerly. She became very nervous. She had had frequent diarrheal movements since October, and although her appetite was good, she stated that she "got out of breath easily." Examination on February 18, 1896 showed some inflammation about the sinus, which was very painful on pressure. On incising the membrane there was a purulent discharge. The abdomen had been very much swollen and painful on palpation, the patient stated.

Further Surgery: On March 4, 1898, the fistulous tract was explored. Coley reported that this operation was as follows: "An incision three inches long was made at the site of the old cicatrix, and the sinus was followed up until it entered a closed pouch containing two or three ounces of mucopurulent fluid. By carefully enlarging the incision the finger was introduced and the pouch proved to be the gall bladder. Several calculi about 1.5 cm. in diameter

SERIES C, TOXIN TREATED SUCCESSES, DETAILED HISTORIES

were found tightly wedged in the cystic duct. These were dislodged with great difficulty and the cavity of the gallbladder drained with iodoform gauze. The peritoneum was opened for a distance of about one inch and quickly closed with catgut sutures. The most careful examination failed to reveal the slightest evidence of the tumor which had been present 18 months before." The patient made an uneventful recovery and was discharged on April 9, 1896, in good condition. In reporting this case Coley stated: "The sarcomatous mass which was originally adherent to the gallbladder probably caused an opening in the gallbladder when it broke down under the toxins, which soon became connected with the sinus." The sinus persisted in 1898, although the patient was otherwise in excellent health. She was again operated upon at Lenox Hill Hospital for gallstones between 1898 and 1902.

Clinical Course: Thereafter she moved to Oregon and was married on September 3, 1904; she gave birth to a healthy daughter sometime prior to 1906. She was then lost to follow-up by Coley. Our search for this patient was successful. One of her cousins stated in 1952 that she "was always frail". In 1943 she developed hypertensive arteriosclerotic heart disease. By February 1944 she had auricular fibrillation and cardiac enlargement. In June 1946, barium enema showed irregularity and possibly a filling defect of the transverse colon. On December 4, 1946 she was admitted to the hospital. Four days later barium enema showed incomplete intestinal obstruction on the left half of the transverse colon. On December 15, 1947 a cholecystectomy was performed and the adhesions were freed. Findings at this time were: "Transverse colon adherent to anterior abdominal wall at site of old incision kinked and obstructed. Gall bladder contracted, full of stones; no evidence of malignant disease." She was again hospitalized in April 1949 with cardiac decompensation, tachycardia 134. In May 1951 she had four to five bloody bowel movements daily for a week. On May 21, 1951 a barium enema was given. This was very difficult due to the age of the patient and the marked amount of pain resulting from the enema. The colon and rectum filled normally, but there appeared to be obstruction at the rectosigmoid as barium scarcely passed this to the splenic flexure and no barium was seen beyond the splenic flexure. The descending colon was distorted with numerous diverticula and some saw toothing. Another barium enema was given on June 15, 1951. The diagnosis was diverticulosis and diverticulitis of the rectosigmoid and possible malignancy. At operation on July 2, 1951, a large growth of the sigmoid was found about 10 cm above the peritoneal reflexion. This had apparently extended through the wall of the bowel and become fixed to the fundus of the uterus at one point and metastasized along the lymphatics and along the aorta above the bifurcation to the inferior mesenteric nodes. None were palpable above the inferior mesenteric. Obstruction was beginning but had produced no dilation or impairment of circulation. No metastases were palpable on the liver. Death occurred the next day, July 3, 1951, at the age of 80, the primary cause being cardiac failure, the secondary cause being the carcinoma of the sigmoid colon with metastases. She had had hypertensive arteriosclerotic heart disease for eight years prior to her death, which occurred 58 years after onset of the lymphosarcoma of the omentum and mesentery of the small intestine, from which she recovered under toxin therapy alone.

References: 18, (case 9); 29 (case 6); 42 (case 30); 85 (case #3127, Book 12, 1895; case #3645, Book 13, 1895; case #4013, Book 15, 1896); 88; 100.

SERIES C, TOXIN TREATED SUCCESSES, DETAILED HISTORIES

CASE 4: Recurrent inoperable small round cell lymphosarcoma of the cervical and supraclavicular lymph nodes confirmed by microscopic examination by Dr. Walter B. Steiner of Hartford Hospital from a specimen removed at the second operation.

Previous History: A.P., female, aged 2 years and 10 months. Three of the patient's aunts died of cancer, one maternal and two paternal. (All were over 50 years old). The child was apparently perfectly normal from birth. She was bottle fed. There had always been a "black spot on the neck." Onset early in January 1902 the mother noticed a "bunch" a little smaller than an egg on the neck at the site of the black spot. This had apparently developed suddenly, as nothing had been noticed previously.

Surgery: An exploratory operation was performed by Dr. E. N. McKnight at the Hartford Hospital on January 27, 1902, but the disease was considered too extensive for removal and a specimen was removed for microscopic examination. Dr. William B. Coley saw the patient in consultation on March 8, 1902, when he found the whole right side of the neck involved by a series of tumors extending from the clavicle to the mastoid bone. The submaxillary and axillary nodes were also involved. The clinical appearance of the disease was typically sarcomatous. Coley advised toxin therapy.

Toxin Therapy (Buxton VI): Injections were made by Steiner and McKnight, the site being the neck, in the vicinity of the tumors. They were given daily for a period of three weeks, at which time there appeared to be no change. At Coley's suggestion, however, they were continued for another three weeks. The dosage used was not recorded.

Radiation: Daily x-ray treatments were given during the latter part of her stay at the hospital (factors not recorded).

Concurrent Infection: The child contracted varicella while in the hospital (at the age of three). No details were available as to this infection, but it may have played a part in her recovery.

Clinical Course: After a total of six weeks' treatment the condition appeared to be so much worse that further injections were deemed inadvisable and the child returned home. Within two weeks there was very definite improvement which continued steadily until all trace of the tumors disappeared by absorption. The child regained her former health. At the age of five or six, she had a very severe case of pertussis. She also had mumps, measles and scarlet fever — ordinary cases. She was presented by Coley before the Congress of Clinical Surgeons of North America on November 12, 1912 and again in November 1918, at Memorial Hospital, New York. She remained in excellent health, married and had four children, three sons and a daughter. The latter had cerebral palsy.

Early in 1949 the patient developed a lesion in the right temporal region. This was removed on April 16, 1949 at the Day Kimball Hospital in Putnam, Connecticut, and proved to be an epidermoid carcinoma, basal cell type. The patient reported on November 30, 1950 that "for many months I had been flowing excessively, really hemorrhaging, so Dr. Philips had me go in for a dilatation and curettage, hoping that would straighten me out. It failed to do that, so in October I went in again for a hysterectomy." (100) The pathological report from the Hartford Hospital was as follows: "Cervix shows some chronic inflammatory change: uterus showed multiple small fibroids, largest one being 1 cm. Tubes and ovaries were also present. Ovaries appeared atrophic. Attached to a tube were two fluid-containing cysts 4 x 3 x 2 cms. in size. In the lining of one of these was a slight papillary projection which was firm. Microscopic: myoma is not remarkable. Cervix is markedly cystic. Endome-

SERIES C, TOXIN TREATED SUCCESSES, DETAILED HISTORIES

trium was atrophic and inactive. Small islets of endometrial tissue found deep in the myometrium. Ovarian cyst adenoma was lined by low columnar epithelium. Diagnosis; Leiomyomata and adenomyosis of uterus. Chronic cervicitis. Papillary cyst adenoma of ovary." (65)

The patient made a good recovery from this operation and resumed her active life at home and in the community. She consulted Dr. Robert Dinolt, of the Day Kimball Hospital, Putnam, Connecticut in November 1951 because of "vague difficulties in swallowing." He found a small pedunculated tumor of the right pyriform sinus which was about 1 cm. in diameter. It appeared cystic and he removed it surgically on December 13, 1951. The histological findings were that of an epithelial cyst.

In December 1953, the patient developed a small lump on her neck at the end of the old incision. X-ray examination showed a shadow in the mediastinum. Dr. Claude C. Kelly of Hartford, Connecticut, removed the tumor of the neck which proved to be a lipoma. Dr. Ralph T. Ogden of Hartford then gave her x-ray therapy over the mediastinum without causing any regression of the mass. Dr. R. Starr Lampson of Hartford operated upon her on April 7, 1954, and removed the mediastinal tumor which proved to be a hemangioma with no evidence of malignancy. She made an uneventful recovery, although it took her some time to regain her strength. The patient was examined periodically by Dinolt. She remained well and was in excellent health when last traced on February 14, 1969, 67 years after onset of the lymphosarcoma.

Comment: It is of interest to note that this patient developed a considerable variety of neoplasms both malignant and benign over a period of 52 years; lymphosarcoma, 1902; basal cell epidermoid carcinoma, 1949; multiple leiomyoma uteri, ovarian papillary cyst adenoma, 1950; epithelial cyst, pyriform sinus, 1951; lipoma, neck, 1953; hemangioma mediastinum, 1954.

References: 34; 40 (case 6); 42 (case 3); 44; 65; 100.

CASE 6: Inoperable lymphosarcoma of the axilla, confirmed by microscopic examination at the West Pennsylvania Hospital, of Pittsburgh. The pathologist reported: "The tumor is composed of small round cells of about the size and appearance of mononuclear leucocytes with a moderate amount of intercellular substance, and shows the reticulum and stroma formed by branching stellate forms, which is characteristic of lymphosarcoma." (46)

Previous History: Mrs. J.G., female, aged 45. The family history was non-contributory. Onset, in December 1905 the patient first noticed a lump in the left axilla which slowly increased in size until March 1906.

Surgery: It was then removed surgically, as completely as possible. It was adherent to the axillary vein, and removal was regarded as incomplete. The patient was referred to Dr. William B. Coley by Dr. K. I. Sanes of Pittsburgh.

Toxin Therapy (Buxton VI): Injections were begun by Coley on March 25, 1906. They were continued for a number of weeks after the patient returned home, by the family physician. Apparently the remains of the tumor in the axilla regressed completely.

Clinical Course: The patient remained in excellent health except for a severe attack of bronchitis in the summer of 1907, followed by an attack of intercostal neuralgia brought on by coughing. She received therapy during her convalescence at Cape May, New Jersey, where she was seen by a specialist who stated there was no evidence of recurrence of the lymphosarcoma. She never had any recurrence. She remained well when last traced ten years after onset, in December 1915.

References: 42 (case 19); 46; 65 (case 42).

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CASE 7: Inoperable round cell sarcoma of the tonsil and cervical lymph nodes, confirmed by microscopic examination of specimens of both tonsil and neck tumors by Drs. Martha Tracy and Bertram H. Buxton of the Loomis Laboratory, Cornell University.

Previous History: A.L., female, aged 11 of Hartford, Connecticut. The family history was negative for malignancy. The patient had always been in good health, except that she had frequent attacks of tonsillitis and the usual childhood diseases. She had a congenital cleft palate and hare lip. Onset, in 1905 she developed a small swelling in one of the nodes on the right side of the neck. In early September 1906 considerable enlargement was noted in this region, which increased rather rapidly. Examination by Dr. William R. Porter of Hartford, in the latter part of October 1906 revealed a large tumor apparently originating in the right tonsil and nearly blocking the pharynx. The child was also examined by Dr. McKnight and a number of other physicians in Hartford, and all considered the tumor inoperable. The patient was referred to Dr. William B. Coley on November 9, 1906. Physical examination at this time showed a growth the size of half a hen's egg, on the right side of the neck, involving the tonsil and pharyngeal wall, nearly blocking the passage. On the opposite side of the neck, just below the angle of the jaw, there was a tumor about the size of a small hen's egg, fairly movable, smooth in outline, fairly firm in consistency. The skin was not adherent.

Toxin Therapy (Tracy's X): Injections were begun by Coley on November 9, 1906, and continued with two or three intervals of rest until the middle of May 1907, the patient receiving in all between 80 and 90 injections, nearly all of which were given into the tumors of the neck, but none into the tonsil. She was rarely able to tolerate more than 2 or 3 minim doses without a severe chill, followed by a temperature of 103° to 105°F. The maximum temperature was 106°F. After two or three weeks' treatment, there was a marked softening of both neck and tonsil tumors. Examination was made in consultation with Dr. W. L. Culbert, who removed a portion of the tumor of the tonsil. It was found that the central portion of this tumor had become necrotic, and several drams of broken-down tumor tissue were curetted out. Coley also removed some tissue from the tumor of the neck, which also was softened and necrotic in the center. Microscopically it was noted that the tumor cells were much swollen and there was a good deal of degenerated, intercellular substance.

In two months the tumor of the tonsil and the neck entirely disappeared. Shortly afterward a new swelling developed in the neck, about 3 cm. higher up. The patient also developed a small nodular tumor on the other side of the neck beneath the sternomastoid muscle. In February, while taking treatment, she developed a severe attack of herpes, involving the right pectoral region and entire right arm. This was extremely painful and she was unable to take treatment for about three weeks. In the early part of May there still remained some swelling on both sides of the neck, rather deep-seated underneath the sternomastoid muscle, and Coley decided to explore under ether. He found the swelling consisted entirely of necrotic material which had not found an easy exit. Some of the tissues from both sides was sent to Tracy at the Loomis Laboratory and microscopic examination showed no evidence of sarcoma remaining. The wound quickly healed.

Clinical Course: The patient was shown before the Clinical Congress of Surgeons of North America in November 1912, in good health. Thereafter Coley examined her periodically for the next 20 years. Between 1920 and 1925 a considerable number of operations were performed by Dr. Frederick B. Moorhead of Chicago, for reconstruction of the congenital cleft palate and

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hare lip. Moorehead reported: "The palate was completely gone and we succeeded finally by using adjacent structures, in building up a fairly good soft palate but did not complete the hard palate." Apparently the result obtained was good, because in February 1943, following examination, Dr. F. Gorham Brigham of Brookline, Massachusetts, reported: "Your mouth, all things considered, was in a healthy condition. Certainly there was a remarkable job done when you had the palate taken care of. There was a small amount of tonsillar tissue but it looked healthy. The scars . . . on your neck were healthy and firm." (46)

In 1930 the patient developed rheumatic fever, following a neglected cold. She recovered without any heart lesion, but was subject to colds thereafter. In April 1933, she was operated upon by Dr. Robert Greenough of Boston, for an ovarian cyst and gallstones. About 1939 or 1940 she developed a chronic abscess in the right breast. This was operated upon by Dr. Grant R. Taylor. The condition recurred from time to time during the next six years. In February 1943 she received a careful general examination by Brigham. The general condition was found to be good, except that there was slightly high blood pressure and the patient was somewhat overweight. Under diet and vitamin therapy she lost 12 pounds and by July 1944, the blood pressure was normal. During 1946 the patient had menopause and was pretty tense and somewhat apprehensive about her health. Her weight then was 138 pounds. She reported on January 5, 1955 that since 1951 she had been in very good health, her weight, 120 to 130, her height 5 feet 5 inches. She was last traced well on April 8, 1969, over 62 years after onset.

References: 34; 40 (case 4, p. 27); 42, case 13; 85; 100.

CASE 8: Recurrent inoperable small round cell sarcoma of the inguinal and iliac lymph nodes, confirmed by microscopic examination by Dr. J.F. Butler of Springfield, Mass.

Previous History: E.C.T.B., male, aged 21, of Winsted, Connecticut. The family history was negative for malignancy, tuberculosis or venereal disease. The patient had always been in good health until January 1908, when he was struck in the left groin by a lever, while working as a blacksmith. One week later he noticed a swelling at the point of injury.

Surgery: This increased steadily in size until February 1908, three weeks after the injury when a tumor was removed by Dr. Dudley Carleton of Springfield.

Clinical Course: A recurrence took place shortly afterwards involving the inguinal and iliac lymph nodes. The patient was referred to Dr. William B. Coley for toxins. Physical examination at this time showed that the general condition was good. The inguinal and iliac nodes were enlarged but the overlying skin was not adherent and there was no tenderness. The tumor was of moderately firm consistency. The patient was admitted to Memorial Hospital.

Toxin Therapy (Tracy XI): Injections were begun by Coley on March 26, 1908 and were all made intramuscularly in the buttocks. They were continued in doses ranging from 0.5 to 5 minims followed by well marked reactions. There were at least two chills and the maximum febrile reaction was 104°F. After the patient had received 27 injections he was allowed to go home as the tumors had almost completely disappeared. He was advised to have the toxins continued by the family physician two or three times a week for six months. The treatment was carried out rather irregularly during the summer and by October 1908 there was evidence of further recurrence. The

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patient accordingly returned to Coley's service at Memorial Hospital.

The toxins were again administered by Coley for 3½ weeks, partly into the tumor of the groin and partly into the buttocks. He received 18 injections in this period, with good reactions. He was then sent home and urged to have the treatment continued for another three or four months by the family physician. This time the toxins were continued for six months, but those given at home did not produce any severe reactions, although chills occurred. The growth again regressed completely.

Clinical Course: There was no further recurrence. The patient was followed periodically. He remained in perfect health with the exception of an acute supra-orbital neuralgia which developed in 1950. On November 1, 1950, Dr. Richard C. Buckley of Hartford avulsed the left supra-orbital nerve which relieved the pain. This neuralgia recurred in March 1955 and Buckley again avulsed the nerve. These operations were performed at St. Francis Hospital, Hartford. In October 1957 the facial neuralgia again recurred and bothered him all the following winter. Dr. Heinz Markwald of New Hartford was consulted. He prescribed pain-relieving pills. Thereafter the patient remained in good health, but was somewhat addicted to alcohol. He was last traced well on April 7, 1969, 61 years after onset of the lymphosarcoma of the groin.

References: 40, case 17, p. 41; 42, case 26; 46; 47; 85; 95, case 13; 100.

CASE 9: Inoperable lymphosarcoma of the ileocecal region, confirmed by microscopic examination by Dr. Paul Klemperer, pathologist at Mount Sinai Hospital, New York. (Acc. #10378-14462)

Previous History: B. S., male, aged 22. The family history was not recorded. The patient had had measles and tertian malaria as a child. Onset, about December 1907 he began to have abdominal cramps which finally became localized in the right iliac region. There was vomiting, but no blood or mucus in the stools. The patient was admitted to Mt. Sinai Hospital on December 5, 1908. Examination revealed a relaxed abdomen but a large tumor mass was felt in the right iliac region. No other masses were felt and the spleen was not palpable. The blood count showed 4,000,000 r.b.c., 14,000 w.b.c., polys 83%; the von Pirquet test was negative.

Surgery: On December 7, 1908 Dr. Howard Lilienthal operated. In addition to the large growth he found many enlarged soft regional lymph nodes. The colon was divided 8 cm. below the growth and carbolized as in appendicitis. The ileum was then treated in the same manner. A side to side ileotransverse colostomy was performed and the nodes were removed "in toto". Lilienthal regarded this as an incomplete removal.

Toxin Therapy (Tracy XI): Shortly after this operation, in December 1908 Lilienthal administered Coley Toxins. The patient rapidly regained his former health and made a complete recovery.

Clinical Course: He remained in good health over three years, until February 1912, when he developed pharyngeal symptoms, and lost 18 pounds in weight. He was readmitted to Mt. Sinai Hospital on August 5, 1912. A mass the size of a large walnut was found in the left tonsil. This was believed to be further lymphosarcoma.

Further Surgery: Dr. Charles A. Elsberg removed as much of this tumor as was possible. The tissue was examined by Drs. Kaliski and Buerger and reported to be lymphosarcoma. (However, in 1936 Klemperer reviewed the slides and stated that the tonsillar tumor in this case was not lymphosarcoma.)

Further Toxin Therapy: The patient was again given a course of toxin therapy. He again rapidly improved in health.

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Clinical Course: He remained entirely well thereafter. He was presented by Lilienthal before the New York Surgical Society on February 26, 1936, over 28 years after onset. Attempts to trace him recently were unsuccessful.

References: 78; 100

CASE 10: Inoperable recurrent round cell sarcoma of the right cervical region, confirmed by microscopic examination at the Department of Pathology, Harvard Medical School.

Previous History: F.H.W., male, aged 58, machinist, of Swampscott, Massachusetts. There had been some tuberculosis on the maternal side of the family. The patient's father is said to have died of cancer of the stomach. There was no history of venereal disease. The patient had had the usual diseases of childhood, including mumps. At the age of 21 he had typhoid fever, at 23 he had "inflammation of the bowels", once in April and once in July. Three years prior to admission he was struck on the head with a Stillson wrench. Three weeks later he began to have trouble with walking, more markedly with the right limb. This lasted six or seven months. At that time (July 1906) he noticed a small painless lump in the right cervical region which grew slowly at first, then more rapidly.

Surgery: At the time of the first operation by Dr. George H. Gray of Lynn, Massachusetts, on November 24, 1908, it had reached the size of a small hen's egg. Part of this growth was removed.

Clinical Course: The patient was referred to Dr. William B. Coley for toxins. He was admitted to Memorial Hospital on December 21, 1908. Examination at this time showed no evidence of metastases, but the anterior margin of the cicatrix was thickened and slightly tender, and there was evidence of recurrence. There had been no loss of weight.

Toxin Therapy (Tracy XI): Coley administered the first 11 injections beginning about December 22, 1908. Five of these were made in the pectoral region, two in the tumor and the rest in the buttocks. The patient was then advised to return home and have the treatment continued by the family physician. A total of 82 injections were given during 10 or 11 months. At the end of six months the injections were made only once a week. The later reactions were mild and during almost the entire treatment the patient was able to continue working. He received Parke Davis XII preparation from February through July 1909, then a bottle of Tracy's XI and finally a bottle of Tracy's filtrate XIF. During treatment all evidence of disease disappeared.

Clinical Course: Coley again examined the patient on November 11, 1909, over 10 months after the toxins were begun. At this time the 8 cm. cicatrix over the anterior sternomastoid region was soft and pliable, with no evidence of tumor remaining. The general health was perfect. The patient was examined periodically. He remained well and free from recurrence until his death which occurred suddenly on June 19, 1938, apparently from coronary thrombosis. This was 32 years after onset.

References: 40 (case 15, p. 39); 42 (case 4); 41; 46; 85 (#56, Vol. LV case #15758); 100; 126.

CASE 11: "Highly malignant small round cell sarcoma of the neck" was the microscopic report of Dr. Eugene Hodenpyl, Pathologist at Roosevelt Hospital, New York.

Previous History: P.K., male, aged 41. The patient was a heavy smoker.

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He first noticed a lump in the submaxillary region in April 1909, which grew rapidly and by June had reached the size of a hen's egg. He was admitted to Roosevelt Hospital on June 11, 1909, on the service of Dr. Charles H. Peck.

Surgery: At operation Peck found a very vascular tumor which had invaded the periosteum of the inferior maxilla. There was also marked infiltration of the muscles and skin. Peck could not make a complete removal. He gave a hopeless prognosis, and referred the patient to Dr. William B. Coley.

Toxin Therapy (Tracy XI): The toxins were administered postoperatively by the family physician, Dr. Lipsett, under Coley's directions. Four injections a week were given at first, later two a week and then one a week, and during the last two months, one in two weeks, a total of 56 injections being given with intervals of rest in the course of one year. Shortly after treatment was begun, the infiltrated area in the region of the cicatrix gradually softened and receded and at the end of three months the remains of the growth had entirely regressed.

Clinical Course: The patient was examined from time to time and found in perfect condition. He was shown before the Clinical Congress of Surgeons of North America in November 1912, and was last traced entirely well in 1923, 14 years after onset.

References: 35; 40; (case 5); 46.

CASE 12: Twice recurrent inoperable malignant lymphoma of the antrum, ethmoid, superior maxilla, posterior septum and nasopharynx, confirmed by microscopic examination by Drs. James Homer Wright and F. W. Whitney, of the Harvard Medical School, from tissue removed at the second and third operations. Wright reported: "Tumor fills up antrum, involves bony parts of the right side of the nasal cavity, and also appears on the outside of the bone at two points. Tumor consists of whitish, translucent, moderately firm, rather homogenous tissue. Microscopic examination: tumor chiefly of cells generally closely packed together, and a relatively small amount of stroma. Masses of cells are like large lymphocyte forms of cells found in lymphadenoid tissue. Some small lymphocytes are present. There are areas of necrosis." Whitney reported on pieces of tissue removed with Crile tube. (115-42): "Round cell sarcoma. . .small round cell tissue with new formed blood vessels and remains of small glands scattered throughout."

Previous History: L.P., female, aged 33, of Boston, Massachusetts, born in Italy. The family history was negative for cancer or tuberculosis at that time, but the patient's mother later died of cancer. Menses began at 14, and had always been regular. The patient had had a cough for about 10 years, "bronchial trouble" for six years, but had otherwise been well. As a child of 10, she was struck on the cheek by a stone thrown by a boy. She was married in 1891 and had three children prior to 1909. In August 1909, she again became pregnant. Onset, a month later, in September 1909, she first noticed that her eyes were very watery and that a lump was present on the inner side of the right cheek, at the site where she had been struck by the stone 22 years before. This increased in size and the patient was troubled with excessive lacrimation in the right eye. The growth was not tender or painful, but every two or three days she had attacks of pain in the right temporal region, also attacks of "head fullness" almost daily. She was admitted to the Massachusetts General Hospital on February 21, 1910, having been in bed with a cold for two weeks. Examination revealed a well-developed, poorly-nourished woman. The right

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eye appeared to be opened wider than the left and to secrete tears more freely. Between the inner canthus of the right eye and the bridge of the nose there was a hard irregular non-tender mass about 1.5 cm. in diameter, apparently comprised of several nodules. It had extended into the right nasal canal causing complete obstruction of air. The throat was reddened and foul looking. In the posterior pharynx on the right side there was a dirty, blood-stained discharge, evidently draining from the right nasal cavity. The breath was very foul. The patient was put to bed. She felt dizzy when she attempted to get up.

Surgery: On March 3, 1910 Scudder operated, removing the right superior maxilla. The ethmoid cells were curetted. The frontal sinuses were not involved. The sphenoidal sinus was opened, contained pus and was curetted. The postoperative course was uneventful.

Toxin Therapy (Tracy XI): Injections were begun by Dr. Torr W. Harmer on March 10, 1910, a week after operation. During the next 21 days 14 were given, the site being the trapezius muscle with one exception, that being in the supraspinatus muscle. The initial dose was 1/8 minim, which was increased to a maximum of 1 1/5 minim. Only one moderate reaction occurred following the injection into the supraspinatus muscle: 101°F. The patient was discharged on April 3, 1910, with no evidence of recurrence.

Clinical Course: Four months later, in February 1911, she had constant pain in front of and inside the right ear, lasting about a week. This subsided completely. She had trouble talking due to the defect in the palate resulting from the first operation and she had some difficulty in eating. Examination on readmission to Massachusetts General Hospital on March 31, 1911 showed a large depression at the site of the first operation, with a sinus leading into the nasopharynx. As the patient was almost at term, it was decided that it would be best to defer operation until after her confinement. Two days after her discharge, on April 3, 1911, she gave birth to a male child. She had a normal convalescence and was readmitted on May 6, 1911. At this time she had considerable dull pain in the right side of the face in front of the ear, which was relieved most by an ice bag. There was a foul odor from the nose and from the opening beside the eye, and there was some purulent discharge each day.

Further Surgery Attempted: A fourth operation was performed by Scudder on May 11, 1911. It had been intended to do a radical operation, with enucleation of the right eye, but on attempting to pass the Crile ether tube through the naris, an obstructing growth was met and the tube could not be passed. A piece of this growth came out on withdrawing the tube and was evidently sarcoma, as confirmed by microscopic examination. As this indicated extension of the disease to the left side of the face and nose, the only possible operation would have involved a resection of the left superior maxilla as well, and this was deemed inadvisable. Further surgical intervention was therefore abandoned. The tissue removed at this operation was reported by Whitney as round cell carcinoma with new formed blood vessels and remains of small lymph nodes scattered throughout. (115-42).

Further Toxin Therapy: Injections were resumed on May 11, 1911, the initial dose being 1/4 minim, given subcutaneously, apparently in the vicinity of the tumor. This caused considerable febrile reaction that evening: 103°F., rapid pulse and much pain about the upper jaw. Three more subcutaneous injections were given on May 14, 16 and 19, 1911, in doses of 3/8, 3/4 and 1 minim. These caused no reaction. On May 20, 1911, the patient was discharged to the out-patient department, where injections were continued for three more weeks. The maximum dose was 3 minims and the reactions were marked. The recurrent growth regressed completely.

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Concurrent Tuberculosis: The patient was followed for five months in the out-patient department, she was then transferred to the Boston Dispensary for consolidation in the right lung, being later treated for pulmonary tuberculosis at Middleboro.

Clinical Course: On February 28, 1914 she was again seen by Harmer. At this time she was thin, but of good color and had been doing all her own housework for the previous year. Examination through the nose and mouth showed no evidence of recurrence. The patient was again pregnant and on March 25, 1914 gave birth to a normal child. The following November Scudder did a plastic operation to cover the defect on the cheek beneath the right eye. He found no evidence of recurrence. The patient was followed from time to time. She had a total of nine children, six of them after onset. (All but two were living in 1947). She remained in good health except for several colds each year and cholecystitis in 1942 and 1944, from which she recovered without operation. In 1942 and October 1944, she was given thorough examinations at Boston City Hospital. X-rays showed a single large gallstone in the left upper quadrant. In October 1944 surgery was advised but nothing was done. In early March 1950 she had a severe virus infection which left her quite weak. During 1951 she was hospitalized twice, first for pneumonia (six weeks) and again for influenza (four weeks). Her son reported on December 24, 1951 that her physician at Boston City Hospital had stated that she would not be completely well again. The Boston City Hospital records at her discharge gave the following summary of her condition: "Chronic bronchiectasis, emphysema, generalized arteriosclerosis, arthritis, albuminuria (traces)". At this time there was also pitting edema of the ankles. Her son stated: "She still shows remarkable powers of recovery . . . is active and up and about and as long as she is kept in a calm, peaceful atmosphere does very well for herself." During the summer of 1954 the patient was injured in a fall in a bus when it stopped very suddenly. She suffered contusions and lacerations of the scalp, thigh, arm and hand. She was immobilized for several weeks and made an apparent recovery. During the next few months she developed hypertension, anorexia, gastric disturbances and she lost several pounds in weight. Subsequently she developed severe headaches occasionally, and a series of tests was made at Massachusetts General Hospital to determine whether the fall had any bearing on these headaches. It is of interest to note that in the year after the fall, the symptoms of chronic bronchitis disappeared; she stopped coughing and expectorating. Her weight in 1955 was between 95 and 98 pounds. On May 18, 1957, she was admitted to Peter Bent Brigham Hospital where the following diagnosis was reported: "recurrent lower lobe pneumonia, bronchiectasis right lower lobe; chronic bronchitis, right lower lobe; senile emphysema, right renal tumor, type undetermined, with chronic pyelonephritis due to mixed flora; gastric ulcer, type not determined; death occurred at the age of 80, at Boston City Hospital on November 5, 1957, 48 years after onset of the lymphosarcoma of the antrum, ethmoid and adjacent tissues.

References: 64 (case 5) ; 65 (case 1) ; 82; 100.

CASE 13: Inoperable round cell sarcoma of the tonsil and neck, confirmed by microscopic examination by William C. Clark, pathologist at Memorial Hospital, following biopsy.

Previous History: C.H.W., male, aged 56, of St. Albans, Vermont. The patient's uncle died of cancer of the leg. The patient's general health had always been good. For five years, however, he had had arteriosclerosis. Onset, in late March 1910 he first noticed a swelling in the right tonsil two months before being referred to Dr. William B. Coley. He had always smoked

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a great deal, but two weeks after noticing this lump he stopped. Two weeks prior to admission he noticed an enlargement of a node on the right side of the neck. He was treated by throat specialists, during which time the swelling increased steadily and rapidly. Four prominent Montreal surgeons pronounced the condition an inoperable malignant tumor. Physical examination by Coley on May 26, 1910 showed the right tonsil enlarged to the size of an almond and ulcerated on its posterior surface. There was a hard movable node the size of an English walnut in the right cervical region anterior to the sternomastoid muscle. The tumors in the neck and tonsil were very hard on palpation, resembling carcinoma rather than sarcoma. The patient was admitted to Memorial Hospital and remained there for six weeks.

Surgery: A biopsy was performed.

Toxin Therapy (Tracy XI): Injections were practically all made intramuscularly in the pectoral region by Coley, the dosage ranging from 0.5 to 5 minims, with fairly severe reactions from the larger doses. The tumor in the neck first became softer and more movable. At the end of a week it decreased in size and finally disappeared under four weeks' further treatment. The tumor of the tonsil diminished more slowly, but at the end of two or three months this too had entirely disappeared.

Clinical Course: The patient's family physician, Dr. E.J. Melville, reported on March 19, 1911: "He is at present perfectly well. There is absolutely no sign of any growth in his tonsil; his recovery here is considered as almost miraculous." On July 10, 1913 his physician wrote that there had been no return of the tumor of the tonsil and that the peritonsillar tissue was normal. He added: "His only ailment is a progressive dementia probably caused by ischemia of the brain." A similar report was made four years after treatment, stating there had been no recurrence, and that his appetite and general physical condition had not changed, including the progressive dementia, which Melville believed due to arteriosclerosis from which the patient had suffered for ten years. Death occurred over five years after onset on August 8, 1915, the cause being arteriosclerosis.

References: 5; 37; 40 (case 13, p. 36); 42 (case 17).

CASE 14: Recurrent malignant lymphoma of the axilla, confirmed by microscopic examination at Memorial Hospital of both the primary and the recurrent tumors. Dr. W.E. Clark examined the primary growth and Dr. James Ewing the recurrence.

Previous History: P.J.B., male, aged 67, merchant, of Los Angeles, California. The family history was negative for malignancy or tuberculosis. The patient had had the usual childhood diseases and scarlet fever, as well as a tendency to grippe and to constipation. There was also a rheumatic tendency. He had had gonorrhoea 25 years previously and lues 11 years previously for which he was treated for five years. Onset, early in 1908, three years prior to being referred to Dr. William B. Coley, the patient first noticed a small lump in the left axilla, under the edge of the left pectoral fold. It apparently remained stationary for about two years and then began increasing in size. Two months prior to admission he contracted the grippe and thereafter the growth rate increased very rapidly so that in six weeks the tumor doubled in size. It was painless, freely movable, hard and nodular. Examination on admission to Memorial Hospital on February 1, 1911, showed it to be the size of a small lemon, 6½ by 8 cm. in diameter. It was made up of a number of more or less discrete enlarged lymph nodes, varying in size from a hazel nut to a walnut, partially fused together. The appetite was poor and the bowels were constipated. The patient believed he had lost some weight.

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Surgery: On February 2, 1911 an operation was performed by Coley under ether anesthesia. The tumor mass was found to extend up beneath the clavicle. There was very little loss of blood but the removal was apparently incomplete.

Toxin Therapy (Tracy XI): Injections were begun by Coley on February 13, 1911, 11 days after the operation. The initial dose was 0.5 minim given intramuscularly. Injections were continued three or four times weekly in the pectoral region gradually increasing the dose to $3\frac{3}{4}$ minims. There were no marked reactions. After three weeks the patient returned home to Los Angeles, California and the injections were continued by Dr. Ferbert. The site, dosage, frequency and duration he used were not recorded. The remains of the growth apparently regressed.

Clinical Course: The patient remained well until September 1913, when he developed a recurrence underneath the pectoralis minor muscle, attached to the subclavian vein.

Surgery: This was removed surgically.

Further Toxin Therapy: Injections were resumed as a prophylactic against further recurrence.

Clinical Course: The patient was last traced by Coley in good health on April 17, 1915, seven years after onset. There had been no further recurrence. Attempts to trace him subsequently failed.

References: 42 (case 23) ; 85 (Book 63; Vol. 2, case #18103, 1911) ; 100.

CASE 15: Inoperable lymphosarcoma of the axillary region, primary in the groin, confirmed by microscopic examination, after both operations, by Dr. J. Homer Wright, pathologist of the Massachusetts General Hospital, Boston, Mass.

Previous History: C.F.R., male aged 29, of Wellesley Hills, Massachusetts. The family history was negative for tuberculosis or venereal disease. The patient's maternal grandmother died of a cancer which was apparently caused by the irritation of a corset. The previous personal history was non-contributory except for a tendency to frequent colds and rather nervous temperament. The patient was a good athlete and interested in all sports. He wrestled and boxed prior to onset and there may have been injuries, his wife stated, but there was no specific antecedent local injury or infection. He married in January 1907, and during the next year his weight increased from 135 to 150 pounds. A daughter, their only child, was born in 1908. Onset, in the autumn of 1909, a lump first appeared in the groin.

Surgery: In the spring of 1910 Dr. Samuel Robinson removed this growth. Fowler's solution was administered following this operation. A second operation was performed on August 8, 1911, for a metastatic tumor involving the right axillary nodes. Coley stated that it was not certain that not all of the diseased nodes were removed. There had been some loss of weight.

Toxin Therapy (Tracy XI): Two weeks after this operation the patient was referred to Dr. William B. Coley for toxins, but as Coley was abroad, the injections were begun by his associate, Dr. Joseph P. Hoguet, about August 23, 1911. They were given daily into the pectoral muscles, alternating right and left, until a chill was produced. (This took two weeks, and indicates that the dosage was increased too slowly.) The patient was then allowed to go home where the injections were continued by Dr. Joseph Stanton, the fam-

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ily physician, until January or February 1912, a total duration of five or six months. Stanton gave the injections on alternate days and later three times a week. Only two chills occurred, one in New York and one at home. It is interesting to note that the patient's widow stated: "The nurses and doctors told us that all patients previous to Mr. R. had their chills within half an hour to two hours. Mr. R.'s first reaction occurred six hours after treatment."

Clinical Course: There was no further recurrence. The patient regained his lost weight and was in good health when examined by Coley in October 1912. On October 23, 1913, Wright, pathologist at Massachusetts General Hospital, Boston, wrote Coley enclosing a section from the tumor removed at the second operation. He stated: "I am much interested to know the outcome in this case. This is the third or fourth case of malignant lymphoma of which I have personal knowledge which recovered" (under toxin therapy). The patient's widow stated: "His health remained excellent for most of the time between 1911 and 1939," his only illnesses being colds and a herniotomy some time between 1917 and 1922. He remained strong and athletic, often playing 36 or more holes of golf occasionally as many as 54 in one day. During the summer of 1939, the spleen became enlarged.

Surgery: It was removed in November 1939 by Stanton at Massachusetts General Hospital, where a pathological examination was made and reported as Boeck's sarcoid. Except for a brief acute respiratory infection in the spring of 1940, the patient's general health appeared to be normal during the first seven months of 1940. On August 15, 1940 he began to cough following a sharp change in the weather. This cough became more and more severe. By Thanksgiving the cervical nodes were enlarged. X-ray examination revealed evidence of Hodgkin's disease. On December 25, 1940 the patient was admitted to the Huntington Memorial Hospital in Boston, where he remained for about two weeks for examinations, blood transfusions and vitamin therapy.

Radiation: He also received x-ray therapy with the million volt machine. The latter appeared to relieve the cough. A lymph node and sternal marrow were removed at this time and diagnosed as Hodgkin's disease.

Clinical Course: Thereafter the disease progressed rapidly with loss of weight and almost constant pain in the legs and lower spine, as well as a peculiar greenish yellow color of the skin. Death occurred on August 15, 1941, 32 years after onset of his lymphosarcoma. Autopsy showed extensive Hodgkin's sarcoma, involving the axillary, peribronchial, mesenteric and retroperitoneal lymph nodes, the lungs, pleurae, jejunum, liver, pancreas, vertebral marrow and thyroid.

Comment: While in this case the toxins were used chiefly as a prophylactic after operation in 1911, it was believed that the diseased nodes were incompletely removed from the axilla. Coley pointed out that "According to Fabian, 'There are no cases of cure by surgery on record, in which the disease (malignant lymphoma) was no longer isolated' ". . . i.e., confined to one node. The case is of unusual interest inasmuch as the patient remained in excellent health and free from further evidence of his lymphosarcoma for 28 years after toxin therapy, at which time he developed Hodgkin's disease which proved fatal in about a year.

References: 40 (p. 118); 42 (case 5, Table of Axillary cases); 100 126.

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CASE 17: Twice recurrent inoperable lymphosarcoma of the inguinal and iliac nodes, confirmed by microscopic examination by Dr. Frank Winders of Columbus, Ohio.

Previous History: Mrs. J.B.M., female, aged 62, of Findlay, Ohio. The patient consulted Dr. J.C. Tritch, President of the Northwestern Medical Society of Ohio, in September 1911, for a tumor which had developed in Scarpa's triangle.

Surgery: On September 28, 1911 Tritch performed the first operation. The femoral vein was involved and obliterated with resultant gangrene in its tract.

Clinical Course: A local recurrence was apparent within five months, but the patient did not again consult Tritch until July 5, 1912.

Further Surgery: A second operation was performed, the recurrent growth being removed.

Clinical Course: By October 8, 1912 recurrent nodules were again apparent above Poupart's ligament. The condition was considered inoperable.

Toxin Therapy (Tracy XI): Injections were begun by Tritch on October 10, 1912, and were given at the hospital until November 4, with no apparent improvement at first. They were continued for three or four months, resulting in gradual diminution in the size of the nodules until they had entirely disappeared. (The slow rate of regression appears to be due to the fact that injections were only given once a week intramuscularly after her discharge from the hospital.)

Clinical Course: One year after beginning the treatment there was no evidence of further involvement. The patient remained well and free from recurrence when last traced over five years later. The exact date of last observation is not known because the hospital records were later destroyed by fire.

Comment: In reporting this case Tritch stated: "The results in this case showed me that the effects of the fluid may be tardy and that you may get results after you have dismissed the case as hopeless." (46)

References: 40 (case 66, p. 159); 42 (case 16 in the Table of other surgeons' cases); 46; 100.

CASE 18: Recurrent inoperable round cell sarcoma of the cervical lymph nodes, confirmed by microscopic examination.

Previous History: P.V., male adult, born in Italy, a physician of Brooklyn, New York. The family history was negative for cancer, tuberculosis or venereal infection. The patient had always been well until early in 1913 when he noticed a swelling in the neck midway between the chin and thyroid. This reached the size of a hen's egg five days after onset. It was considered at first to be inflammatory and was opened by Dr. Russell B. Fowler, of Brooklyn. A few drops of pus were obtained.

Surgery: Several days later Fowler removed the whole mass. After microscopic examination this was pronounced "infective granuloma", but this diagnosis was later revised to round cell sarcoma.

Clinical Course: Four weeks after operation a recurrence developed in the right cervical region. This grew rapidly, soon reaching the size of a fist, extending from the mastoid to the clavicle. It was regarded as inoperable.

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Toxin Therapy (Tracy XI): Injections were begun by Fowler on April 10, 1913, the initial dose being $\frac{1}{4}$ minim, which was increased daily by 0.5 minim until a dose of $1\frac{1}{2}$ minims was reached. The tumor responded at once by decreasing in size. It also softened and opened spontaneously, discharging necrotic material. Early in May the patient's general condition appeared to be poor, apparently due to absorption of considerable necrotic tumor tissue. As the tumor had disappeared except for infiltration in the lower portion of the sternomastoid, Fowler decided it would be best to ease up on the treatment. Accordingly, he diminished the dose, by half a minim daily until it was $8\frac{1}{2}$ minims, a decrease of 6 minims, whereupon the tumor began to increase again rapidly and some thickening appeared at the upper end of the sternomastoid on the anterior surface, the lower infiltration which had remained having disappeared. Fowler immediately began increasing the dose again by 0.5 minims a day, and on May 15, 1913 referred the patient to Dr. William B. Coley. Physical examination at this time revealed a mass on the anterior portion of the neck, beginning a little to the left of the median line and extending to the angle of the jaw. This measured about 8 cm. in diameter laterally. It was very firm in consistency and much harder than ordinary sarcoma, more like carcinoma. There were several other small and discrete tumors in the cervical and supraclavicular regions. The skin was adherent only in the region of the cicatrix and was not reddened. The tumor was not attached to the trachea or to the thyroid cartilage. The general condition was good but the patient had lost 15 pounds in weight. He was admitted to Memorial Hospital on May 16, 1913 where he remained a week receiving five injections in the pectoral muscles, causing febrile reactions of 100° and 101° F. The tumor regressed markedly during this week from $6\frac{1}{2}$ by 8 cm. to a small nodule $2 \times 2\frac{1}{2}$ cm. in diameter. The Memorial Hospital records state: "In the right cervical region the irregular mass, apparently consisting of masses of glands, some very hard, some rather soft, and fairly discrete, in contradistinction to the firm hard mass there a week ago."

The patient returned home, and Coley urged Fowler to push the treatment to the limits of safety. Under increased dosage, given daily or every other day, the patient's condition quickly showed signs of improvement. In advising Fowler regarding this case, Coley wrote in June 1913: "I have been more than pleased with the very rapid decrease in size of the tumor in the submental region and a general disappearance of the indurated area in the whole right cervical region. I believe that with a judicious adaptation of the dose to this case we are going to get a complete cure. It is very important not to stop too soon. I would give him daily doses when he gets no reaction and when he does, give an interval of rest, one day. . . No matter what happens, it seems a remarkable illustration of the inhibitory action of the toxins in a case of extreme malignancy." The improvement continued, and when Coley again examined the patient on July 18, 1913, the tumors in the cervical and submental regions had almost completely disappeared, and the general condition was good. At this time the dose had been increased up to 20 minims given in the pectoral region. Coley again wrote Fowler, on September 11, 1913: "I have just seen Dr. V. and am perfectly delighted to find that every trace of the tumor had disappeared from the neck and that he has gained 12 pounds since I examined him on the 20th of July. . . I would strongly advise not to stop the toxins altogether at present, but to continue at least once a week, in moderate doses — not enough to cause a severe reaction. I should think that about 5 minims would be about right. If this does not give any reaction at all, you might increase the dose. Usually after a week or two of rest the susceptibility returns and one cannot give as large doses as when the

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patient is taking the treatment regularly. I think very probably he would not have any more trouble if we stopped, but I have had a number of recurrences which I feel would probably have been averted had I continued longer with the toxins. On the basis of this experience, it is my present policy to go on with the treatment for a long period after the disappearance of the disease." Examination on January 20, 1914, showed the neck to be entirely normal, with no suspicion of enlarged nodes. The patient's weight had increased from 212 to 222 pounds.

Clinical Course: There was no further recurrence or metastases. The patient remained well at least 15 years and then died while on a trip to Europe. He was drowned. It is not known whether this occurred accidentally or was a suicide, but the patient was very worried about a legal difficulty which had arisen. (He was being sued for malpractice by an unscrupulous patient.)

Comment: This case is important because it clearly illustrates the narrow margin between success or failure to gain complete control of the neoplasm. Fortunately the details of technic are carefully recorded. It appears that a definite amount of toxin must be administered before a soil unfavorable to neoplastic growth is produced in the system, thus preventing further recurrence or metastases. Dosage and frequency must therefore be maintained, and not decreased too soon, in order to produce permanent results. It is possible that when a tumor is destroyed rapidly, thus liberating large quantities of necrotic or partially necrotic tumor cells, that these may depress or inactivate the reticuloendothelial system. The slower growing tumors that respond less rapidly to toxin therapy do not present this problem.

Fowler apparently recognized the importance of technic for he stated in a letter to Coley in 1916: "The few cases in which I have had the opportunity of encouraging the patients in the use of the toxins have been for the most part successful. I believe the matter to be one of dosage in relation to tumor, and I am glad to add my testimony to the efficiency of the treatment, when properly carried out in a sufficient number of cases to warrant its trial in all." (46)

References: 40 (case 12, p. 36); 42 (case 7); 46; 85 (case #20450, 1913); 95 (case 21, p. 61); 100.

CASE 19: Recurrent inoperable lymphosarcoma of the submaxillary and cervical nodes, confirmed by microscopic examination by Dr. James Ewing and other pathologists. Ewing stated that mitotic figures were abundant, and that the structure of the nodes was obliterated.

Previous History: H.W., male, aged 55, of Northampton, Massachusetts. The patient had been in good health until the early part of May 1913, when he noticed a small painless lump under the jaw on the right side, in the region of the submaxillary nodes, which grew rapidly in size.

Surgery: He was operated upon by Dr. Frederick B. Sweet of Springfield, Mass. A tumor the size of a pecan nut was shelled out of its capsule "like a pea from its pod." There was no infiltration of the surrounding tissues nor was the tumor attached to the bone.

Clinical Course: Shortly after the operation another node developed beneath the right sternomastoid muscle.

Further Surgery: This was also removed surgically. It was found to be lying between the carotid and the internal jugular vein, and was about the size of a small cherry. Ewing examined a portion of this tumor.

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Clinical Course: Within a week a rather diffuse swelling developed at the right of the incision. No attempt at further removal was made for fear of injuring the facial nerve. The patient was referred to Dr. William B. Coley.

Toxin Therapy (Tracy XI): Injections were begun by Coley on June 5, 1913, in gradually increasing doses, but no reactions were obtained until 8 minims had been reached. There was no rise in temperature from the smaller doses, although they caused considerable depression. During this phase of the treatment two or three very small nodes appeared at the site of the second operation over the carotid vessels. These grew steadily until they had reached the size of a hazelnut. After the first reaction was obtained there seemed to be no further increase in the size of these growths. The patient returned home on July 26, 1913 and treatments were continued three times a week by Dr. Shores, the family physician, in doses ranging from 7 to 9 minims. On Coley's return from Europe at the end of August, the patient came to him for examination and advice. Coley found the cervical nodes had not increased in size during his absence, and that there was no return of the tumor in the submaxillary region, which had disappeared under the toxins.

Further Surgery: In order to lessen the duration of treatment, and also in the hope of increasing the chances of controlling the disease, Coley decided to operate again, and to remove the tumors in the carotid region. This was done on October 7, 1913. Coley found the tumors very deeply placed about the carotid vessels, and removed three growths ranging from the size of a pecan to that of a hazel nut. Coley believed that there were undoubtedly nodes higher up, which were not removed; the wound was fulgurated for five minutes.

Further Toxin Therapy: Injections were immediately resumed, and the dose increased to 9 minims which gave a good reaction. On September 11, 1913 the patient was discharged and returned home where treatment was continued three times a week for two months, after which they were omitted for one week. On December 2, 1913 he was examined by Coley who found his weight had increased considerably, and the condition of his neck revealed no trace of the former tumors. The patient stated that he "had not felt so well in a long, long time." The toxins were continued for over a year: total number of injections, 150; maximum dose, 9 minims.

Clinical Course: Examination on November 1, 1915 showed no trace of recurrence and the patient's health was excellent, his weight normal. He was examined in January 1913 when he had a slight stroke, and the doctor reported no return of the disease. He had a cerebral hemorrhage which proved fatal in April 1918, five years after onset.

Comment: This case indicates the need for more aggressive initial treatment before the patient loses his susceptibility to the toxins, (no reactions were obtained at first). Mild reactions appear to cause greater general depression without producing rapid regression of the neoplasm. Note that during this phase of the treatment in this case several small recurrent nodes appeared, but that after the first good reaction was obtained the disease was controlled.

The patient's family physician, Dr. Shores, became very interested in the toxins as a result of observing this case, and he wrote Coley for further details as to the origin and history of the treatment. He then reported the case to the local Medical Society in December 1913. He describes the meeting thus: "There was a good hot discussion, some supposing the "Coley treatment" was dead years ago, some claiming that quite a large percent of operated sarcomas would not return anyway, while a few more urged that the pathology was probably at fault, and that no pathologist could be certain of round cell sar-

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coma. But the majority was deeply interested and expressed a desire to try the treatment at the first opportunity." (46)

References: 40 (case 11); 42 (Case 9); 46.

CASE 20: Inoperable rapidly recurrent malignant lymphoma of the groin and pelvis, confirmed by microscopic examination of the primary growth by Dr. F. W. Whitney at Massachusetts General Hospital (#143-45): "A tumor the size of a croquet ball with smaller nodules in a chain at one point. Soft grey homogenous section. Microscopic examination showed a structure of lymph node with well marked follicles and great increase in pulp. Lymphoma."

Previous History: A.A.K., male, aged 25, Syrian, clerk, of Boston, Massachusetts. The family history was negative for cancer or tuberculosis. The patient had always been well prior to onset, his only operation having been a tonsillectomy at the age of 11. Onset, in March 1913 a tumor the size of a pecan nut was first noticed in the left groin. It remained stationary in size for two months, then increased gradually until the last two weeks prior to admission when growth was very rapid, causing constant pain. The patient stated that he also had a sore throat for the three weeks prior to admission. He was admitted to Massachusetts General Hospital on March 7, 1914. Examination at this time revealed a well-developed and well-nourished young man in good general health. There was a hard mass the size of a small grapefruit covering Scarpa's triangle on the left and passing 2 cm. beneath Poupart's ligament. In places the growth was "questionably fluctuant", slightly movable and tender. The throat was generally reddened.

Surgery: On March 8, 1914 Dr. D.F. Jones operated. A semicircular flap was turned inwards, exposing the growth, which was found firmly investing the femoral vessels. The incision was carried above Poupart's ligament and dissection made along the iliac vessels retroperitoneally. The chain of involved nodes was felt extending far back in the pelvis. Eradication was impossible. Recurrence developed and grew steadily.

Radiation: X-ray therapy was started on March 12, 1914 and was given daily for ten minutes. Despite radiation within a month the growth filled Scarpa's triangle, and extended above Poupart's ligament into the pelvis. The mass was firm, about 9 by 15 cm. in diameter.

Toxin Therapy (Tracy XI): Injections of Coley's toxins were begun on April 9, 1914, one month after the incomplete operation. They were given by Dr. Torr Wagner Harmer, and *were made into the growth* every second or third day, the maximum dose being 11 minims. Reactions were often marked with temperature and chills. At first there was marked softening and decrease in size of the mass, then it began to grow, producing considerable varicocele. The injections were continued, however, and a gradual diminution occurred. The growth then ruptured and discharged necrotic tumor tissue several times. By February 1915 there remained a mass about 2.5 by 4 cm. in diameter just below and another about the size of a small egg above Poupart's ligament apparently distinct from the first, which evidently extended into the pelvis. The patient was in excellent condition as regards weight and color. He had received toxin therapy for ten months. The exact duration of treatment is not stated, as the case was published by Harmer at that time.

Clinical Course: He was again examined at the clinic on March 27, 1915, stating that he felt very well. He remained well and strong, the tumor apparently regressed completely. There was no recurrence or metastases. The

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patient never married. In later years he was said to be a heavy drinker. He died suddenly following an overdose of Epsom salts which he had taken "because of a heavy feeling in his abdomen". A violent attack followed which was believed to be a ruptured appendix. Death occurred between 1940 and 1942 according to surviving relatives. This was over 27 years after onset.

Comment: Compare this case with those in whom preliminary radiation was not administered, and the toxins were given somewhat more aggressively. These patients responded more rapidly to treatment, making the period of disability less prolonged. The case also suggests the possible need of establishing surgical drainage in such patient rather than waiting for the degenerating tumor to rupture.

References: 65; 84 (case #194236); 100.

CASE 21: Inoperable round cell sarcoma of the right pharynx and nasopharynx, confirmed by microscopic examination after incisional biopsy by Professor Tiedemann of the Jewish Hospital, St. Louis, Missouri. Sections were also examined independently by the pathology department of Washington University and St. Louis University. Dr. Lister Tuholske stated, "by three of our ablest pathologists." Sections were sent to Dr. William B. Coley, who had them examined in New York by Dr. James Ewing of Memorial Hospital, who also confirmed the diagnosis.

Previous History: M.B., male, aged 30, of St. Louis, Missouri. The family history was negative for cancer or venereal disease. The patient's father had died of chronic alcoholism, a brother of tuberculosis. The patient did not have a tendency to colds or sore throat, nor did he have bad teeth. He did not remember having had any childhood diseases. He was married at 19 and had one son born about a year later. There was no history of antecedent local trauma or infection in the nose or throat. When first seen by Dr. Lister Tuholske of St. Louis, having been referred by Dr. Kaplan, the patient had a tumor of the right pharynx and nasopharynx of such size that it caused almost complete obstruction of air. A tracheotomy had been advised by Kaplan. This did not seem to be immediately necessary, so after determining the nature of the tumor, following biopsy, Tuholske decided to try Coley toxins, as the growth was inoperable because of its size, location and involvement of the surrounding tissues. Tuholske had become familiar with the method while at the Augustana Hospital in Chicago, under Drs. Albert Ochsner and Nelson Percy.

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

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

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discharged from the hospital on June 28, 1915, feeling perfectly well. The injections were continued twice a week for another two months, and then the patient left the city.

Clinical Course: Sometime during the late summer a recurrence developed on the other side of the pharynx. The patient did not return until November 11, 1915 at which time there was a good-sized tumor apparent. He was immediately readmitted to the Jewish Memorial Hospital. Examination revealed that the left pupil was slightly smaller than the right, with a tendency to rectangular shape. Both pupils responded well to light and accommodation. There was partial paralysis of the left abducens nerve. The patient could carry the eye outward about 30°. The fundus and discs were normal in outline and color.

Further Toxin Therapy: Tuholske resumed the injections on November 13, 1915, giving 15 minims daily for a week, without getting any reaction, either local or general, and the tumor continued to grow rapidly. On November 18, 1915 he wrote Coley asking if intratumoral injections would be advisable. (Whether any were given is not evident from the subsequent correspondence.) On November 30, 1915 Tuholske again wrote stating that he was happy to report that in the preceding two weeks a very remarkable improvement had been evident. Prior to November 15, 1915 injections had been made into the patient's arms, except for the first which was made into the back and which was so painful that the patient pleaded that further treatment be given in the arms so that he could lie comfortably on his back. As the arms were somewhat indurated Tuholske felt that this induration interfered with the proper absorption of the toxins, for they failed to act. On November 16, 1915 therefore, he began giving the injections into both thighs on alternate days, and also into the superficial layers of the abdominal wall. These produced quite severe reactions and a wonderful improvement in the patient's condition. In fact, he considered himself cured on November 30, 1915 after only two weeks. The injections were continued about every other day until the last week in January, almost three months. By this time all manifestations of the sarcoma had disappeared except the abducens nerve paralysis, which was supposed to be due to sinus or brain involvement.

Clinical Course: About January 25, 1916 the patient began to vomit and was drowsy most of the time, becoming irrational at night. There was no elevation of temperature. His kidneys and bowels continued to function normally but he gave the impression of being in a toxic state. No injections of toxins were given during this period, and only such nourishment as he was able to retain; glucose proctoclysis, hypodermoclysis, and neutral camphor, and stimulants, strychnin and digitalis.

The patient remained in a coma for 3½ weeks, during which time the temperature frequently dropped as low as 95°F. for hours at a time. Tuholske held little hope for his recovery. During the worst period early in February, the patient weighed only 89 pounds. By the last week in April he had gained 28 pounds, and he was then discharged from the hospital. A careful examination of the nose and throat by Kaplan, the laryngologist who had referred the case, failed to reveal any abnormalities, barring scars. The patient's speech, hearing and sight were normal. The paralysis of the left abducens nerve had cleared up and the movements of the eye were normal. Tuholske reported: "The period of one month was a perfect blank to the patient; he had no recollection of what had happened except that he fell asleep worrying about his tumor, and when he woke up it was gone." (46) The patient stated that when he returned to consciousness he noted a considerable change in his skin: it was dry and scaly, and there was no hair below the neck, and the testicles were considerably atrophied.

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

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

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

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

The patient died of a coronary occlusion and arteriosclerotic heart disease on November 23, 1948, at the age of 63. This was 33 years after his recovery from sarcoma under toxin therapy.

It should be emphasized that this is the only patient in over 1000 studied that were treated by toxin therapy, who later developed symptoms of hypothalamic dysfunction. It would appear that after the diencephalic metastasis was destroyed by the toxins, the involved tissues did not regenerate.

Comment: This history deserves careful study because it emphasizes several important points regarding toxin therapy: (a) the difficulty of obtaining favorable results with a weak preparation: no effect whatever, even with massive doses; (b) the danger of stopping the injections too soon, even though the neoplasm may have regressed completely; (c) the important role that the site of injections may play in determining success or failure: unless absorption is rapid and complete, a good result may not be obtained even with a potent product; (d) this patient appears to have had a brain metastasis, in the region of the hypothalamus: no other case has been found in which brain metastasis was present and regressed permanently as a result of toxin therapy.

It is now apparent from Coley's correspondence files and records that he used Buxton's or Tracy's preparations in the majority of his own cases and was therefore not fully aware of the comparative weakness of the commercial product. After hearing of Tuholske's experience, he wrote to the Director of

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Parke Davis and Company Research Laboratories, asking him to get in touch with Dr. Martha Tracy, and urging him to make their product conform to Tracy's standards. This was done and as a result it was found that Parke Davis had been taking nitrogen determinations (Kjeldahl method) before heating the toxins for sterilization. This one factor apparently made Tracy's product at least ten per cent more potent. Other differences were also discovered.

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

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

References: 46; 95, case 23; 100.

CASE 22: Extensive malignant lymphoma of the abdominal and cervical nodes, confirmed by microscopic examination by MacCarty, pathologist of the Mayo Clinic. The sections were reviewed in February 1945 by Dr. A. C. Broders, of the Mayo Clinic, who concurred in the diagnosis, stating that the tumor was of the reticulum cell type.

Previous History: F.M., male, aged 40, of Princeton, Indiana. The family history was negative for malignancy, tuberculosis or venereal disease. Onset, in the autumn of 1916 a tumor appeared on the patient's back. In December 1916 he had an attack of grippe. Thereafter there was general weakness and loss of weight. During the next few months he caught cold and he had pain in the lower abdomen, but not at other times. "Whatever he ate or drank his stomach felt abnormally full and he suffered from belching and sour stomach."

Surgery: Six months after onset the tumor on his back was excised.

Clinical Course: Three or four months later a node was discovered in the right cervical region. The patient slept poorly and could not get into a position of comfort, and he always felt tired. He had been constipated and had lost 25 pounds in weight in six months. At the suggestion of his physician, Dr. Marshall P. Hollingsworth, he went to the Mayo Clinic on June 12, 1917. He was seen by Dr. W.E. Sistrunk, who reported the condition as follows: "We found on examining Mr. M. that he has extensive lymphosarcoma involving the glands of the abdomen and neck. The condition is so extensive that operative interference would be wrong, and we will have to depend upon treatments with the Coley serum and the use of x-ray. (X-ray was not given.) Of course the condition is an extremely serious one and his chances of recovery are practically none. However, we know of a few instances where very great benefit has resulted from the use of Coley toxins. We thought it would be best for him to return home and allow you to administer the toxins." (100)

Surgery: While the patient was at the Mayo Clinic a cervical node was excised for microscopic examination, as reported above.

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Toxin Therapy (Tracy XI): Injections were begun by Hollingsworth on July 9, 1917 with an initial dose of $\frac{1}{4}$ minim. During the next month nine injections were given, and the dose was doubled each time, so that by August 11, it was 14 minims. The reactions following the larger doses were very severe, and the patient declined to continue treatment after August 11, 1917.

Further Surgery: He then went to St. Louis, Missouri, where he succeeded in getting a surgeon to perform an exploratory operation, which consisted, Hollingsworth stated, of "slashing the tumor from one end to the other end and then sewing up the opening in the tumor and closing the abdomen." (This letter was written to Coley by Hollingsworth in reporting the progress of the case in 1918.) He added: "M. has improved very greatly. The tumor, which occupied half of the abdominal cavity is now barely perceptible on palpation. Dr. Charlie Mayo was more than surprised to see M. recently — practically recovered." (46)

Further Toxin Therapy: The patient then decided to resume toxin therapy and the second course of injections were begun on August 3, 1918 by Hollingsworth, who had obtained a fresh supply of toxins from Tracy. The initial dose was $\frac{1}{4}$ minim. During the remainder of 1918 and all of 1919 they were administered in alternate months, two to four injections a month, (a total of 22 in 17 months). From November 1919 until April 17, 1920, none were given (a period of six months). They were then resumed and during the first week were given daily, the dose being increased 1 minim daily. During the remainder of 1920 the injections were given four or five times a month, making a total of 45 injections in 1920. The dosage used that year ranged from 8 to 52 minims. When the latter was reached the injections would be suspended for three or four weeks and then resumed at 8 minims, again increasing daily.

During 1921 the dosage ranged from 5 to 34 minims, and the injections were usually given once a week, with periods of four to six weeks' rest every three months. The toxins were continued during the first six months of 1922, but after February only six injections were given, the final one being on June 10, 1922. The dosage used during this last six months was somewhat reduced, being 5 to 20 minims. After 1921 the Park Davis XIII was used, as Tracy XI was no longer being made.

In describing the treatment Hollingsworth stated that the patient insisted on the larger doses. He added: "the reaction was sometimes extreme, and often required morphia on account of pain or shock. . . Pain was always controlled by hypodermics or morphia". As to the technic used, Hollingsworth had been advised by Sistrunk to administer the toxins aggressively, Sistrunk stating: "It is necessary that a reaction be produced in order that there be any benefit following administration." (100) Sistrunk added that the toxins could be continued off and on for considerable periods. It is probably due to this suggestion that Hollingsworth continued the treatment with intervals of rest for a total period of five years, lacking a month. (Only a very few cases treated during Coley's lifetime are known to have received toxin therapy for more than 18 months).

Clinical Course: The patient made a complete recovery and there was no recurrence. The tumor disappeared under treatment. In 1922 the patient returned to work on the Southern Railroad. He was road foreman, and his work was more arduous than that of the ordinary locomotive engineer as his duties consisted of inspecting and testing all defective engines of his division. This he continued to do for the next six years and his health remained good. On June 16, 1928 he had an attack of angina pectoris. A second attack occurred the following day, causing his death on June 17, 1928, at the age of 51. Hol-

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lingsworth stated that clinically he appeared fully recovered from the malignant lymphoma during the last 10 years of his life.

Comment: Note that no radiation was given in this case.

References: 46; 84; 100; 126.

CASE 24: Twice recurrent lymphosarcoma of the groin, confirmed by microscopic examination at the Methodist Hospital, Brooklyn, New York by Dr. T. H. Dexter.

Previous History: Mrs. F.B.H., female, aged 41. The family history was negative for tuberculosis or cancer. The patient had always been healthy, but had had no children. There was no suspicion of lues. A tumor developed in the groin at about 12 years of age, which remained stationary and painless for some years, and then suddenly began to grow and rapidly reached the size of a grapefruit. This was removed at the Rebecca Hospital in St. Louis and was said to be non-malignant. Onset, in 1915, a small painless lump appeared at the same site; there was no loss of weight and the general health remained good.

Surgery: The small encapsulated tumor was removed at the Methodist Hospital, Brooklyn, and found to be a "small round-cell sarcoma — evidently a lymphosarcoma." This opinion was based on the morphology of the cells and on the type of vascular channels. Four years later there was a recurrence and two masses the size of lemons were removed by Sherwood of Brooklyn. Eight months later, in August 1919, there was another recurrence which Dr. Henry T. Graham removed at the Methodist Hospital.

Toxin Therapy (Tracy XI): Intramuscular injections of Coley's toxins were begun on August 10, 1919 by Graham and during the next 16 days were given daily, the dosage being increased from $\frac{1}{4}$ to $4\frac{1}{2}$ minims. These caused mild reactions, the maximum temperature being 100°F. , with chills on three occasions.

Clinical Course: In December 1919 another recurrence developed.

Further Toxin Therapy: Treatment was resumed — exact date not known. The patient stated that the tumor decreased while injections were administered and increased when none were given.

Clinical Course: She was admitted to Memorial Hospital on April 14, 1920 and physical examination at this time showed a firm rather hard mass 4 cm. in diameter, firmly fixed to the deeper structures on the right side, and very slightly movable. It was tender on deep pressure. The overlying skin was normal. Below it, along Poupart's ligament, were the cicatrices of the former operations.

Further Toxin Therapy Combined With Radiation: Injections were resumed on April 14, 1920 the initial dose being 0.5 minim, which was increased daily by 1 minim to a maximum of 12 minims. The maximum febrile reaction was 104°F. The patient also received 5 radium pack treatments, totalling about 60,000 mch. at 6 and 10 cm. distance. The first was given on April 30, two weeks after the toxins were begun, the others on June 12, September 17, 18 and December 3, 1920. There was no radiation sickness. The toxins were continued at home daily, in doses of 3 to 12 minims, and caused a few chills. By September 15, 1920 the patient had gained weight and was

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in much better general condition. By December 2, 1920 there was no longer any definite mass in the groin.

Concurrent Infection: She had two large abscesses in the groin where her doctor had injected the toxins. The whole thigh was swollen around these areas.

Further Toxin Therapy: The patient then was taught to give herself the injections and continued them for two years. Another radium treatment was given over two areas of the red scar in January 1922. The patient wrote in answer to our questionnaire: "The injections were given first at the Methodist Hospital, then at Memorial Hospital, then by Dr. Ronty in Cos Cob, Conn. Then I began giving the injections myself in arm, right and left, or fleshy part of leg. I sterilized everything and was most accurate in measuring the toxin and experienced no ill effect until the chill which put me in bed and always made me feel better afterwards. The toxins used were given me by the Memorial Hospital or by Dr. Coley. I went to see him several times while I was giving them to myself over a period of two years." The dosage was as follows: "Starting with $\frac{1}{4}$ drop, and then $\frac{1}{2}$ drop, $\frac{3}{4}$ drop and continuing until chill at six drops one time, another seven drops. Treatment discontinued for a couple of weeks or more until feeling fine, then starting over with $\frac{1}{4}$ drop and continuing until chill."

Clinical Course: There was no further recurrence. The patient was followed periodically by Memorial Hospital and remained in good health until about 1942 when it was found that she had diabetes mellitus with a blood sugar of 174 mg. She was treated by diet only. At this time she developed a swelling in front of the left ear. This was excised at the Charlotte Hungerford Hospital, Torrington, Connecticut, and proved to be a tumor of the left parotid gland. It was examined microscopically by Dr. C. J. Bartlett of New Haven, who reported: "Sections show a little cellular glandular tissue and continuous with this is a tumor growth. The latter shows an adenomatous structure and is not a so-called mixed tumor. . . of a low degree of malignancy, Grade I. . ." The family physician at that time, Dr. G. M. K. Wallach, stated that during his observation of the case, there was no return of this tumor nor of the lymphosarcoma of the groin. The patient reported on April 9, 1947 that she was in failing health, with "infection of some sort and anemia." At this time she weighed 160 pounds and was taking iron and vitamin pills. In October 1947 she developed congestive heart failure in addition to her diabetes mellitus. She was digitalized and carried on diet and insulin. By August 1948 she weighed 135 pounds (height 5 feet 5 inches), and her blood sugar was 151 mg.

The patient was admitted to the Methodist Hospital, Brooklyn, N.Y. on August 6, 1949, with a history of bleeding which she thought came from the gastro-intestinal tract, but which proved to be hematuria. Cystoscopic examination showed tumors of the bladder, for which she was operated upon on August 17, 1949. The tumors were excised and the base fulgurated. The patient made an uneventful recovery. The histological diagnosis was: papillary type transitional carcinoma, Grade I, of the bladder. Dr. Timm of the Brooklyn Hospital reported on October 12, 1949: "The patient's present physical examination reveals an individual approximating her age with a good hemic component. The patient is mentally alert and physically active. She has a diabetes for which she is taking insulin, and a moderate hypertension 180/90. Bimanual examination reveals no evidence of pelvic disease, and there is no inguinal or other adenopathy. Right inguinal region shows evidence of extensive scarring with telangiectasis characteristic of post-operative radiation." The patient was readmitted to the Methodist Hospital on Novem-

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ber 2, 1949. The next day the bladder was examined and a small recurrent papillary tumor along the left lateral wall was noted, with a broad and bleeding base, $\frac{1}{2}$ cm. in diameter. This tumor was thoroughly fulgurated. The patient was discharged on November 4, 1949. She was admitted to the Waterbury Hospital in April 1951, because of further trouble with the bladder, pus in the urine, frequent and painful micturition. A complete cystoscopic examination was made at this time which showed a chronic cystitis but no evidence of any malignancy of the bladder. During 1952 she gradually developed more difficulty with the heart disease, the diabetes being fairly well controlled. The bladder symptoms continued. By March 1953 she required mercurial diuretics. The urinary symptoms became worse. On September 14, 1953 she developed hematemesis and melena. She was hospitalized in New Milford. For six days she continued to lose blood and expired on September 20, 1953. Permission for autopsy was refused. At this time the liver was enlarged and nodular, and there was a definite mass in the right lower quadrant of the abdomen. It was felt that the patient died as a result of general intra-abdominal metastases from the carcinoma of the bladder. This occurred 38 years after onset of the lymphosarcoma.

Comment: Note that this patient developed four different types of neoplasm, a benign lesion in the groin at the age of 12, lymphosarcoma in 1915 at the age of 38, an adenocarcinoma of the parotid in 1942 and a papillary adenocarcinoma of the bladder in 1949.

References: 46; 85.

CASE 25: Inoperable small round cell sarcoma of the axilla, confirmed by microscopic examination at the Augustana Hospital, Chicago, Illinois, following incomplete removal.

Previous History: Mrs. V. H., female, aged 17. The family and previous personal history were non-contributory. Onset, in early February 1910 the patient began to complain of pain in the right shoulder, especially when lying on the right side. She then noted a swelling in the right axilla which rapidly increased in size. She was admitted to the Augustana Hospital on March 10, 1910, a month after onset. Examination at this time was negative except for a mass in the right axilla. The superficial vessels over the tumor were dilated and tortuous, the skin tense, dry and somewhat discolored.

Surgery: Dr. Edward H. Ochsner operated the following day, March 11, 1910. A tumor about the size of a grapefruit was excised, but it had so completely surrounded the axillary vessels and nerves that not all of it could be removed. The upper, outer fourth of the mammary gland and portions of the pectoralis major and minor muscles were also removed. The wound was closed, and a split rubber drain and two cigarette drains were inserted through a stab wound. The post-operative course was uneventful.

Toxin Therapy (Parke Davis XII): Injections were begun by Ochsner about two weeks after the operation. They were made into the deltoid muscles, every five or six days. Marked febrile reactions occurred, from 102°-105°F. The injections were continued at home by the family physician for about six months. The remains of the growth regressed and the patient made a complete recovery.

Clinical Course: She was examined periodically by Ochsner and remained free from recurrence. She married and had three children, a son who was in the Air Force in World War II, and two daughters. She was last traced in excellent health on December 18, 1946, over 36 years after treatment. Attempts to trace this patient thereafter have proved unsuccessful.

References: 100.

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CASE 26: Twice recurrent inoperable lymphosarcoma of the neck, confirmed by microscopic examination at the Royal Army Medical College.
Previous History: M.M., male, aged 26, of the British Army. The patient first noted a swelling in the left side of the neck, early in 1911, which enlarged slowly. In February 1912, examination disclosed a soft rounded freely movable tumor beneath the left sternomastoid.

Surgery: This growth was excised on March 6, 1912. Recurrence took place very rapidly, the left side of the neck becoming filled with masses of enlarged nodes. On March 29, 1912, an attempt was made to clear out the posterior triangle on the left side, but removal of the growth was incomplete. The wound healed well, but again recurrence took place very quickly.

Toxin Therapy (Parke Davis XII): Injections were begun on April 6, 1912, by Major C. J. Spencer, Royal Medical Corps. The initial dose was 0.5 minim, which was gradually increased for three weeks, injections being given almost every day. By April 26, 1912 the daily dose was 10 minims, and this amount was continued until May 11, 1912. A well marked reaction with a good deal of local inflammation followed each injection. Except for the first few days, all injections were made into the tumor itself. After the first week of treatment there was no further increase in the size of the growth, and decrease in its size soon became apparent, though this was masked to some extent by local inflammation and thickening set up by the injections. After they were suspended, the inflammatory swelling subsided, and in a few days nothing could be felt of the tumor. A further course was given from May 29 to June 29, 1912, 10 minims being given on alternate days.

Summary of Treatment: Initial course: April 6 to 25; 0.5 minim to 9 minim, 16 injections, total 76 minims; second course: April 26 to May 11, 14 injections, total 140 minims; third course: May 29 to June 29, 15 injections, 10 minim doses, total 150 minims; total amount given 366 minims, mostly by intratumoral injection, total duration 2½ months.

Clinical Course: The patient was kept under observation for two months. In June 1913 he returned to active duty in the army. At that time there was no sign of further recurrence and he appeared in perfect health except for the fact that at the second operation the spinal accessory nerve was injured causing some weakness of the shoulder. He was presented before the Leeds and West Riding Medico-Chirurgical Society on December 13, 1912. He was last traced in 1923 in perfect health, over 12 years after onset.

References: 40 (p. 139); 46; 117; 118.

CASE 27: Inoperable lymphosarcoma of the retroperitoneal nodes. The diagnosis was based on the x-ray examination of Dr. John Barnes and microscopic examinations at the State Institute for the Study of Malignant Disease in Buffalo and at the Millard Fillmore Hospital. The report stated that the growth was composed of "round spindle shaped cells which vary markedly in shape and size . . . some mitotic figures."

Previous History: Mrs. M.M., female, aged 50 of Buffalo, New York. The family history was negative for tuberculosis or specific disease. The maternal grandfather is believed to have died of carcinoma of the stomach. The patient had measles, mumps, pertussis, diphtheria and pneumonia in childhood. Menses began at 14 and were normal. She was married in 1909 at the age of 27 and had one son after a full-term, normal pregnancy and confinement. In the autumn of 1924 she had nephritis and became very anemic, the hemo-

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globin being 60%. The anemia persisted. Menopause occurred in 1927-28 at the age of 46-47, with hot flashes and nervous symptoms. During a vaginal examination a small, extramural uterine fibroid was discovered early in 1928. The cervix uteri had several mucus cysts, with mucopurulent discharge from the canal. On March 26, 1928, Dr. Julius Richter removed this fibroid together with the appendix, at the Lafayette Hospital, Buffalo, New York. Onset, at Christmas 1931 the patient noticed an enlargement of the abdomen. Early in 1932 she consulted Richter again, her chief complaint being that she was troubled with much gas in the digestive tract, with considerable backache and that her abdomen was growing very large. These symptoms had been present about four months. Examination at this time revealed a large retroperitoneal tumor in the upper part of the abdomen, which was nodular, immovable and about the size of a large melon. It was not tender on pressure. A radiologist at first regarded the condition as a pancreatic cyst. Dr. Marshall Clinton was seen in consultation and he regarded it as an ovarian cyst.

Surgery: An exploratory operation was performed by Richter on February 18, 1932, at the Millard Fillmore Hospital, Buffalo. A right rectus incision was made, which disclosed a soft, solid tumor springing apparently from the retroperitoneal tissues, protruding forward through the root of the mesentery. An incision was made in the mesentery and a specimen taken for biopsy. The tumor was very friable and was entirely inoperable. The abdomen was closed in layers without drainage.

Radiation: Two x-ray treatments were apparently given at the Millard Fillmore Hospital prior to beginning the toxins.

Toxin Therapy (Parke Davis XIII): Injections were begun by Richter on March 14, 1932, almost a month after the exploratory operation. They were given daily by the intramuscular route and the febrile reactions averaged 101° to 103°F. after the fourth injection. The site was the hip and absorption was complete, no induration remained at the sites of injection. Several chills were produced and some nausea, but no headache or vomiting. From March 26 to April 7, 1932 they were given every two days and the dose was 8 minims, which consistently produced a febrile reaction of 102.6° to 103.6°F. At the end of three weeks' treatment there was evidence of loss of appetite and general depression, but Richter reported to Coley that all palpable evidence of the growth had disappeared. The injections were then stopped.

Further Radiation: On April 20, 1932 the patient was examined at the State Institute for the Study of Malignant Disease and nodular tumors were noted, evidently retroperitoneal, scattered throughout the abdomen. There were no nodes palpable in the neck or axillae. On that date the patient was given one x-ray treatment at the Institute (200 K.V., HVL 9 cu. ant. post. abdomen, a total skin dose of 1062 r.).

Further Toxin Therapy: Injections were resumed on May 19, 1932 but thereafter they were given very spasmodically, i.e., May 24, June 2 and 20, July 5, 19, 25, August 1, 29, September 6 and 12, 1932 a total of 11 injections in four months.

Further Radiation: One more x-ray treatment was given in August 1932, (200 K.V., 1062 r.) over the anterior posterior abdomen.

Clinical Course: The patient was re-examined at regular intervals at the State Institute for the Study of Malignant Disease. During 1933 and 1934 some nodes were palpable either in the groins, axillae, cervical or retroperitoneal nodes at each examination.

Further Radiation: She was given further radiation at the Institute in June 1933, to the left axillae, 890 r.; in March 1934 to the left supraclavicular region and the anterior portion of the left proximal chest, 984 r.

Clinical Course: On September 16, 1935 the State Institute reported: "There are no retroperitoneal nodes palpable. The liver and spleen are not palpable. No nodes in neck, axillae and groins." She had a heart block beating about 40 per minute 120/70 and was advised to be treated for cardiac condition. Periodic examinations were continued.

Further Radiation: No x-ray therapy was given for 5½ years, until October 1, 1939, (200 K.V., left axilla, 388 r.). On January 10, 1940 she was given 2752 r. total skin dose over the anterior posterior mediastinum and on March 11, 1942 800 r. to the left axilla.

Clinical Course: At examination by Richter in April 1942, the patient had absolutely no complaints. Thereafter she was seen every six months at Roswell Park Memorial Institute in Buffalo, and no nodes were found either by palpation or x-ray examination. She reported on April 6, 1946 that her height was 5 feet 1 inch and her normal weight was 120 pounds and that in recent months she had gained three or four pounds. She added "Have been doing all my housework and outside of getting pretty tired at times I have been feeling very well." She had a sudden attack of cholecystitis in September 1951, for which a cholecystectomy was performed. The surgeon reported that there was no evidence of recurrence or metastases of the lymphosarcoma. She lost a little weight after this operation, but by September 1952 her weight was 126 pounds, a gain of about five pounds. In September 1952 she was given a thorough physical examination by Dr. Nolan Kaltreider of Rochester, New York who found her in good condition. She stated then that she felt very well. During the summer of 1954 she was given another check up at the Roswell Park Memorial Institute and they reported no change in her condition and told her they did not think her old trouble would recur. She moved to Florida in 1954. She remained in very good health until January 1960 when she had a left cerebral hemorrhage causing right hemiplegia. She was hospitalized for about three weeks. There was recovery of 70% of physical capacity, but mental defect remained. On July 1, 1960 she developed acute intestinal obstruction. This was handled by a long tube for one week and then an exploratory laparotomy was performed "for relief of adhesions." The patient died three days later on July 10, 1960, at the age of 78, from localized peritonitis with multiple peritoneal adhesions and early gangrene of the transverse colon. Death occurred 30½ years after onset of the lymphosarcoma.

Autopsy revealed no evidence of lymphosarcoma. There was marked arteriosclerosis throughout the mesenteric vessels and the aorta; especially the lower thoracic and abdominal aorta was the site of extensive severe calcifying arteriosclerosis. The pathologist also noted: 1. myocardial fibrosis, old; 2. renal cortical infarct, recent; 3. pulmonary atelectasis, both lower lobes; 4. pulmonary adhesions, mild, right; 5. pulmonary emphysema, bilateral, mild; 6. chronic pyelonephritis; 7. chronic perisplenitis; 8. aortic atherosclerosis, severe; 9. cerebral atherosclerosis, mild; 10. cerebral infarct, left caudate nucleus; 11. hiatus hernia; 12. esophagitis, severe; 13. cystitis; 14. postoperative status: exploratory laparotomy with relief of adhesions; 15. moderate intestinal distention.

References: 46; 100.

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CASE 28: Recurrent inoperable lymphosarcoma of the supraclavicular, cervical and axillary nodes, bilateral and of the mediastinum, confirmed by microscopic examination by Dr. A.C. Broders, a pathologist at the Mayo Clinic, on April 18, 1932, and at the Deaconess Hospital, Cincinnati.

Previous History: H.P.J., male, aged 33 of Wyoming, Ohio, a test engineer. The family history was negative for tuberculosis or malignant disease. The patient was color blind and had nystagmus: his eyes did not develop (limited vision). He had had the usual diseases of childhood, also a tendency to furunculosis in early life, but no serious illnesses. There was no history of trauma, but the patient had an infected tooth root in the left superior maxilla prior to onset. He was married in 1929, about a year after moving to Cincinnati, an unusually congenial marriage, but there were no children. He was inclined to be very apprehensive and "more or less lived with mental, emotional or economic stress" prior to onset, which occurred when the economic depression was at its worst. Onset, in the summer of 1931 the left supraclavicular nodes began to enlarge. There was no special soreness or physical disturbances.

Surgery: Dr. Charles Goosman of Cincinnati operated in September 1931, removing the enlarged nodes.

Radiation: X-ray therapy was then administered, 11 treatments being given in 17 days, beginning October 2, 1931.

Clinical Course: X-ray examination in January 1932 showed a shadow in the upper mediastinum. There was a recurrence of the nodes in the supraclavicular region and the axillary nodes were involved on the left side.

Further Radiation Combined With Further Surgery: Another course of x-ray therapy (17 treatments) was given between February 29 and March 22, 1932, following a second operation. The growths diminished considerably under radiation.

Toxin Therapy (Parke Davis XIII): Injections were begun on April 25, 1932 and were made into the left arm, intramuscularly and intravenously. The initial dose was 1/20 minim, which was increased to a maximum of 2 minims, which was all the patient could tolerate, as he appeared to be very susceptible. The injections were given every other day for six months. They caused very marked reactions, with fever, nausea and some diarrhea. There was regression of the affected nodes, and when Desjardins of the Mayo Clinic examined the patient on September 19, 1932 there were only a few very slightly enlarged nodes in the axillae, especially on the left side, and there was no further evidence of mediastinal involvement.

Further Radiation: The patient received further roentgen treatment to the axillary regions, (500 r. 135 K.V. each).

Further Toxin Therapy: After a month's rest the toxins were resumed and continued another six months. After a second rest period of a month, the injections were again resumed and given once a week for another six months, the total duration of toxin therapy being 20 months. The injections caused much local pain at the sites of injection, with febrile reactions to 103°F. During the early part of the treatment the patient lost 30 pounds in weight.

Clinical Course: He gradually regained his weight and strength, and all evidence of the disease disappeared. His general health remained good (except for some sinus trouble and an occasional cold or hay fever) until Febru-

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ary 1951 when he developed symptoms of a gastric ulcer. This occurred in a period when his work was "very trying, with heavy responsibilities." He then consulted Dr. Charles H. Foerimeyer of Cincinnati. Examination revealed a diaphragmatic hernia with a possible ulcer. Further examination in consultation with Drs. Elmer R. Mauer and Goosman confirmed the diagnosis with the presence of a short esophagus. An ulcer diet was recommended and followed for six weeks. By October 1951 he was back on a fairly normal diet and had very little digestive trouble. His weight remained about 185 pounds, his height being six feet. He remained in good health on January 2, 1954. On May 5, 1955 he fell off a ramp while at work testing an engine and "very seriously tore the ligaments in his right shoulder," requiring surgical repair by Dr. Theodore H. Vinke. Thereafter he suffered "a lot of aches and pains" but continued with his work in a more or less limited capacity. In 1965 he had shingles. In 1966 he had a coronary and was hospitalized from April 19 to May 18. It was then discovered that he had mild diabetes which was controlled with Orinase. He made an excellent recovery and was last traced in good health on April 2, 1969, over 37½ years after onset.

References: 46; 84; 100.

CASE 29: Large lymphosarcoma of the neck, confirmed by microscopic examination after surgical biopsy at the New Haven Hospital.

Previous History: J.P.G., male, aged 23 of New Haven, Connecticut. The family and previous personal history were non-contributory. The patient had a tendency to colds and "had been nervous for years", stated that the least bit of excitement made him "jumpy". He had been in good general health except for gastric pains, due to an ulcer. He was a machine operator. He was six feet, three inches tall and weighed about 160 pounds. Onset, about January 7, 1942 he first noticed a tumor in the submaxillary region. In less than two weeks it increased to the size of a baseball. No doctor was consulted. The patient was admitted to the New Haven Hospital on January 27, 1942, three weeks later, because of a perforated peptic ulcer. At examination on admission, in addition to the abdominal signs, a mass of rubbery nodes measuring 6 x 5 x 3 cm. in diameter was noted in the right submaxillary region. The tentative diagnosis was malignant lymphoma. He was operated upon about half an hour after he was admitted, the ulcer on the pre-pyloric stomach being plicated.

Concurrent Infection: Twelve days after this operation, the patient developed a pulmonary infarct from an embolus. It evidently became infected and he ran a stormy course for about a week, during which his sputum contained hemolytic streptococci. On February 8, 1942 the temperature rose suddenly from normal to 103°F. The next two days it was 104°F; then slowly but steadily subsided and reached 99°F. on February 15, 1942. Dr. Jules Plaut stated that two days after the infection developed, "everybody realized that the lump in the neck had disappeared."

Clinical Course: By February 28, 1942 it was noted that the tumor had recurred, and was increasing slowly in size. On March 13, 1942 the nodes were biopsied and reported to be lymphosarcoma. At this point Plaut wanted to give the patient Coley toxins, but the staff favored x-ray therapy. Apparently Plaut "convinced the staff that a preliminary course of injections could do no harm."

Toxin Therapy (Parke Davis XIII): On April 1, 1942 Plaut began the treatment, and during the next four days four intramuscular injections were given in the following dosage: 0.1, 0.3, 1 and 3 minims, but these caused no reaction.

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Special Research Preparation: (Made up by Parke Davis using Buxton's VI formula): On April 6, 1942 the research preparation was begun, the initial dose being 0.1 minim, the second 0.2 and the third 0.6 minim, all given by the intramuscular route. These all caused little apparent reaction (100.2°F.) The intravenous route was then tried, on April 9, 1942 a dose of 0.1 minim caused a febrile reaction of 105.8°F. and a severe headache, a chill and marked cyanosis, etc. The same dose was repeated on the next three days and produced chills each time with febrile reactions of 105°, 103.4° and 101.2°F., the chills being gradually less severe on each successive day. On April 13, 1942, 0.2 minims were given, causing a temperature of 104.4°F. and a severe chill. Thereafter the dose was increased daily as follows: 0.2, 0.4, 0.8, 2 and 5 minims, the febrile reactions ranging from 102.8° to 104°F. In describing the treatment Plaut stated: "All the reactions began 40 to 45 minutes after the intravenous injections and lasted about half an hour. They were accompanied by marked general cyanosis and severe headaches. On several occasions there was nausea and vomiting. There was very little other reaction. Usually I gave the toxin about 9 a.m.; the chill came at about 9:45, the maximum temperature about 11:30 and thereafter the boy felt pretty well. He had little appetite for lunch but usually ate a good dinner. He got so that he actually looked forward to the injections, inasmuch as he was anxious to get well. The intramuscular shots were wholly ineffective and made the local area pretty sore. There was no pain with or after the intravenous injections."

Clinical Course: After 13 injections of this new preparation had been given, the treatment was stopped as Plaut felt "they had had little or no (apparent) effect on the lymphosarcoma," and he believed this was a fair trial of whether or not this particular patient would be benefited by the toxins.

Further Radiation: Deep x-ray therapy was then begun, and six or eight treatments were given.

Clinical Course: The patient was discharged improved, on May 19, 1942. The growth regressed completely and did not recur again. The patient returned to the New Haven Hospital Clinic for follow-up examination on July 7 and November 24, 1942, showing no evidence of disease. He was followed periodically thereafter, being visited on several occasions by follow-up workers; he claimed to be feeling well, was gaining weight and working every day. By 1946 he weighed between 190 and 200 pounds. On February 17, 1948 he wrote: "I have had no further trouble with my neck." By July 1948 his weight was 240 pounds, an increase of 80 pounds in six years. He stated that his nerves were still "jumpy". In June 1952 he weighed 246 pounds. As he was still suffering a good deal from gastric symptoms a second operation was performed, much of the stomach being resected. During convalescence his weight declined to 185 pounds and he felt better in every way. On June 10, 1966 he suddenly became blind in the right eye due to retinal hemorrhage. Thereafter he was unable to obtain work for about two years. He remained in very good health working in a library when last traced on April 5, 1969, over 27 years after onset.

References: 100.

CASE 30: Inoperable retroperitoneal lymphosarcoma confirmed by microscopic examination by two competent pathologists. The sections were also seen by Dr. A.C. Broders of the Mayo Clinic who concurred in the diagnosis.

Previous History: Mrs. R.Q.B., female, aged 37, of Clinton, Mississippi. The family history was negative for cancer, tuberculosis, diabetes or allergy. The patient had never had any serious illness. There was no history of antecede-

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dent local trauma prior to onset. Menses began at 13, and were painful and irregular. The patient was married but had never been pregnant. Her normal weight was 135 pounds, her height being five feet, seven inches. Onset, during 1942 she gradually lost weight and in December 1942, during an attack of influenza, a tumor was first noticed in the abdomen, with slightly bloody stools. The growth increased rapidly in size until by February 1943 it extended from the region of the spleen, dipping over the pelvic brim.

Surgery: Dr. Joseph F. Armstrong performed an exploratory laparotomy on February 10, 1943 at St. Dominic's Hospital, Jackson, Mississippi. A biopsy was taken. No treatment was given prior to toxin therapy.

Toxin Therapy (Parke Davis XIII): Injections were begun on February 13, 1943, three days after the exploratory incision. The first 17 were given daily into the arm; thereafter, the frequency was once a week until the final injection on April 16, 1943, a total duration of about two months. The reactions were very mild at first, but the sixth dose caused a severe reaction, with intense nausea followed by a hard chill and a temperature of 103°F. Thereafter, they usually caused marked reactions, with hard chills and high temperature, nausea, etc.

Radiation Combined With Further Toxin Therapy: Beginning on February 21, 1943, a week after the toxins were begun, deep x-ray therapy was instituted, treatments being given on the same day as the injections. They were continued until April 1, 1943, a total of 28 treatments. The growth regressed completely during the combined therapy.

Clinical Course: About May 1, 1943, two weeks after the final injection, the patient started having abdominal hemorrhage. She was hospitalized for about six weeks and in bed at home until August. During this time she received vitamin therapy and her condition improved. Armstrong reported on July 26, 1944: "The tumor mass. . .has entirely disappeared. . .She has gained 30 pounds in weight, is doing her usual household duties and apparently has no disability whatsoever." On July 26, 1946 the patient reported that she was stronger than at any time since her illness. Armstrong reported on July 22, 1946 that he had examined her recently and added: "I find her in excellent condition and not a trace of the old trouble. It is my opinion that she has recovered completely." Rembert reported at this time that she had recently been given an x-ray diagnosis of peptic ulcer. However, this was not mentioned by Armstrong or the patient. Rembert reported on November 19, 1948 that she remained in apparently very good health and had had no recurrence. However, she was not robust. "No further signs of sarcoma. Has had a bad gallbladder for years, so is never very well." In 1958 she gained weight (from 98 to 103 pounds). Her physician reported that efforts to get her off laxatives had been unsuccessful. In June 1962 she had a cerebral accident which left her with poor residual coordination in speaking. She remained in relatively good health thereafter until her death in November 1963 from a second cerebral accident. This was 21 years after onset of her lymphosarcoma.

Reference: 100.

CASE 31: Originally this was regarded as reticulum cell sarcoma, (later this was changed to giant follicular lymphoblastoma of the left axilla and inguinal region) with what was regarded as metastases to the distal and proximal ends of the right femur and to the left lung. The biopsy material was taken from two tumors in the left axillary region on March 19, 1948. The section was reviewed in 1955 by

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Dr. Reese, Pathologist at the Orange County General Hospital, Orange, California and by Dr. Henry L. Jaffe. The section showed a tremendous amount of follicle hyperplasia.

Previous History: S.E., female, age 14 months, of Norwalk, California. The child's maternal family history was non-contributory except that the mother had "many colds." The child's father had never been healthy and worked only occasionally. "They do not know what is the matter with him but his is always sick." The parents were divorced. There were three other children. The child weighed $7\frac{1}{2}$ pounds at birth and was healthy for about four months and then began to lose weight. She "had bad tonsils all her life and has had continual respiratory infections with temperatures." Onset, about February 3, 1948, the child began to drag her right leg, and that same week her left forearm was burned.

Concurrent Infections and Inflammation: The burn became infected and healed in one week. At this time the child's mother first noticed a hard painful lump in the left axilla which increased in size. The baby was admitted to the Orange County General Hospital on March 4, 1948. It was stated that for a month she had had a cold: "running nose, fever for two weeks up to 104°F." Examination on admission showed the tonsils red, infected, huge; small nodes palpable on both sides of neck. There was adenopathy of the left axilla, and inguinal regions and the right leg was dragging. X-ray examination showed a destructive lesion in the upper right femur, which was thought to be metastatic. A blood count taken March 11, 1948, showed R.B.C. 2,780,000; W.B.C. 9,100; polymorphonuclears 50, lymphocytes 48, monocytes 2. She was thought to have chicken pox on March 14, 1948, but apparently this was true measles.

Surgery: On March 19, 1948 a 3 cm. tumor was excised from the left axillary region; also a smaller one 1.5 cm. in diameter.

Fever and Further Infection: The temperature rose to 102°F. after this procedure and there was pain in the right hip and leg. The sedimentation rate was 30. The lungs were negative.

Clinical Course: On March 24, 1948 she was discharged home for four weeks. Upon readmission, x-ray examination revealed a mass in the left hilum of the lung.

Radiation: X-ray therapy (218 K.V.) was given to the anterior left axilla (1208 r.), anterior and posterior mediastinum (875 and 850 r.) and the anterior and posterior epigastric regions (175 and 100 r. each) between April 27 and May 30, 1948.

Further Concurrent Infections: During this cycle of x-ray therapy, on May 15, 1948, she developed chicken pox, with fever of 103°-104°F. She was allowed home on May 30, 1948. In early August she developed conjunctivitis.

Toxin Therapy (Parke Davis XIII): Injections were begun by Dr. Mildred F. Wehrly on August 18, 1948, a total of 15 being given in 27 days. The first seven were given intramuscularly in doses of 1/10, 1/5, 1/2, 1, 2, 3 and 4 minims, causing febrile reactions averaging 101.4°F., (minimum 100.2°, maximum 102.6°F.). A blood count taken October 4, 1948 showed R.B.C. 4,280,000; W.B.C. 5,800; polymorphonuclears 48, lymphocytes 52.

Further Radiation: Between September 16 and October 19, 1948 x-ray therapy was given to the lesions in the right femur as follows: 218 K.V., 2 cu., 4 al, anterior upper 900 r., lateral upper 675 r., anterior lower 825 r., lateral lower 600 r., anterior left femur 75 r. totalling 3075 r. By October 13, 1948

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the child weighed 21 pounds 8 ounces, and x-ray examination showed that the proximal lesion of the right femur was smaller and that the distal lesion had disappeared.

Clinical Course: At examination 14 months later, December 17, 1949 she weighed 25 pounds and was irritable.

Fever: It was noted on February 13, 1952 that she had a temperature of 103.2°F., her tonsils were enlarged, she had dental caries, and was undernourished.

Clinical Course: On March 6, 1952 she weighed 33 pounds. On July 27, 1953 she weighed 40 pounds, but had "pain in left hip, unable to walk for a time, not eating well, daily fever." At examination on December 1, 1953 she weighed 41¼ pounds.

Further Infection: On July 20, 1954 she weighed 44 pounds. Her temperature was 99.2°F. she had a "sore throat and tonsillitis." She was given penicillin for four days (6,000,000 units daily).

Clinical Course: At examination January 19, 1955 she weighed 47 pounds. There was "numbness and tingling" of the legs, some shortening and slight atrophy of the right thigh. There was no evidence of residual disease. She was found to be anemic and on January 19, 1955 was given 500 cc. of blood and put on Feosol. Wehrly noted that "home conditions of the child were very poor, and she had many minor illnesses. She needs dental work and tonsillectomy."

Further Infection: On May 13, 1955 the child had an infection of the right foot with right inguinal adenopathy. Penicillin was administered for three days (300,000 units daily). At this time the hemoglobin was 10.0, W.B.C. 6,500, polymorphonuclears 72, lymphocytes 28.

Clinical Course: She had a tonsillectomy in January 1956 and thereafter her general condition improved. She was home from school a good deal during the fall of 1956. In November 1956 she was believed to have herpes zoster. The patient married. She remained free from recurrence or further metastases when last traced in May 1964, over 16 years after onset of the giant follicular lymphoblastoma. Attempts to trace her since have failed.

References: 100.

CASE 32: Inoperable lymphosarcoma of the cervical nodes, confirmed by microscopic examination at Memorial Hospital by Dr. Fred W. Stewart on March 7, 1947 (V-9000), who reported that the original sections from tissue removed at biopsy at Staten Island Hospital on November 26, 1946 showed either lymphosarcoma or neuroblastoma (V-4840). Examination of the recurrent tumor excised on March 7, 1947 was reported by Stewart as lymphosarcoma (V-9000).

Previous History: J.M., male, aged 3, of Staten Island, New York. The family history was non-contributory. The child's mother had been married previously and divorced, and she had two children by that marriage. The child's father was 48. At birth he had a very loud systolic murmur which was later diagnosed as a patent interventricular septum. His general health, growth and development were otherwise normal until onset. In 1944 he developed pertussis. In December 1945, at the age of two, he had his tonsils and adenoids removed. Six months later he was hospitalized for one week for acute bronchitis. There had been no other illnesses. Onset, in late September 1946, ap-

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proximately 2½ months prior to admission to Memorial Hospital, a small apparently non-tender mass the size of a cherry was noted by the parents in the right upper neck near the angle of the jaw, which progressively increased in size. There was no pain or dysphagia at any time. When the lesion was first noted the child was taken to a local physician who said it was a "gland" and treated it with black salve. When it became the size of a large plum another local physician was consulted, and the child was admitted to the Staten Island Hospital on November 18, 1946.

Surgery: On November 26, 1946 an incisional biopsy was done. Microscopic examination showed gland acini infiltrated by neoplastic cells which was diagnosed as 'undifferentiated carcinoma (lympho-epithelial or embryonal'').

Clinical Course: X-ray examination of the region revealed no bone involvement and chest ex-rays were said to be negative. The child was then referred to Memorial Hospital for diagnosis and treatment. Examination on admission on December 6, 1946 showed a hard fixed slightly irregular non tender mass 10 cm. in diameter in the right upper neck (parotid region), which exhibited venous distention in the overlying skin, with a well-healed biopsy incision over the central portion. There was a group of nodules, immediately lateral to the mass which were thought to be involved regional lymph nodes. An examination of the buccal cavity and nasopharynx was impossible because of failure of the child to cooperate. He was a well-developed alert three-year-old white male who appeared in good general health.

Radiation and Concomitant Toxin Therapy (Sloan-Kettering XIV): A total of 10 x-ray treatments were given totalling 2000 r. Injections were begun by Dr. Laske on December 7, 1946 and were given every 48 hours intravenously. The first five doses (1/100 each) caused febrile reactions varying from 100.4°F. to 104.2°F. The dose was then increased as follows: 1/80 (twice), 1/50, 1/80, 1/60, 1/50 (twice), 1/40 (twice), 1/20 (twice), 1/10 (twice), 1/50, 1/40, 1/20, 1/10 (each of the following were given twice): 1/3, 1/2, 3/4, 1. Thus a total of 25 injections were given in 50 days. Febrile reactions averaged 102°F. to 104°F., (minimum 100.4°F., maximum 104.2°F.) Chills occurred on nine occasions and were never severe (lasting 5 to 15 minutes, usually slight or moderate.) By December 14, 1946, one week after toxins were begun, the tumor had decreased considerably in size. Regression continued steadily. On December 22, 1946 the child climbed over the top of the crib and fell to the floor, striking its head. The only damage appeared to be a bruise over the left temple. Three weeks after the first injection there was complete regression of the tumor.

Clinical Course: At this time he was reported as "well, with no evidence of tumor, although the skin over the right parotid area seems a little thicker and heavier than that on the right." The child was discharged home on January 23, 1947. He was readmitted on February 20, 1947 with a 3 x 4 cm. recurrence in the center of the radiation field. This smooth rounded mass under the tail of the parotid was somewhat movable from side to side. His mother stated he had been in excellent condition since his discharge a month previously, with a good appetite and no weight loss.

Concurrent Infection: On March 2, 1947 he had a mucopurulent discharge from both nares. The pharynx was slightly infected. This nasopharyngitis caused the operation, which had been scheduled for the next day, to be postponed until March 7, 1947. It was noted during these five days that the tumor of the neck decreased in size and measured 2 x 3 cm.

Clinical Course: On March 7, 1947 the recurrent tumor was excised under drop ether. The post-operative recovery was good. There was considerable edema of the neck at the operative site. Penicillin was given prophylactically.

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Further Radiation: Another course of x-ray therapy was begun on March 17, 1947: 250 r daily for 10 days to the right upper neck totalling 2500 r.

Further Infection: On March 31, the child developed a mild nasopharyngitis and laryngitis with no fever. He was given sulfamerazine, 0.5 t. i. d. He continued to have a low squeaky voice for several days, reduced to a whisper on April 5, 1947.

Clinical Course: He was discharged on April 9, 1947. He remained symptom free.

Further Infections: In January 1948 he developed varicella and in the fall of 1948 he developed impetigo of the face and hands, which cleared up by December 10, 1948.

Clinical Course: The child was readmitted to Memorial Hospital on January 6, 1949. His general health had been excellent, there was no evidence of dissemination of the malignancy, but about a month prior to admission a mass was noted in the left submental region and "the parent was advised to wait and watch." The child's principal difficulty had been his unmanageable behavior. He was aggressive and destructive. He lit fires, turned on the gas, bit his playmates, smeared his feces and was enuretic. Two months prior to admission he was seen at Bellevue Hospital and the mother was told "There has been some brain damage secondary to surgery." The home situation was unsatisfactory: the mother had been separated from her second husband for a month. An older half-brother had been at Letchworth Village because of mental retardation. Physical examination at Memorial Hospital on January 6, 1949 revealed a well-nourished, well-developed, wiry aggressive youngster who did not look ill. The impression: "(1) possible metastatic lymphosarcoma cervical nodes, liver, spleen. (2) Congenital heart disease, probably patent I-V septum with left to right shunt. (3) Behavior problem, severe." A careful work up was done, including "CBC, urine, S & T, x-ray of chest, skull, abdomen, EKG, fundoscopic examination" and the findings were essentially negative except for an "eosinophilia which he had always had (sometimes to 20%) now 7 to 11%, which might represent an intestinal parasite (pin-worm) or possibly Hodgkin's disease or eosinophilic granuloma." A consultation with a psychiatrist from the Payne Whitney Clinic resulted in the suggestion to place the child in an institution on Staten Island for about six months as the boy was unable to "relate" to anyone in the home environment, and if it were possible for him to do so elsewhere there was a hope of solution to his problem. He was not institutionalized, however.

Virus Infection: In October 1949 he was admitted to the Willard Parker Hospital with poliomyelitis. This produced a partial paralysis of the left lower extremity. A left long leg brace was supplied to him in January 1950.

Clinical Course: At examination in Memorial Hospital on January 18, 1950 his general condition appeared good, and there were no significant findings in the neck other than beginning atrophy and telangiectasis in the skin on the right side at the site of the x-ray therapy. On February 16, 1950 the patient developed a very tender mass just medial to the previously irradiated skin 3 x 2 cm. A punch biopsy was performed on February 24 and reported as "chronic inflammation in subcutaneous tissue only." The mass disappeared completely thereafter. In 1950 he was committed to the care of the Sisters of St. Dominic at St. Joseph's School, Blauvelt, New York, where he remained for 18 months and made considerable progress. On September 27, 1951 the child was seen at Memorial Hospital suffering from a severe case of scabies,

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being extremely uncomfortable due to severe itching. On October 1952 he was admitted to Bellevue Hospital "because of his mother's inability to handle him." He was transferred to Memorial Hospital on December 1, 1952 for observation of the present status of his lymphosarcoma prior to placement in a home for chronic care. His I. Q. had dropped from 84 to 68 in the previous three years and he had in recent months developed neurological changes (inequality of pupil changes, athetoid movements of the outstretched arm and immature posturing particularly on the left.) While the child was at Bellevue there was no problem in his management, although he was still enuretic at times. The impression was possible recurrence of lymphosarcoma with skull and/or intracranial lesions, possible intracranial disease of unknown origin. A careful work up resulted in the following diagnosis: (1) "a six-year cure of lymphosarcoma with no evidence of recurrence. (2) congenital heart disease, acyanotic in type, probably a septal defect. (3) post-poliomyelitis paralysis of the left leg and foot. (4) emotional and behavior problem with slight evidence of mental retardation and no evidence of organic cerebral lesion." He has been seen periodically at Memorial Hospital. He obtained a job, married in 1965 and had a daughter in September 1967. He remained in very good health when last traced September 27, 1967, 21 years after onset.

References: 85, 100.

SERIES D: LYMPHOSARCOMA UNSUCCESSFULLY TREATED BY TOXIN THERAPY ALONE OR COMBINED WITH SURGERY AND/OR IRRADIATION: 54 CASES, ALL INOPERABLE EXCEPT CASES 13, 36 AND 37.

The name in parenthesis following the case number refers to the physician, surgeon or hospital handling the case. At the end of each case abstract the bibliography reference numbers are given. The cases are listed chronologically according to the type of toxin used. For a brief description of the formulae used in making these preparations of Coley toxins see references 92 and 95. The detailed histories of all but two of these cases are available at the New York Cancer Research Institute. Of special interest are cases 4, 6, 9, 10, 29, 30, 38 and 39 and their detailed histories are given here following the brief abstracts.

*Period of
Survival*

1. (W. B. COLEY): A. W., male, aged 49; inoperable small round cell sarcoma right cervical nodes size of large orange, also left cervical nodes; tonsil and roof of mouth extensively involved; onset, January 1894, untreated except for biopsy; toxins begun July 10, 1894 (Buxton V, Filtrates); *marked decrease in size during 1st wk. (to size of egg)*; no further improvement, though injections were resumed briefly; death September 4, 1894. (16, case 17; 42; case 10; 85) 8 mos.
2. (COHEN): R. C., male, aged 19; recurrent inoperable lymphosarcoma of supraclavicular, cervical (size of egg) and axillary nodes (size of orange and egg); onset, July 1894; primary excised recurrence untouched; July 1895: toxins (Buxton VI) for 4 weeks; *temporary diminution in size, increased mobility*; no further improvement; chylous ascites, death November 1895. (23, pp. 610-611; 46) 16 mos.
3. (W. B. COLEY): G. S., male, aged 5½, inoperable small round cell sarcoma inguinal and iliac nodes; apparently well until early May 1899, then fell, injuring right groin; few days later soft rapidly growing tumor developed; explored: very vascular tumor; following operation iliac nodes rapidly became involved; late May 1899: toxins (Buxton VI); *temporary effect; tumor much more movable, perceptibly smaller*; after 2-3 wks. again increased in size; death September 1899. (42, case 52) 4 mos.
4. (W. B. COLEY): Miss M. L. A., female, aged 40; inoperable lymphosarcoma cervical, axillary and mediastinal nodes (small round cell type); edema of lower extremities; onset, September 1898, mass over clavicle removed, September 1899; recurrence, axillary involvement; latter excised July 1900; when toxins begun, September 26, 1900 main tumor mass extended from clavicle to mastoid; mass above sternum appeared to cause dyspnea; toxins (Buxton VI) given in small doses, *marked regression, increased mobility in 1st 3 months, then improvement ceased*; 156 doses in 9 months apparently given i.m.; growths slowly began to increase, later grew rapidly; bedridden, severe dyspnea; x-ray then tried (4-6 weekly); caused remarkable regression after 3 weeks; in 6 months all growths entirely disappeared, patient gained lost weight; further recurrence September 1902 in parotid region; multiple metastases, 1 in abdomen size of cocoanut; further radiation caused temporary regression of masses in parotid and groin, decrease in abdominal mass; then multiple metastases (hundreds of small nodules pea to egg-size over entire body); Coley believed radiation had lowered her resistance to the tumor; death June 1904. (23, pp. 702-703; 24, case 1; 42, case 60; 85) 5¾ yrs.

5. (W. B. COLEY): J. A. P., male, aged 32, inoperable twice recurrent lymphosarcoma of neck; date of onset not recorded; 2 operations early 1902, 1904; 2nd recurrence size of half coconut, left cervical region; March 4, 1904: toxins (Buxton VI) 10 to 14 days i.m. given concurrently with x-ray (4 weekly); *disease not controlled*, death. (5, 85) over 2½ yrs.

In the following three cases both Buxton VI and Parke Davis IX were given. The first of these patients observed repeatedly how much more potent and effective the Buxton product was.

6. (W. B. COLEY): E. H. M., male, aged 35; recurrent inoperable small round cell sarcoma of pectoral region and axilla; onset 1898, mass in anterior axillary line of pectoral region; November 1900, extensive removal including part of muscle by Richardson; recurrence in 6 months, grew very rapidly; October, 1901, severe almost fatal hemorrhage at 2nd operation; disease then spread with frightful rapidity; December 8, 1901, 3rd operation, disease too extensive for interscapulothoracic amputation, movements of shoulder greatly restricted; referred to Coley; December 18, 1901, toxins begun 5 or 6 a week for 3 months i.m. in pectoral region, only 6 febrile reactions of 102°-103°F.; *tumor softened; in 3 weeks sinus opened spontaneously evacuating a pint of necrotic tumor tissue, growth regressed to 1/3 former size; after week without injections, early February 1902, tumor increased considerably; x-ray given concurrently; mass in axilla then regressed completely, movements of shoulder practically normal, gained 20 lbs., in excellent health; toxins stopped, returned to hard physical work, long hours as plumbing contractor (was in debt due to illness); growth recurred November 1902, 5 months after toxins stopped, increased rapidly; toxins resumed i.m. by Coley, continued at home by family physician and patient himself, slight reactions; February 1903, Coley gave toxins into tumor (both Buxton VI and Parke Davis IX: it took 8 minims of P.D. IX to give same reactions as 1/4 minim of Buxton VI); x-ray (9 more); again complete regression, general health perfect by March 23, 1903; another slight recurrence 9 months later; toxins and x-ray resumed; again regressed completely; (total duration of toxins, given at intervals, about 2 years); another recurrence May 1905, disease not controlled; extended to lungs, pleura, death September 1905.*

Note that toxins were not begun until after 3rd operation, never given intravenously or sufficiently aggressively as regards dosage due to patient's economic problems, weaker product used much of time, combined with a good deal of radiation. (24, case 3, and discussion by Richardson; 25, 26, 27, 46).

7 yrs.

7. (W. B. COLEY & WILSON): Mrs. W., female, aged 26; extensive inoperable intra-abdominal round cell sarcoma, involving mesentery, mesenteric nodes and small intestine; onset October 1903; exploratory laparotomy by Conant November 19, 1903, tumor size of closed fist biopsied, no attempt at removal; early December 1903, toxins (Buxton VI) 5 and 6 weekly concurrently with x-ray; *immediate decrease in size; regressed to size of orange; treatment stopped due to colitis; gas and bloody stools subsided, but growth increased in size and innumerable small metastases appeared all over abdomen (marble to billiard ball in size); toxins resumed daily for 3 weeks; large primary regressed completely, only 6 very small metastatic lesions remained; again developed colitis; toxins suspended, resumed for 3 weeks; then developed acute local peri-*

tonitis due to necrosed portion of small intestine, fecal fistula developed below navel; *septic temperature for many wks.*; slowly recovered; toxins (Parke Davis IX) in small doses given for some time by Wilson; remained well until February 1905; recurrence; toxins again resumed; *recurrence nearly disappeared*; general condition fair; spring of 1905, ascites; retroperitoneal metastases; toxins not resumed; death January 1906. (27; 29; 40; 41; 42, case 28; 46; 135) 27 mos.

8. (W. B. COLEY): A. L. C., male, aged 33; recurrent inoperable retroperitoneal round cell sarcoma; date of onset not recorded; 1st operation October 1901; recurrence early February 1904; toxins begun April 18, 1904, 45 in 61 days (26 Buxton VI, 19 Parke Davis IX) i.m., no marked reactions, given concurrently with x-ray; *improved*; explored 3 wks. later, specimen removed; 1 or 2 more injections (Buxton VI) given, 1 marked reaction; death March 12, 1905. (5; 85). 31½ yrs.

The following two cases received Buxton VI at first, later Tracy's preparations; case 9 also received the weaker Parke Davis XII and XIII.

9. (W. B. COLEY & MIXTER): Dr. J. B., male, aged 56, inoperable round cell sarcoma of mesentery and small intestine; onset summer 1904; incomplete removal tumor mass weighing 2 lbs. December 1904; 10 days later Mixter began toxins (Buxton VI), given 2 months, with x-ray; *remaining induration disappeared*; 2nd course toxins March 1905 for 2 months (self-administered), combined with heat therapy (hot air cabinet); well nearly 2 years, then local recurrence in right pelvis, central mass size of 2 fists, several smaller ones; toxins resumed by Mixter (Tracy XI): *rapid regression; dose soon reduced, tumor then increased rapidly in size, anorexia, indigestion, lost 19 lbs., increasing weakness*; further toxins and x-ray under Coley; *disease held in check*; another incomplete surgical procedure, portion of tumor weighing 4½ lbs. removed by Mixter; toxins again resumed (Parke Davis XII and XIII, also Tracy XIF, all weaker than Tracy XI); *improved, gained 12 lbs.*; February 19, 1909, another attempted removal of remains of growth proved fatal due to shock at operation. (Note that radiation was given during 1st 2 courses of toxins and 4 incomplete operations were performed; also no intravenous or intratumoral injections were used, and duration of 1st course was only 2 months). (42, case 29; 46; 85; 126).

10. (W. B. COLEY): H. M., male, aged 32; recurrent inoperable lymphosarcoma of left tonsil and neck; onset mid-August 1905; incomplete removal, late August 1905; post-operative x-ray every 48 hours, also radium internally and externally, little effect; portion of growth excised October 13, 1905; referred to Coley 3 days later; left cervical mass size of half orange, tonsils 2 or 3 times normal size when toxins begun, October 20, 1905 (Buxton VI); given alternately into cervical tumor and pectoral muscles; *decided decrease in size, increased mobility in less than 1 wk.; complete regression of both masses in 6 weeks; injections nevertheless continued for total of 1 yr.; in excellent health 6 years, then recurrence in opposite tonsil and neck; cervical mass removed by Erdman December 1911; recurred very rapidly; (larger than former size in 3 weeks); very extensive operation by Coley and Downes early January 1913; toxins resumed (Tracy XI) January 16, 1912; 6 small doses in 7 days in pectoral muscles; no reactions; patient lost hope, declined further hospitalization; few more doses given at home; tumor grew with great rapidity after toxins were stopped*; death March 1912. (29, case 22; 31; 40, case 3, p. 24; 42, case 14; 46; 85) 61½ yrs.

TOXIN TREATED FAILURES, ABSTRACTS

Period of
Survival

The following case received the Lister Institute preparation of Coley toxins

11. (WILLETT) : P. C., male, aged 22; inoperable recurrent lymphosarcoma of axilla; onset, early June 1897; 2 incomplete curettages October 2 and 16, 1897; wound suppurated for several weeks; mass increased to size of orange by February 19, 1898; toxins begun March 3, 1898, 11 in 51 days, only 5 marked reactions; discharge increased; no apparent benefit; after toxins were stopped patient sank rapidly; death, July 27, 1898. Autopsy showed growth had ulcerated through thoracic wall into upper right lung, and into clavicle and humerus causing necrosis; lesions in liver, spleen and kidneys were undergoing fatty degeneration. (134) 13 mos.

The following two cases had the Parke Davis IX preparation of Coley Toxins:

12. (NEWCOMET) : A. D., young adult male, inoperable recurrent round cell sarcoma neck; date of onset not recorded; most of mass removed surgically spring 1903; remains of tumor disappeared under combined toxin and x-ray therapy; local recurrence 6 months later; removed surgically in 3 months; again recurrence involving whole right base of neck; toxins and x-ray resumed; at first tumor continued to grow but in 4 months it decreased to size of walnut; further evidence of activity winter 1906-07; intense pain, further x-ray, no apparent benefit; death late spring 1907. (98) 4 yrs.
13. (MULLER) : Male, aged 28; recurrent lymphosarcoma neck; large primary growth dissected out; recurrence developed in a month, along trapezius; removed at second operation 1907; toxins begun immediately thereafter, technic unknown; patient well 4 years; then further recurrence developed, lost 30 lbs.; general health deteriorated rapidly; toxins resumed (technic unknown); disease not controlled; died 1912. (42, case 4 in table of other men's cases) . 5 yrs.

The following 20 cases received Tracy's preparations of Coley Toxins (Type X, case 14, Type XI the others). Tracy's products were more potent and less variable than any of the other preparations available during Coley's lifetime (46, 92, 95). Five of these 20 patients also received the weaker commercial preparations (Parke Davis XII or XIII: Cases 16, 17, 29, 30 and 31).

14. (W. B. COLEY) : W. C. C., male, aged 42; inoperable small round cell sarcoma of tonsil, extensive metastases to both cervical regions extending nearly to clavicle; nasopharynx obstructed, speech affected, general condition markedly deteriorated; rapid weight loss; onset following tonsillitis, January 1906; prognosis seemed hopeless, no biopsy done prior to toxins, begun May 29, 1906; injections alternately into tumors of neck and i.m., pectoral region; 30 in 50 days; reactions 102°-104°F., marked softening, considerable regression apparent after 2 weeks; x-ray begun June 11, 1906, 2 or 3 weekly; continued to lose weight, general condition bad; softening continued after toxins were stopped, several severe hemorrhages from mouth that summer; tumors all entirely disappeared; recurrence under left maxilla January 1907; did not return for further treatment until April 1907, when mass was size of orange; tumor incised, incompletely curetted, found to be necrotic in center; toxins resumed April 27, 1907, 10 in 17 days, mostly i.m., few in tumor; refused further therapy; other tumors then quickly developed in neck, causing death within a year. (30, case 3; 40, case 14; 42, case 15; 46; 85). 2 yrs. case 14; 42, case 15; 46; 85). 2 yrs.

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15. (R. M. GREEN): F. J. S., male, aged 12; inoperable round cell sarcoma axillae, right groin, right chest wall (latter appeared March 3, 1908, following a blow); large tumor on chest and inguinal mass removed March 24, 1908; x-ray given; toxins April 2, 1908: 9 i.m. in 9 days; 3 adequate reactions (102°-104°F.); *disease not controlled*, multiple tumors appeared rapidly, death September 6, 1908. (82; 100) 6 mos.
16. (W. B. COLEY): G. A. L., male, aged 31, inoperable recurrent large round cell sarcoma, cervical and submaxillary nodes; (from 1903 patient had been subject to recurrent tonsillitis); in 1906 heavy piece of wood fell striking neck; thereafter area became indurated and painful during each tonsillar infection; onset, October 1908, usual disappearance on recovery from tonsillitis did not occur; removed surgically when size of walnut, late October 1908, prompt recurrence, cervical lymphadenopathy; toxins (Tracy XI) begun by Coley November 1908, given i.m. in pectoral region, slight febrile reactions; continued by family physician; *complete regression in 6 wks.*; toxins then stopped; evidence of recurrence June 1909; injections resumed, given intermittently for about 1 yr., using weaker Parke Davis XII, *little or no effect*; January 1910: inguinal and right cervical nodes removed at operation; thereafter pressure symptoms due to masses filling abdomen; death November 5, 1910. (42, case 41; 85; 126) 2 yrs.
17. (STANTON, McMULLEN AND LATER W. B. COLEY): Capt. W., male, aged 35; inoperable large round cell sarcoma of tonsil, very extensive involvement of superficial and deep lymphatics on right side, pharynx nearly blocked; during summer of 1909 right tonsil repeatedly enlarged, usually accompanied by high temperature; about September 20, 1909, during such an episode, large ulcer formed on tonsil; culture positive for diphtheria and streptococci; onset, November 1909; arsenic applied, caused sloughing, did not materially retard growth; whole chain of nodes on right side involved; several pieces of tonsil removed surgically; toxins (Tracy XI) begun April 3, 1910, 23 in 38 days. i.m. in pectorals; *noticeable change in 2 wks., complete disappearance in 5 weeks*; injections continued at home, 5 in June; thereafter weaker Parke Davis XII used, 1 in July, 3 in August; beginning in July slight irritation noted on swallowing cold water; recurrence in tonsil, August 1910; biopsied early September; toxins then resumed (Parke Davis XII): 23 in 51 days i.m., *again complete disappearance within 3 weeks of resuming treatment*; again recurred locally in tonsil January 1911, tonsil three times normal size but no cervical lymphadenopathy; toxins resumed: 9 in February, 7 in March, *some into tumor, causing large slough of upper portion*; referred to Coley February 1911; he gave Tracy XI and XIF (filtrate) i.v., with marked reactions; *temporary improvement*; toxins continued at home by McMullen through January 1912 (total of about 300 injections in almost 2 years); disease progressed, death February 1912. *Autopsy revealed not a single metastasis anywhere outside chain of cervical nodes draining tonsils; long use of toxins in large doses had produced no changes in heart or kidneys.* (35; 37; 42, case 16; 46) 27 mos.
18. (W. B. COLEY): J. M., male, aged 27; recurrent inoperable small spindle cell sarcoma cervical, supraclavicular and mediastinal nodes; onset fall 1907; left cervical nodes excised; ("thought to be tubercular"); recurred; 2nd operation, April 1911, nodes removed from neck, supraclavicular region; 3rd operation, incisional biopsy, October 11, 1911;

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post-operatively, 3 doses toxins i.m., *no appreciable reaction*; in good health except for severe cough, infiltration in suprasternal, supraclavicular region, especially left side encroaching on larynx; toxins resumed January 15, 1912; 31 in 57 days i.m., 1 marked reaction; later given spasmodically as an out-patient; January 13, 1913, 16 i.v. and subcut., *causing some regression*; thereafter given irregularly; *when toxins stopped summer 1914 growth increased markedly, hacking cough*; again slight regression when toxins resumed; *incision, large amount partially necrotic tumor evacuated*; toxins stopped; thereafter disease progressed rapidly, involved pleura, lungs; death January 1915. (42, case 11; 85) 7¼ yrs.

19. (WALTERS) : H. T., male, aged 33; inoperable small round cell sarcoma, apparently primary over acromion process right clavicle, multiple metastases on head, back, sternum (size small orange); (regarded as lymphosarcoma when reviewed at Mayo Clinic 1944); onset pain in right shoulder March 1911, shortly after "grippe"; in 7 months disease metastasized as above; October 21, 1911 sternal mass removed at Mayo Clinic, Coley toxins advised by Dr. W. J. Mayo; begun at home November 1911 after growth over sternum had recurred, 3 other lesions on head, 1 on shoulder, 1 on back present; given i.m. and i.t., *marked reactions*; *all growths regressed completely*; *disease controlled, in excellent health over 2 years*; then recurrence, metastases; no further toxins given; death. (46; 84; 125) 3½ yrs.
20. (HILL) : R. I., male, aged 6; inoperable retroperitoneal lymphosarcoma; onset mid-November 1911, following kick in abdomen by another boy; constant pain, finally interfered with bowel movements (none for 4 days), emesis for 5 days prior to exploratory operation January 21, 1912; inoperable irregular mass seen; no attempt at removal; toxins (Tracy XI) begun a day later, 10 i.m. in 43 days in buttocks, *little or no reactions*; *no apparent effect, tumor increased in size*; *growth incised February 24, 1912 (obtained only small amount of serum)*; feet, legs very edematous by March 12, 1912; death 3 days later. Limited post-mortem revealed large nodular masses originating from region of spine extending from pelvis well up to diaphragm, attached to abdominal wall about scar, and proceeding between layers of mesentery; *upper part of mass had begun to respond to toxins (reddish purple pulp)*. (68). 3½ mos.
21. (W. B. COLEY) : W. C. D., male, aged 24; inoperable lymphosarcoma of groin; onset, fall 1909; mass size of croquet ball present when first seen, October 1912, causing swelling and edema of lower extremity, 10 lb. weight loss, cachexia; incomplete excision October 17, 1912; toxins (Tracy XI) begun October 21, 1912, 38 in 44 days, 8 into tumor, rest i.m. in pectorals and buttocks; *only 1 marked reaction*; *remarkable improvement in 1st 5 wks., mass reduced to 1/3 its former size*; thereafter lost control; final injection December 3, 1912; disease progressed, death January 13, 1913. (42, case 50; 85) 3¼ yrs.
22. (BRAINERD) : C. H. O., male, aged 24; inoperable large round cell sarcoma of pharynx and cervical nodes; onset 1912; toxins (Tracy XI) begun January 30, 1913; 14 i.m. in 18 days in pectorals, deltoid; febrile reactions 101.8°-104.2°F.; marked improvement in 1st 2 wks.; *sore throat disappeared, pharyngeal tumor more movable, much smaller (from small orange to hen's egg)*; later disease not controlled; death August 3, 1913. (5; 46) 18 mos.
23. (W. B. COLEY) : J. McA., male, aged 26; inoperable extensive recurrent large or medium cell lymphosarcoma tonsil involving, bilateral cervical

- nodes, also axillary and inguinal nodes; onset, late June 1913; under local applications throat improved, tonsil swelling disappeared; recurred early September 1913, of rapid growth, phonation, deglutition difficult; mass in left neck; specimen removed from tonsil October 21, 1913; when toxins were begun right cervical mass 10 x 15 cm., large mass in right tonsil; node in left cervical region, axillary and inguinal nodes also enlarged; toxins (Tracy XI) begun November 10, 1913, 38 in 75 days i.m., 1 marked reaction (104°F.); *marked decrease in size of tonsillar and cervical tumors soon apparent* but only temporary; extensive neck dissection by Downes January 15, 1914, external carotid tied; (*specimen showed much necrosis, foci of large round atypical cells*); autogenous vaccine made from tumor, injected 8 times, causing considerable decrease in size by February 15, 1914; soon tumors again grew rapidly; 4 doses diphtheroid toxins, March 1914, caused considerable temporary diminution; x-ray tried for few weeks caused marked temporary improvement, but after 4 weeks disease progressed more rapidly than ever; death June 14, 1914. (42, case 40; 85) 1 yr.
24. (W. B. COLEY): D. C., male, aged 44; recurrent inoperable lymphosarcoma of tonsil, pharynx, cervical nodes, (small round cells); onset, January 1914; tonsillectomy; local recurrence of rapid growth filling pharynx; February 3, 1915: toxins (Tracy XI) i.m. *marked temporary diminution to 1/3 former size, swallowing easier*; remains of growth enucleated; toxins stopped after 3 1/2 months; recurrence; toxins resumed i.m. August 1915 for 3 weeks, no marked reactions; mediastinum became involved; radium (640 mch.) caused burn on tongue; marked very temporary regression; x-ray, 1 more radium treatment; September 1915; disease not controlled; *prognosis hopeless when pneumonia developed, fever to 104.4°F.; markedly enlarged nodes in both cervical regions regressed completely; no evidence disease in tonsil, pharynx and neck*; recurrence 1 mo. later; further radiation not effective. (42, case 18; 85) over 2 yrs.
25. (W. B. COLEY): J. D., male, aged 17; generalized lymphosarcoma throat, face, arm, right knee, thorax, cervical, axillary, epitrochlear, femoral and inguinal nodes; (nodes in groins had been enlarged for as long as the patient could remember); onset, September 1915; nodule right side roof of mouth; metastases to right cheek bone (site traumatized 9 months previously); rapid generalization; mid-December 1915 axillary node biopsied; December 23, 1915, toxins (Tracy XI) 14 i.m. in first 35 days, (*1 marked reaction, sometimes none at all*); x-ray; toxins resumed February 23, 1916, 9 more i.m., Tracy XI, (*3 adequate febrile reactions*) and Tracy XIF (filtrates, *no reaction*); *disease not controlled*; death, May 16, 1916. (46, 85) 9 mos.
26. (W. B. COLEY): S. O., male, aged 47; inoperable lymphosarcoma of groins, axillae; very severe pain; onset June 1915; (20 doses mixed vaccine, few doses gonococcus vaccine prior to being referred to Coley, caused transient pain relief); excisional biopsy; February 7, 1916: toxins, (Tracy XI) 20 i.m. in 38 days, causing painful indurations in gluteal and deltoid regions; *only 1 marked febrile reaction from single injection given in groin*; x-ray (7) *begun a week after toxins, given concurrently*; *no palpable tumor remained 5 weeks after toxins begun*; *disease not controlled*, spinal metastases, death, September 15, 1916. (5; 85) 15 mos.

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- ✓ 27. (MOFFAT): D. B., female, aged 14; inoperable lymphosarcoma cervical, supraclavicular and inguinal nodes; onset, fall 1912; parotid gland enlarged to size of small egg anterior to ear; *under course of hot baths it diminished in size, disappeared following measles, fall of 1913; series of colds, 1914; appendectomy, May 1915; December 1915 left tonsil and parotid began to enlarge during a cold, following diphtheria; Christmas 1915 cervical lymph nodes enlarged (bilateral); February 1916, acute inflammatory rheumatism involving all joints in turn; severe endocarditis, resulting in serious cardiac dilation, mitral insufficiency; biopsy, June 1916; toxins (Tracy XI) begun June 28, 1916, given i.m. every third or fourth day, all in thigh near groin, mostly left side; no apparent benefit until after marked reaction July 10, 1916 (102.1°F.); the more severe the reaction the more marked reduction in size occurred; slow, steady regression; 1st radium treatment August 1916, causing burn; regression more marked for a while, then slower; toxins continued; 2nd radium given November 1916; toxins continued, brief intervals of rest; 3rd radium, July 17, 1917; general condition, including heart very much improved; toxins continued about 3 years, controlling disease; death August 20, 1920. Case suggests that toxins may be given intramuscularly to patients with serious heart conditions without ill effects. (46; 100; 126.)* 8 yrs.
28. (W. B. COLEY AND FAMILY PHYSICIAN): Mrs. A. M., age 32; inoperable lymphosarcoma involving scapular, cervical, axillary, pectoral regions to clavicle and scalp; onset neuritic pain right shoulder December 1916; iodine "injected with electricity" by local doctor, caused severe burning, edema; onset, right cervical lymphadenopathy, March 1917, following tonsillitis; tonsillectomy; slight reduction in size of nodes; massage (5) caused increased inflammation, swelling; excisional biopsy supraclavicular nodes; couldn't use right arm; whole lower scapular region involved when toxins (Tracy XI) begun September 1, 1917; given daily for 6 days i.m., (no marked reactions 1st 5 doses); radium pack; further toxins 29 in 59 days i.m., moderate reactions; *in 6 weeks mass in axilla, large mass filling pectoral region to clavicle, mass above spina scapula all disappeared except for nodule size of hazel nut; general health good, movements of arm normal; injections omitted for 8 weeks; resumed, (3 a week) in moderate doses part of 1918; also further radium totalling 77,867 mch. in 14 months, because of recurrences in axillary and pectoral regions; toxins again resumed, slight reactions; condition improved markedly; disease not controlled, death April 14, 1919. (46; 85)* 28 mos.
- ✓ 29. (W. B. COLEY): R. T., male, aged 34; extensive inoperable lymphosarcoma mesentery and small intestine; always well until fall 18 feet to cement floor, striking abdomen; onset 6 or 7 months later, January or February, 1917, pain at site of injury; explored at Mayo Clinic December 1917, inoperable tumor of mesentery and small intestine 20 cm. in diameter, (no attempt at removal); January 8, 1918 radium pack (15,000 mch.); severe radiation sickness, lost 8 lbs.; January 15, 1918: toxins (Tracy XI); *decreased 50% in 8 days, much more mobile; 2 more radium packs February and March 1918, (16,000 and 10,000 mch.); toxins continued, 2 or 3 a week i.m. by family physician; almost complete regression, leaving barely perceptible mass; 2 more radium pack treatments (18,000 each) July 1918, further radium 1919 (totalling 44,283 mch.); small doses toxins given spasmodically at home; complete regression primary tumor by May 1920; 2 very small cervical nodes, right and left; radium to neck (3000 mch. to each side); toxins resumed i.m.; cervical*

- nodes responded visibly to marked febrile reactions*; November 1920, radium (6344 mch.); toxins resumed (Parke Davis XIII); August 1921, radium to supraclavicular region (2870 mch.); small doses toxins i.m.; January 1922 small nodule on left elbow disappeared after x-ray; January 1923, radium pack to abdomen (18,026 mch.); toxins given with intervals of rest to November 1923 (5½ yrs.); 2 months after last injection axillary metastases, size of small orange, recurrence in abdomen, involving retroperitoneal nodes; January 1925, radium (12,000 mch.) to abdomen, to left pectoral region and left axilla, (10,000 mch. each); February 1926, excision of axillary mass; disease progressed, death September 1928. *At autopsy disease confined to mass 13 x 18 cm. recurrent at original site.* Prolonged intermittent toxin therapy appeared to protect this man against deleterious effects usually seen after such heavy radiation: over 210,000 mch. of which 180,000 mch. was to abdomen. (44; 46; 85) 11½ yrs.
- 30 (*W. B. Coley and Reynolds*): B. H., male, aged 46; inoperable lymphosarcoma primary in nodes on both sides of neck, (supraclavicular to mastoid), few enlarged nodes behind sternomastoid and above clavicle, evidence of mediastinal involvement; onset, June 1917, 5 months after grippe and 2 months after typhoid; swelling then regressed markedly spontaneously, except for 1 or 2 nodes; recurred November 10, 1917, with mediastinal involvement; January 21, 1918, toxins (Tracy XI) daily marked reactions, (very susceptible); *immediate regression, walnut-sized nodes in mid-cervical region disappeared in 4 days*; given daily first 10 days, then every 24 to 48 hrs., *complete regression all nodes in less than a month*; lost 14 lbs. in hospital, gained 15 lbs. in next month; toxins continued at home for 2 more weeks in small doses, i.m. by Reynolds; against orders returned to work (farmer); in 2 weeks bilateral axillary and inguinal lymphadenopathy, rapid increase in size; toxins resumed by Reynolds April 10, 1918, i.m. every 48 hours; Coley excised larger, more superficial nodes from groin: reported as "simple inflammatory lymphoma, has some characteristics of lymphosarcoma"; toxins resumed by Coley, both Tracy XI and Parke Davis XIII, about 9 more, i.m. moderate reactions; by May 15, 1918 extensive mediastinal tumor present; x-ray (13) then given to all affected areas *causing marked temporary improvement*; death October 24, 1918. (46; 85) 16 mos.
31. (*W. B. Coley and Martin*): G. H., male, aged 17; inoperable lymphosarcoma nasopharynx, (nares completely obstructed), involving bilateral cervical nodes, sternomastoid to clavicle; onset early 1918; biopsy at Mayo Clinic September 1918; referred to Coley as inoperable, September 27, 1918, toxins (Tracy XI) i.m.; 2 days later radium (1000 mch. to each side of neck), causing much prostration; toxins resumed 2 or 3 days later, 50% regression in a week, *all tumors completely disappeared in 6 weeks*; toxins continued at home by Martin; local recurrence right cervical region January 1919; another radium pack; toxins resumed (details unknown); disease not controlled, death, August 1919. (46; 85) 18 mos.
32. (*Coley, W. B.*): R. McC., male, aged 52; inoperable generalized malignant lymphocytoma (small lymphocytes) involving whole lymphatic system; onset, early 1920, following slight submaxillary lymphadenitis; by early 1921 general weakness, extreme pallor, liver and spleen markedly enlarged, also nodes of right and left neck, groin; (Coley believed

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primary in mediastinum); considered at 1st to be Hodgkin's disease; marked anemia; July 1921 radium pack to mediastinum (9000 mch.), 4 days later same dose to spleen; 1 x-ray each to nodes of neck, axillae, groins; marked leukopenia: wbc. 1000, rbc. 2,210,000, hemoglobin 35%; toxins (Tracy XI) begun August 1, 1921; only very small i.m. doses tolerated; node excised at this time showed only lymphadenitis; *all enlarged nodes disappeared in 7 weeks., liver, spleen normal size*; leukopenia responded promptly to transfusion and toxins; blood count normal by February 1922; small doses toxins continued; September 1922, 1 more x-ray given to axillae, neck, groins; 2nd transfusion September 22, 1922, very much less marked response; further mediastinal enlargement November 1922; had numerous abscessed teeth, 2 extracted; patient rapidly weakened, blood again deteriorated; 3rd transfusion; another radium pack; 2 more teeth extracted November 1922; *during December 1922 steady rapid improvement, well all winter*; slight lymphadenopathy (cervical, axillary and inguinal) by May 1923; radium to groin (9000 mch.) June 1923; x-ray to other areas; toxins then resumed (Parke Davis XIII); *no evidence disease in mediastinum summer of 1923*; transfusion given every 4-5 weeks, next 18 mos. 600-1000 cc. each time; died pneumonia of 2 days duration, December 6, 1924. (44; 46; 85)

almost
5 yrs.

The following 19 cases had Parke Davis XII or XIII preparations of Coley Toxins (1st four had XII, others XIII):

33. (Joseph): M. E. R., elderly female adult; inoperable lymphosarcoma femoral nodes; also had exophthalmic goitre; onset, early 1910, mass 8 x 10 cm. below Scarpa's triangle; biopsy; May 1910: toxins, *1st dose caused very severe chill, very marked effect on tumor which shrank in size, became very flabby*; refused further treatment for some weeks, then resumed for few weeks, with *temporary cessation of growth*; developed pernicious anemia, causing death. (85; 126)

over
1 yr.

34. (GOLDMAN): male, aged 60; inoperable round cell sarcoma tonsil, pharynx and cervical nodes; onset 10 months prior to toxin therapy; 21 doses in 3 weeks i.m., *no reactions at all, but clinical improvement evident, slept much better, appetite and strength returned; regression, increased mobility of cervical nodes, deglutition less painful or difficult*; after a few weeks, tonsillar and pharyngeal tumors increased rapidly; death shortly thereafter. (46)

over
1 yr.

36. (Kirk & Coley): N. H., male, aged 50; recurrent lymphosarcoma neck; onset, November 1912; primary growth excised; recurrence a year later in region of left tonsil; block dissection including sternomastoid; June 1, 1914: toxins (Parke Davis XII) by Kirk, 1 or 2 a week i.m., only one marked reaction; injections resumed later by Coley, given daily in pectorals; *no febrile reactions or chills; disease not controlled*; death November 6, 1915. (46; 85; 100)

3 yrs.

37. (Coley & Kathan): C. J. V., male, aged 45; recurrent inoperable reticulum cell sarcoma thigh; onset, February 1920; primary excised June 3, 1920; recurrence involving upper $\frac{2}{3}$ right anterior thigh; toxins begun June 25, 1920, 5 small doses in 12 days i.m., little or no reaction; radium

given day after 1st injection; *groin softer, edema of leg decreased*; toxins continued i.m. (poor absorption) at infrequent intervals for 6 months, combined with x-ray (1 a week), developed diabetes (?); liver metastases, death December 28, 1923. (46; 85; 100) almost
4 yrs.

38. (W. B. Coley): M. A., female, aged 18; inoperable lymphosarcoma cervical, supraclavicular, axillary nodes; onset, node in left neck enlarged October 1919; iodine salve for 2 weeks, tuberculin injections for a year; *sudden regression 7 months after beginning tuberculin*, but similar enlargement on right supraclavicular region increased to size of orange; shortly afterward huge mass over whole left anterior, posterior supraclavicular region and sternum 11 x 12 cm; swelling on right side not quite so large; nodes in both axillae also enlarged; October 16, 1921: node biopsied; October 17, 1921: x-ray, 2 each to axillae, right & left chest, also 2 radium packs (10,280 mch.) to chest; October 28, 1921: toxins begun following radiation; small doses i.m. for about 7 weeks; marked decrease in mediastinal shadow evident November 3, 1921; November 10-15, 1921, radium packs (16,490 mch. to neck); *steady progressive improvement*; 2 more x-ray to chest, 1 more radium pack, January 1922; by February 15, 1922 *sternal, axillary and cervical masses had disappeared; gained 31 lbs. in 4 months, general health improved*; only 1 small node remained in left axilla; some widening of mediastinum; 1 x-ray March 13, 1922; in excellent condition; 2 radium packs to chest July 1922 (17,928 mch.); considerable decrease in mediastinal mass; x-ray over entire chest, radium pack to sternum, August 1922 (16,000 mch.); toxins given summer 1922; *continued to improve, mediastinal mass almost disappeared by October 1922*; then given x-ray to axillae (1 each); toxins February 1923; summer 1923 left arm swelled; toxins resumed September 1923: 23 in 49 days, only 3 or 4 marked reactions; *improved temporarily*; death March 5, 1924. (46; 85) 4½ yrs.

39. (W. B. Coley and Rolleston): J. G. A., male pathologist, aged 62; generalized pseudoleukemia; never ill; since early manhood had always worn 17½ collar, during World War I neck gradually increased in size, by 1919 wore 18½ collar; (onset, autumn 1920,) enlarged nodes anterior triangle behind jaw, bilateral, also axilla; by 1921 inguinal nodes and prostate enlarged; then took small doses thyroid, good effect on prostate, lymph nodes; disease progressed slowly to end of 1923; by then patient exhausted; 3 teeth removed; 4 months holiday southern Italy during May 17, 1924 polyvalent vaccine from oral and nasal organisms given, with minute doses arsenic in this period; lost 21 lbs., *but marked diminution in size of nodes in left neck, axilla, less regression on other side*; able to wear 17 collar (4 cm. decrease in size); by July 1924 liver, spleen enlarged; then referred to Coley by Rolleston; biopsy August 6, 1924; toxins i.m.; *in 3 wks. complete regression all affected nodes except 1 indurated mass size of pea in right supraclavicular region* (site of 1st detected in 1920); *hemoglobin increased from 75% to 94%*; *general condition good*; toxins continued, small doses i.m., in England, with 1 or 2 week rest periods; returned to work as head of university; severe cold, December 1924, also duodenitis; put on low fat, low carbohydrate diet, took pancreatic extract; thereafter only 1 dose toxins a week, also minute doses arsenic and iodine; *gradual, steady improvement, no evidence disease, strong* (walked 10-15 miles daily on holiday);

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- 4 minim dose toxins each Sunday 1924-25, no febrile reactions after fall 1924; *blood count excellent until September 1925*; large fairly hard node right groin, November 1925; radium pack to groin December 1925; *caused very marked decrease in size, hardness*; toxins resumed 5 days later; only 1 reaction above 101°F.; bronchitis late January 1926; returned to Coley for 2 weeks.; radium pack to groin March 1926; thereafter strength failed; exhaustion, anemia progressed alarmingly during July 1926, bedridden August; death August 29, 1926. (46; 85) 6 yrs.
40. (W. B. Coley and family physician): M. B., male, aged 32; inoperable lymphosarcoma cervical, supraclavicular, axillary and inguinal nodes, bilateral; onset, June 1923; 1st symptom, pruritis heels, legs, intensified by clothing, by June 1924 intense under belt and collar; onset, 6 months after itching started, nodes in left neck enlarged; slowly extended to areas mentioned above; June 1924, supraclavicular node biopsied; June 22, 1924: radium (2 packs) x-ray to left neck, axilla; July 1, 1924: toxins, 14 in 1st 21 days i.m., 7 more x-ray given concurrently; toxins continued at home 1 or 2 a week, for 11 months; *apparent complete regression, regained all lost weight; in very good health about 2 years*, then disease recurred, no further treatment; death November 23, 1927. (46, 85) 4½ yrs.
41. (Rabinowitz): I. S., male, aged 46; inoperable lymphosarcoma right inguinal, left axillary nodes; had "sacroiliac disease" at yearly intervals following typhoid fever, 1922; onset late November 1924; mass in nodes in right groin and left axilla; biopsy; x-ray January 14, 1925 (for 1 week); toxins January 23, 1925, 19 in 60 days i.m., *complete regression, mediastinum clear, general condition excellent*; toxins combined with some radiation given at intervals for several years.; *remained in good health while under treatment*; when toxins were stopped disease recurred, progressed, death 1934 or 1935. (46; 100) over 10 yrs.
42. (W. B. COLEY AND FAMILY PHYSICIAN): E. H., male, aged 44, recurrent inoperable lymphosarcoma cervical, axillary nodes; tonsils in bad condition; onset, February 1925, slight swelling cervical region, treated medically 6-8 months, no benefit; March 20, 1926, tonsillectomy, no benefit; June 8, 1926: 12 cervical nodes excised by local doctor; axillary involvement then occurred; August 17, 1926: toxins, 5 i.m.; then radium packs to both sides of neck (18,000 mch.), x-ray (3) to right axilla; *mass in neck decreased noticeably*; toxins resumed by family doctor; *complete regression cervical nodes, general condition excellent* by October 14, 1926; attack of grippe, constant fever, December 1926, lost much weight; thereafter liver enlarged, metastases deep abdominal nodes, no further treatment, death March 29, 1927. (46; 85) 25 mos.
43. (W. B. COLEY): B. B., male, aged 40; inoperable lymphosarcoma mesentery of intestine or retroperitoneal nodes; onset, August 1926, severe lumbar pain, mass left side; September 20, 1926: exploratory laparotomy, specimen removed; pain-free 12 days, then x-ray begun, severe radiation sickness; by October 1926, whole left upper abdomen enlarged, appetite poor, tumor mass large; toxins 14 i.m., emesis from radiation reaction persisted; toxins had to be stopped; *no apparent benefit*; death December 2, 1926, (46) 4 mos.
44. (FAMILY PHYSICIAN): J. S. McF., male adult; advanced lymphosarcoma originating in lower lobe bronchus with metastases in 2 ribs, 2 vertebrae, humerus and scapula; (date of onset not given); diagnosed by

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biopsy through bronchoscope September 1926 at Mayo Clinic; x-ray October 1926, complete regression; immediate metastases as above; again x-ray, no further improvement; November 1926, toxins for about 2 months; *pain subsided, appetite increased, temporary arrest*; death September 1927, extensive skeletal metastases. (46; 83; 100)

over 1 yr.

45. (SHILLING) : Dr. H. E. S., male, aged 52; generalized lymphosarcoma; in good health until onset, May 1928, indigestion, edema of legs, ascites, fluid in chest cavities, enlarged nodes; x-ray May 1928, (14, totalling 2000 r.); biopsy; x-ray (30 more) ending September 1928; very weak, thin, lost 40 lbs.; but fluid cleared in chest, later in abdomen; October 1, 1928: self-administered toxins, 2 or 3 a week i.m. in deltoid for 3½ months; *skin infection on neck, face, scalp, fever few days*, January 15, 1929; toxins resumed February 15, 1929, twice weekly, with 1 week rest interval every 4 weeks; after 1 such interval, 2 nodes enlarged on upper inner thighs; April, May 1929 toxins injected directly into these tumors 2 or 3 times a week., *no reactions, no apparent affect*; at Coley's suggestion *dose increased* June 1929, given i.m. in deltoid; x-ray (2 each) to these tumors June 15-30, 1929, followed by *complete disappearance*; toxins resumed after 2 week interval also given i.v., continued with further intervals of rest (1 of 4 months), total duration about 22 months; during 1930 also received further x-ray (about 12,000 r.) *disease fairly well controlled*; returned to work (general practitioner); no toxins after August 1930; disease then progressed, death December 6, 1930. (46; 100)

2½ yrs.

46. (SURLS) : Miss E. G., aged 31; inoperable lymphosarcoma left inguinal nodes; onset, August 1928, vague digestive symptoms, epigastric pain; treated 6 months for stomach trouble; small hard mass left groin excised April 1929; radium (1); April 1929, toxins, 2 or 3 a week, i.m. for 7 months; *not effective*; generalized adenopathy right axillary, right cervical and submental regions by August 1929; *dosage then increased, marked reactions; this more aggressive technic caused arrest of growth of all nodes except in left groin (radium treated area)*; in very good condition by December 1930; *disease apparently controlled over 3½ years*, then swelling both thighs; toxins resumed July 1934; *improved, no recurrence* April 1935; disease later progressed, extreme cathexia, death cerebral metastases November 4, 1936. (46; 100)

8 yrs.

47. (W. B. COLEY) : E. L. M., male, aged 66; generalized lymphosarcoma, axillae, groins, cervical and supraclavicular regions; (onset late April 1931, right axillary egg-sized mass;) then groin, neck became involved; cervical node biopsied; radium (to 7 different areas); toxins July 1, 1931, 10 i.m. in 13 days, 1 marked reaction; *definite improvement; disease not controlled*, death November 8, 1931. (46; 85)

6½ mos.

48. (W. B. COLEY) : C. R., male, aged 19; inoperable lymphosarcoma retroperitoneal, cervical and supraclavicular nodes; onset, February 1931, 1 month after severe trauma to upper abdomen by steering wheel in auto accident; exploratory laparotomy, Mayo Clinic, July 20, 1931; retroperitoneal grapefruit-sized mass left upper abdomen biopsied; x-ray partially controlled this mass, but cervical nodes become involved; lost 30 lbs. July 1932 - July 1933; radium packs to abdomen, back (40,000 mch.) to neck, (15,000 mch.); late July 1933: toxins, 21 in 35 days i.m., average reactions moderate; *cervical nodes much smaller, more movable*,

TOXIN TREATED FAILURES, ABSTRACTS

Survival
Period of

supraclavicular node disappeared, mass in l.u.q. smaller, softer, more movable; general condition good; disease later progressed, death March 3, 1934, (46; 84; 85; 100) 3 yrs.

49. (B. L. COLEY): Dr. C. C., male, aged 39; inoperable lymphosarcoma retroperitoneal, femoral and cervical nodes and interscapular region, with involvement of ischium (Brill Simmers type); radiologist, married 13 yrs., wife had 1 pregnancy ending in miscarriage; (onset, early May 1932); enlarged node, left femoral triangle, ascribed to ringworm, 2-4 mos. later nodes right cervical region; January 1933, pain left hip, radiating to knee, causing limp, due to destructive lesion left ischium; tonsillectomy March 17, 1933; no benefit; cervical node biopsied April 12, 1933; large femoral node removed 12 days later, followed by slight fever; lost 8 lbs., night sweats, general fatigue; May 3, 1933; 2 cycles x-ray left ischium, groin, trunk, right, left neck, totalling 5700 r, ending June 21, 1933 when pain in base of right lung developed; during July became incapacitated, bedridden over 6 weeks.; early October 1933 mass 5 x 6 cm. in right interscapular region; November 6-11, 1933; x-ray to this area; November 15, 1933, toxins, 5 i.m., 7 i.v. in 21 days, marked reactions from i.v.; *mass in right interscapular region disappeared after 4th dose; lesion in pelvis showed some repair in 4 weeks.; no effect on general health;* 1 more x-ray to right posterior chest, December 1933; disease progressed, death January 27, 1934 (85) 21 mos.

50. (ROSS AND W. B. COLEY): A. R., male, aged 6¾; inoperable lymphosarcoma retroperitoneal nodes; metastases to chest; onset March 1934, slight disturbance, pain extremities, trunk; cried with pain when jolted; 2 severe traumas to right kidney area late spring and summer 1934; July 1934, distinct mass found; child listless, inactive, easily fatigued, irritable, pain in neck; aspiration biopsy negative, August 1934; tonsillectomy; started school, lost 6 lbs. in 5 weeks.; *diathermy daily for 3 weeks to back, right leg, some pain relief, improvement general condition;* diathermy continued in November, seemed to increase pain; condition gradually worsened, limped; explored December 21, 1934, hard, indurated, immovable, inoperable tumor mass extending between transverse processes lumbar vertebrae, right side, at angle 12th rib; biopsy taken; 3 radium needles inserted (853 mch.); *low fever several days; pain subsided entirely;* January 1935: metastases to chest; January 7, 1935; toxins (18 i.m. in 25 days), moderate reactions; x-ray to right cardiophrenic angle begun day after 1st toxin, caused severe radiation sickness; more x-ray February 2 to 12, 1935, to loin and chest, totalling 2,400 r.; again severe radiation sickness; *in 3 or 4 days greatly improved;* toxins resumed, 31 in 62 days i.m., moderate reactions; 3rd cycle x-ray (13) to primary and chest (3300 r.); radiation sickness; anemia; toxins stopped because of *measles, deep cough*, lost 5 lbs.; toxins resumed July 2, 1935 (6 in 21 days, moderate reactions); gained 3 lbs.; severe cold August 1935; toxins resumed 2 a week for 6 months i.m.; March 1936 small lung metastases; x-ray to chest 4200 r.; anemia; transfusion, bone marrow given; *marked improvement in lung lesions;* toxins resumed i.m. 2 a week, received total 8 courses (128 doses) in 2 years, in gluteal muscles except last course i.v.; discontinued on several occasions because of severe colds or infections; *some regression; disease apparently arrested for nearly 2 yrs.;* final x-ray caused severe pain, progressively worse, death January 17, 1937. (46; 85) 2¾ yrs.

51. (CAMPBELL): Mrs. E. M., aged 64; inoperable lymphosarcoma axillary, inguinal, cervical nodes, bilateral; onset in left axilla, July 1943; itching on neck, chest, 6 months later; by January 1945, all areas cited above were involved; left axillary nodes removed; x-ray (13 to affected areas) given concurrently with toxins i.m. begun January 24, 1945 given daily for 1 month; *all nodes disappeared by April 1945, gained weight, felt well, blood picture good*; shortly thereafter recurrence; another brief course toxins, *marked reactions; affected nodes again completely regressed*; well and free from disease 2 years, then disease again reactivated; refused further toxins; palliative x-ray; death September 1947. (100) over 4 yrs.

The next case received the Sloan-Kettering Institute XIV preparation and the Johnston XV preparation of toxins.

52. (CASPER AND RULON): Mrs. J. N., female, 45; twice recurrent inoperable reticulum cell sarcoma, primary in skin over right tibia, subcutaneous and inguinal metastases, repeated trauma to leg for 5 years prior to onset, November 1954; excision 2 weeks after onset; 2 recurrent nodules apparent January 1955; widely excised March 3, 1955; further local recurrences May 1955; amputation, groin dissection advised, refused; inguinal node metastases removed at Mayo Clinic, July 1955; x-ray to tibia, right groin, left axilla (550 r each); recurrence right leg present when toxins (S.K.I. XIV) begun August 28, 1955; 21 i.v. in 22 days, marked reactions, to 105°F., chills; *recurrence regressed completely*; further x-ray October 1955 to nodule on leg; November 1955; metastases right breast excised; then further x-ray to right groin, breast (500 r each), January 1956, multiple metastases, breast, back, abdominal wall, left chest; x-ray to abdominal wall, anterior chest; low back pain present; toxins resumed January 31, 1956: 32 in 40 days, marked febrile reactions from 1st 5 (S.K.I. XIV); thereafter Johnston XV used, all i.v. except 3 into metastatic nodules, further subcutaneous metastases, also pulmonary lesions (grew rapidly); *no apparent benefit from this course of toxins*; expired March 31, 1956. (100) 16 mos.

The following two cases received the Johnston XV preparation of Coley toxins:

53. (JOHNSTON): B. B., male, aged 7; lymphosarcoma involving the cervical and sternal nodes, as well as those in the abdomen and groin; onset 6 months prior to receiving toxins, biopsies of neck and sternal nodes; x-ray to abdomen, chest, groin and cervical nodes (4200 r); excruciating pain in both legs due to matted large hard inguinal nodes requiring narcotics; toxins (Johnston XV) 43 i.v. in 3 months; *pain diminished rapidly, narcotics no longer required; no apparent change in nodes, but subjective improvement evident during toxin administration*; died 3 months after 1st injection. (73) 9 mos.
54. (JOHNSTON): E. J., female, aged 51; inoperable generalized lymphosarcoma, pericarditis with effusion, partial intestinal obstruction, hepatomegaly, nodes on scalp; onset 3 years prior to toxins; radiation to multiple sites totalling 7200 r; toxins (Johnston XV) 33 i.v., 1 i.t. in 8 weeks; *decrease in pain and abdominal tenderness, no other evidence improvement*; died a month after last injection. (73) 3 $\frac{3}{4}$ yrs.

Detailed Histories of eight of these 54 failures are given below as they appeared to be of special interest.

SERIES D, TOXIN TREATED FAILURES, DETAILED HISTORIES

CASE 4: Recurrent inoperable lymphosarcoma of the cervical, axillary and mediastinal nodes, confirmed by microscopic examination of the axillary growth and a node removed in June 1902 from the sternomastoid muscle was examined by Dr. George Biggs, pathologist of New York Hospital, who reported: "Typical appearance of small round cell sarcoma with some degenerative changes." (42, Case 60)

Previous History: Miss M.L.A., female, aged 40, librarian. The patient had had the usual childhood diseases, two attacks of pneumonia, one as a child and the other at about 20. She had had membranous dysmenorrhea and retroflexion, but was relieved by a pessary which she continued to wear. Onset, in the late summer of 1898, a small freely movable tumor developed just over the clavicle on the right side. It was painless and did not increase in size rapidly until the patient injured it. Then it became painful and assumed a purple tint and the capillaries over it became dilated.

Surgery: One year after onset it was removed under cocaine by Dr. C.B. Nancrede of Ann Arbor, Michigan. A recurrence soon developed on the posterior border of the sternomastoid on the right side, near the angle of the jaw. This increased in size very gradually. In March 1900 a swelling developed in the right axilla with neuralgia of the arm. These growths increased very rapidly in size. The axillary tumor was removed by Nancrede in July 1900.

Clinical Course: The tumor of the cervical region involved the deeper structures so extensively that it was considered entirely inoperable. Dyspnea and edema of the lower extremities developed early in September 1900. The patient was then referred to Dr. William B. Coley and was admitted to Memorial Hospital on September 25, 1900, two years after onset. Examination showed a tumor in the right cervical region extending from the clavicle to the mastoid process of the temporal bone. There were some enlarged nodules below the clavicle and several smaller tumors in the region of the cicatrix in the axilla. There was another mass of enlarged nodes just above the sternum. The latter appeared to be the cause of the dyspnea.

Toxin Therapy: (Buxton VI) Injections were begun by Coley on September 26, 1900, the initial dose being 1 minim. They were continued daily but the dose was increased very slowly. During the first two months the maximum dose was 4 minims. During December 1900 the highest dose given during the entire treatment was reached, 8 minims. The number of injections given was as follows: September 26 to 31, 4; October 29 to November 22, 22; December, 22; January, 22; February, 21; March, 19; April, 16; May, 20; June, 10; — a total of 156 injections in almost nine months. There was a decided decrease in the size of the tumors and increase in their mobility during the first three months, after which improvement ceased and the growths slowly began to increase in size. The patient was discharged in fair condition on June 19, 1901.

Clinical Course: During the summer of 1901, Coley gave only palliative treatment. The tumors slowly but steadily increased in size. By February 1902, a tumor mass encircled the entire neck ending at the vertebral line, and extending from the mastoid process to the clavicle on the left side; on the right side the entire cervical, axillary, supraclavicular and pectoral regions were involved. The largest protuberance was in the right cervical region and was about the size of two fists. The constriction of the trachea was such as to cause frequent severe attacks of dyspnea. The patient was bedridden most

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of the time. With little hope of causing even temporary improvement, more as a matter of experiment, Coley decided to try x-ray therapy.

Radiation: On February 10, 1902, x-ray treatments were begun, four to six exposures a week being given at a distance of 20 cm. Remarkable improvement occurred, more striking than in any other cases Coley had observed under x-ray treatment. At the end of three weeks the mass in the neck had decreased fully one-third in size and had become very movable. (For photograph of the patient taken at intervals during radiation, see 24, Figs. 1, 2, 3, 4). By June 18, 1902, there remained only a small nodule the size of a marble anterior to the sternomastoid muscle.

Surgery: This was removed that day for microscopic examination, and Biggs noted that necrotic changes were present.

Clinical Course: The patient was discharged on July 8, 1902, apparently well. She regained her former weight and spent the summer in the country. However, on September 24, 1902, she returned with a local recurrence the size of an English walnut in the left parotid region and both groins were filled with multiple tumors varying in size from a pigeon's egg to a hen's egg. In addition there was an intra-abdominal tumor the size of an orange, smooth, globular, fairly mobile, apparently originating in the colon or mesentery. There was constriction of the bowel at this point.

Further Radiation: X-ray treatment was resumed. In three weeks the nodule in the parotid disappeared, those in the groin regressing in six weeks, while the abdominal tumor decreased to about half its former size. Treatment was kept up during the entire winter with steady decrease in the abdominal growth. It was continued in the summer of 1903 by Nancrede at Hanover, New Hampshire.

Clinical Course: The patient returned to Coley in the fall of 1903. Another nodule had appeared in the cervical region, the tumor in the abdomen seemed to be somewhat larger, and a few nodules were beginning to appear subcutaneously on the thighs and abdomen. The general health had also deteriorated.

Further Radiation: X-ray therapy was resumed for a few weeks but the patient grew worse very rapidly, new tumors appearing almost every day.

Clinical Course: Toward the end she suffered a great deal of pain in the sciatic and crural nerves. The disease progressed causing death in June 1904, 5¾ years after onset. At the time of her death, in addition to the very large tumor in the abdomen, there were hundreds of small nodules, varying in size from a pea to a small egg, situated in the subcutaneous tissue and scattered over the entire body. One of these was removed for microscopic examination at the Loomis Laboratory by Dr. B.H. Buxton, and was reported "small round-cell sarcoma, apparently very little changed by treatment." (24, Case I).

Comment: This case indicates the need for more effective administration. Some regression occurred from small doses given intramuscularly remote from the tumor but this treatment was not sufficiently aggressive. It should be stated that during 1900 Buxton began using a double sterilization in preparing the toxins and this factor is believed to have been one of the main reasons his preparations appeared to be much weaker after 1899. Coley does not seem to have realized this, however, and he did not increase the dosage to

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compensate. Certainly the records indicate that fewer successful results were obtained with the Buxton preparation as made after 1899 than were produced with this preparation from 1894 to 1900. Note the dramatic temporary effects achieved by radiation in this case, which was one of the first treated by x-ray therapy at Memorial Hospital. (The first x-ray machine had been installed at Memorial Hospital that year at Coley's suggestion, and through funds he had raised. This dramatic response to radiation following preliminary toxin therapy is of interest. It is unfortunate that toxins were not resumed after radiation had caused regression.)

References: 23 (pp. 702-763); 24 (Case 1); 42 (Case LX); 85.

CASE 6: Recurrent inoperable small round cell sarcoma of the axillary nodes and pectoral region confirmed by microscopic examination of the primary growth by Dr. W.F. Whitney, pathologist at Massachusetts General Hospital, Boston (24, Case III, 1st series and discussion.)

Previous History: E. H. H., male, aged 35, of Woonsocket, R. I. The family history was non-contributory. The patient had had the usual diseases of childhood, including scarlet fever. He was a plumbing contractor, was married and had children. Onset, three years prior to admission to Memorial Hospital, in the latter part of 1898, a small lump appeared in the right pectoral region near the anterior axillary line. This continued to increase in size until it was about 8 cm. in diameter.

Surgery: Extensive removal of the mass and part of the muscle was performed in November 1900 by Dr. Maurice H. Richardson, in Boston, Massachusetts.

Clinical Course: About six months later a recurrence was noted which grew very rapidly.

Further Surgery: A second operation was performed in October 1901. The disease then involved the pectoral and axillary regions so widely that it was impossible to make a complete removal. Hemorrhage was so excessive that the patient almost died on the table. "The disease spread with frightful rapidity following this operation," Richardson stated, and a third operation (also incomplete) was performed on December 8, 1901. At this time the disease was considered too extensive for an interscapulo-thoracic amputation. Richardson accordingly referred the patient to Dr. William B. Coley for toxins.

Toxin Therapy: (Buxton VI) Injections were begun by Coley on December 18, 1901, and were continued five or six times a week for three months, the dose being gradually increased until a reaction of 102° to 103°F. was produced. (The site used is not recorded.) The febrile reactions averaged 99.5°F. or less, and only six times reached 102° to 104°. However the tumor began to soften and in January 1902, a spontaneous opening formed with evacuation of about a pint of necrotic tumor tissue, as a result of which the tumor diminished two-thirds. After a week in which no injections were given in early February, it was noted that the growth had increased considerably in size.

Radiation: Beginning on February 10, 1902, x-ray therapy was given for two weeks, without producing any decrease in the size of the tumor.

Further Toxin Therapy: The toxins and x-ray were then given in combination four times weekly, for a total of 22 treatments ending in May 1902. Both the Buxton VI and Parke Davis IX preparations were given intramus-

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cularly in the pectoral region. By early June the mass in the axilla had entirely disappeared and the movement of the shoulder which had been greatly restricted was practically normal. (The patient could clasp his hands behind his back for the first time in eight months.) There remained only a very small, freely movable, very superficial mass about 5 cm. in diameter in the pectoral region. This was believed to be only the induration caused by the toxin injections. A specimen from this mass, removed under cocaine on June 7, 1902 was examined by Dr. E.K. Dunham, Pathologist of Memorial Hospital and proved this supposition to be true: "no evidence of malignancy". (For a photograph of the patient at this time, see 24, Figure 6.)

Further Toxin Therapy: The injections were resumed, at first by the family physician, and then continued by Coley at Memorial Hospital, combined with further x-ray therapy. Doses of 2 to 7 minims of the Parke Davis preparation were given (P.D. IX) and on four occasions quarter minim doses of Buxton's VI. The patient wrote Coley on December 11, 1902 that so far as his health and strength were concerned he had never felt better, his appetite was extremely good and he had gained so much weight that he weighed half a pound more than he ever had and was working very hard every day. He added that due to his illness he had been unable to earn any money for almost a year, and had therefore run very much in debt, because his children had to be supported. When he returned home from New York he was given a very large plumbing and heating contract, and so he worked very hard every day for two months. He stated that it was difficult for him to spare an hour from his work so he had refrained from taking any toxins. In this period of two months the growths had increased to twice or three times their former size. (He also noted that the bottle of toxins he had kept during this period had evaporated 25 to 30%. (This is of interest in denoting how poorly the material was stoppered in that period.) The patient again wrote Coley on December 30, 1902, asking him to send some of Buxton's preparation and he stated: "You know the Parke Davis did not prove to give the satisfaction that the Buxton did." He added: "I am now taking $4\frac{1}{2}$ and 5 minims with but slight chills and little temperature. The nodule is smaller." (46) Coley again examined him on January 5, 1903, and found the general condition still perfect, but 5 cm. below the clavicle in the pectoral region there was a small movable nodule the size of a hickory nut. The patient was readmitted to Memorial Hospital on February 10, 1903. This time Coley made the injections directly into the tumor, using both Buxton's VI and Parke Davis' IX. It was found that $1/4$ minim of Buxton's caused the same reaction as 8 minims of the Parke Davis product (indicating the latter was about 30 times weaker.) Nine more x-ray treatments were given at this time. The patient was discharged on March 23, 1903. The injections were continued at home by the family physician. Within six weeks after the toxins were resumed (by April 1903), the recurrent growth had again entirely disappeared and the general health remained perfect. The patient was presented before the American Surgical Association in June 1903, apparently free from disease. In December 1903, there was a slight recurrence. The patient wrote Coley on January 7, 1904: "My general condition has been and is extremely fine. So far as the growth is concerned, it does not seem to increase a particle, neither does it seem to diminish. . . I use the toxins very regularly, and up to as high as 10 minims a day, an amount I never before had taken. The x-ray has been very regular and I have received one burn and was on the verge of another when I called to see you. Now as the results heretofore, or rather under your treatment, . . . Dr. Kennedy came to the conclusion that it would be advisable to use some of the Buxton toxins in connection with the Parke Davis, . . . Parke Davis one day, and Buxton the next. The Buxton toxins we will be very careful of, as I have

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used it before, and the doctor understands that it requires very little to cause a reaction." This recurrence also disappeared under persistent toxin therapy, which was continued until May 1904.

Clinical Course: The patient remained well for another year, until the early part of May 1905, when he developed another local recurrence which never entirely disappeared. He wrote Coley on May 31, 1905, stating that he was working every day. On July 5, 1905, Coley examined him and found an extensive local recurrence and evidence of involvement of lungs and pleura. The patient was much emaciated and in a hopeless condition. Death occurred in September 1905, seven years after onset. (27)

Comment: This case clearly illustrates the comparative potency of the two unfiltered products available at that time used in the same individual. Unfortunately very few physicians realized how weak the commercial product was (Parke Davis IX) and the same dosage was advised for both, although as seen in this case it took 30 times as much of the latter to induce the same febrile reaction. (A few cases of sarcoma treated by this weaker product were cured but these patients received more aggressive as well as more prolonged treatment which compensated for the weakness of the product.) Note that in the above case the toxins were not begun until three operations had been performed, the last two being incomplete, that during the first 14 months no injections were made into the tumor, and usually rather moderate or very mild reactions were obtained. Apparently the patient did not dare stop work for more than two or three weeks at a time, due to his worry about economic factors, and while he was working, only small doses were given which produced little or no reactions. Compare this case with others treated in this period in which the toxins were begun before several operations had been performed, and were given persistently in and near the tumor with little or no radiation.

References: 24 (Case III and discussion by Richardson); 25; 26; 27. (Case II); 46.

CASE 9: Inoperable round cell sarcoma of the mesenteric nodes and small intestines, confirmed by microscopic examination.

Previous History: J.B., male, aged 56, a physician. The patient's grandmother had had cancer. In 1872, at the age of 38, the patient had syphilis, and was not treated at that time. In 1889 he developed gonorrhoeal rheumatism. In 1900 he had exfoliation of bone in the roof of the mouth. This improved under K.I. treatment. Onset, in the summer of 1904, a tumor developed in the lower abdomen, just above the bladder. This increased very rapidly in size and by September 1904 it was the size of two fists.

Surgery: In December 1904, the growth was incompletely removed by Dr. J.S. Mixter of Boston. It weighed two pounds.

Toxin Therapy: (Buxton VI) In the hope of causing regression of the remains of the tumor, injections of Coley toxins were administered by Mixter for two months beginning ten days after the operation.

Radiation: Some x-ray therapy was also given at this time.

Clinical Course: The remaining induration disappeared.

Second Course of Toxin Therapy Combined With Heat Therapy: Injections were resumed the following March and given for about two months. The patient wrote Coley on March 27, 1905, regarding the effects of this

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course of treatment, which he administered himself, stating that the toxins "seemed to have become a tonic." He added: "Last week I took it every two days and ran up to 9½ minims. Today after receipt of yours of the 25th I cut down to 7 minims. I have never had a headache and the last three days have felt all tuned up and have worked now for a week every evening until about 12 o'clock. . . I feel stronger than for the last four years. . . I feel as if I could work all night, and lately my eyes have not given out in the evenings as they always used to do after a couple of hours' application. If it is not the toxins having this beneficial effect I don't know what it can be." He added: "I have lost four pounds in three weeks, but for a week have taken a good sweat to limber up my joints in hot air cabinet." (Possibly his feeling of well-being may have been due to the stimulus of these heat treatments as well as to the toxins.) During the next month, five minim doses of toxins were given, causing no effect except a dull and tired feeling next day. They were given intramuscularly, apparently in the gluteal region, causing some lameness at times. Injections were discontinued about April 24, 1905, at the end of approximately two months.

Clinical Course: The patient remained well nearly two years, until about February 1907, when a local recurrence developed in the right side of the pelvis causing some pain and a sense of fullness. A central mass the size of two fists and several smaller ones were palpable at this time.

Further Toxin Therapy (Tracy XI): In early April 1907, the injections were resumed by Mixer and the tumors regressed rapidly. During May the dose was reduced with the result that the tumor again began to increase in size.

Clinical Course: Injections were suspended about June 4, 1907. The tumors then increased very rapidly in size. The patient lost 19 pounds in weight, and became much weaker. He suffered from indigestion and had very little appetite. He was constipated and had difficult and frequent micturition. He was then referred to Dr. William B. Coley. Examination on admission to Memorial Hospital revealed the liver palpable 5 cm. below the costal margin. The lower abdomen was full and rounded, more so on the right side. The tumor was palpable, arising from the right pelvis, reaching to the crest of the ilium up to the umbilicus in the mid-line. There was an old cicatrix above the pubes in the mid-line. The tumor mass was soft and uneven.

Further Toxin Therapy: Injections were resumed by Coley on June 14, 1907, the initial dose of this series being 4 minims, which caused a febrile reaction of 102.8°F. and a chilly feeling. During the 43 days the patient was at Memorial Hospital he received 22 injections in doses of 3 to 6 minims given in the gluteal region. These caused mild reactions except on three or four occasions when the temperature rose to 101°F. There were only three chills and each time this was associated with nausea and vomiting. Apparently the patient did not feel he could take higher doses at this time on account of the "severe local reactions." The injections in this course were always given in the evening between 8 and 9 p.m.

Radiation: During this period two x-ray treatments were given. The patient was discharged on July 27, 1907.

Further Surgery: The disease was held in check until November 1907, when another incomplete operation was performed by Mixer in which a portion of the tumor weighing 4½ pounds was removed. The patient made a good recovery.

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Further Toxin Therapy: Two weeks after this operation the toxins were again resumed. The patient's appetite improved very greatly, and on December 7, 1907 his general health appeared better than it had been for a year. He gained 12 pounds during the month following the operation. Injections were continued through the winter of 1907-8. Beginning about January 8, 1908 the less potent Parke Davis XII preparation was administered, and two weeks later the Parke Davis Filtrate (XII F), as well as some of Tracy's Filtrate (XI F) was used. These three preparations were all less potent than Tracy XI, used during 1907.

Clinical Course: In view of the good condition of the patient, Mixer believed it possible to remove the remaining portion of the tumor, and therefore another operation was performed. This proved fatal, the patient dying from shock on February 16, 1909, 4½ years after onset.

Comment: This case may be compared with others of this type in which the disease was completely controlled and a permanent result obtained. Note that radiation was administered during the first and second course of toxin therapy and that four incomplete operations were performed. Any factor which alters or destroys the vascular or lymphatic channels through which the toxins must reach the neoplasm, or which depletes the lymphoid or reticuloendothelial tissues or inhibits the regeneration of normal tissue, appears to seriously limit the effectiveness of subsequent toxin therapy. Note that in this patient the toxins were never given directly into the tumor or intravenously and that unpleasant indurations developed at the sites of intramuscular infections. Note also that the duration of the first course of injections was only two months. When recurrence developed treatment was not resumed until the tumor was extensive, and soon after this the dose was reduced, resulting in immediate increase in the tumor growth. The case is one of several which clearly indicate the danger of reducing the dosage or the frequency too soon, thereby losing control of the disease.

As regards incomplete removal in lymphosarcoma, Coley stated in 1915: "In many cases it is almost certain that operation, particularly incomplete operation, causes the tumor to grow more rapidly than before. Hence I believe that 'palliative operations' or partial operations in this class of cases are contraindicated." (42)

References: 42 (case XXXIX); 46; 85; 126.

CASE 10: Recurrent inoperable lymphosarcoma of the tonsil and neck, confirmed by microscopic examination of the primary growth by Dr. F. M. Jeffries, Director of the Pathological Laboratory of the New York Polyclinic Hospital who reported: "The neoplasm submitted has the character of large round cell sarcoma. The cells are a mixture of small and large. The tumor appears decidedly malignant, and has probably extended beyond local limits. Examination shows that the cells have invaded the blood vessels, and could easily have been swept into the current." Sections removed from the recurrence in the opposite tonsil, seven years later, were examined by Dr. Douglas Symmers, Pathologist at New York Hospital who reported: "The tissue is irregularly covered by stratified squamous epithelium. The main body of the tissue is made up of round cells, the nuclei show many mitotic features. These cells are closely packed together and show no attempt to reproduce lymphoid follicles normally encountered in the tonsil. The cellular foci are definitely

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surrounded by connective tissue. The diagnosis rests between a sarcoma of the tonsil and a granuloma. From the histological appearance it is impossible to decide. Blood from this patient fails to give a Wassermann reaction." Dr. James Ewing examined the tissue removed on January 15, 1912 and reported: "Sections show a diffuse growth of medium-sized round cells. Nuclei are moderately hyperchromatic; mitoses are occasionally seen. No reticular stroma is visible but the tumor is infiltrating the muscular and fat tissues after the manner of a malignant growth. Diagnosis: Lymphosarcoma." (29, case XXII)

Previous History: H.M., male, aged 32, harness maker. The family history was non-contributory. The patient had scarlet fever at 10, his only illness. His general health had always been excellent. Onset, in the middle of August 1905, he first noticed an enlargement of the left tonsil and a swelling on the left side of the neck, just behind the sternomastoid. There was no pain at first, but as both tumors increased very rapidly in size, the neck soon became so stiff and painful that the patient could scarcely move his head.

Surgery: In the latter part of August 1905, Dr. Carl Beck attempted to remove both tumors, at St. Mark's Hospital. It was impossible to make a complete excision.

Radiation: The patient was immediately given x-ray treatments every other day, and he also received radium externally and internally. The latter, however, had little effect in checking the rapid growth.

Further Surgery: On October 13, 1905, while under the care of Dr. Goldwater at Polyclinic Hospital, a portion of the tumor was excised and examined as stated above.

Chemical Course: On October 17, 1905, Dr. William B. Coley first examined the patient, who had been referred to him by Dr. Arpad G. Gerster. He found a large globular tumor on the left side of the neck, the size of half an orange, extending from the angle of the jaw in front, to the mastoid process behind and downwards nearly to the clavicle. Its consistency was about the same as is ordinarily found in lymphosarcoma. The overlying skin was not adherent. The left tonsil was enlarged to two or three times its normal size. The general health had been but little affected. The patient was admitted to Memorial Hospital on October 17, 1905.

Toxin Therapy (Buxton VI): Injections were begun by Coley on October 20, 1905, and were given daily alternating the site; one day directly into the cervical tumor, the other into the pectoral region. The maximum dose was 9 minims, the febrile reactions ranging from 99.5°F. to 103°F. There were seven chills, five of them severe. In less than a week there was a decided decrease in the size of the tumor and increase in mobility. Diminution continued steadily until at the end of six weeks both the cervical and the tonsillar tumors had apparently completely regressed. The patient left the hospital at the end of seven weeks. Although there were no visible remains of the tumors, injections were continued two or three times a week and later once every two weeks in order to prevent possible recurrence. These later injections were all given in the pectoral region. Treatment was continued until October 1906, for one year.

Clinical Course: Gerster wrote Coley on December 1, 1905, six weeks after the toxins were begun: "It is my agreeable duty to congratulate you most sincerely on the brilliant achievement in the patient Miller. Most certainly I have never seen anything like it. The tonsil looks now like a normal

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organ, and the large glandular and periglandular swelling of the neck has entirely disappeared." He wrote again in 1908: "It is the most gratifying case within my experience."

(Note: Gerster was one of a committee of three appointed by the New York Surgical Society in 1896 who had rendered an adverse report as to the value of the Coley toxins. He later revised his views and referred several patients to Coley.) This patient was shown before the Harvard Medical Society on November 25, 1905 and before the New York Surgical Society in January 1906, in perfect health. He remained in good health for six years, until the fall of 1911. At that time he developed a recurrence in the opposite tonsil and a tumor on the other side of the neck.

Further Surgery: The latter was removed by Dr. Erdman in December 1911. The cervical growth recurred very rapidly and in less than three weeks had become larger than at the time of the operation. In early January 1912, the patient was admitted to Memorial Hospital and Drs. Coley and Downes performed a very extensive operation, removing a mass the size of an orange and several smaller nodules around the clavicle as well as the entire sternomastoid muscle. The patient made a good postoperative recovery. This tumor was carefully examined by Ewing, as stated above, and pronounced lymphosarcoma.

Further Toxin Therapy (Tracy XI): Injections were resumed on January 16, 1912 and during the next seven days six were given into the pectoral muscles, in doses of 0.5 to 3 minims. These caused no reactions. The patient refused to remain in the hospital for further toxin therapy. The latter was therefore administered at home for a few weeks by the family physician. The technic used or reactions elicited are not recorded.

Clinical Course: The patient then lost hope and declined further treatment. The tumor grew with great rapidity as soon as the toxins were stopped, causing death prior to March 12, 1912, less than two months after the last operation; this was 6½ years after onset.

Comment: When recurrence developed in the opposite tonsil and neck it is unfortunate that toxin therapy was not resumed at once and administered aggressively, partly into the tumor and partly remote from the tumor. When the toxins were finally resumed following operation in 1912, only a few were given intramuscularly and caused no reactions. Incomplete though extensive operations appear to stimulate the growth rate of these tumors. In treating similar cases it may be best to administer the toxins intensively first, at times limiting the surgical procedure to establishing free drainage of necrotic tumor tissue where necessary.

References: 29, case 22; 31; 40; 42; 46; 85.

CASE 29: Large inoperable lymphosarcoma of the mesentery and small intestine, confirmed by microscopic examination at the Hospital for Special Surgery, New York and also by Dr. A.J. Broders of the Mayo Clinic, Rochester, Minn.

Previous History: R.T., male, aged 34, of Walla Walla, Washington. The patient's father died of cancer of the stomach. The patient had always been in good health until July 3, 1916, when he fell from a building a distance of 18 feet, striking a cement floor. He landed in such a position that his abdomen received a sharp blow from his doubled-up elbow. Onset, six or seven months later he began to feel pain in the upper left abdomen at the

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site of the injury. He consulted a number of physicians and surgeons in the state of Washington, who made different diagnoses: floating kidney, enlarged spleen or pancreas, sarcoma, tuberculosis of the peritoneum, etc. The patient's own diagnosis was "internal cancer". In mid-December 1917, he consulted Dr. Charles H. Mayo, who made a clinical diagnosis of lymphosarcoma of the small intestine.

Surgery: Mayo performed an exploratory operation, by a left rectus incision, revealing a large inoperable tumor of the mesentery and small intestine. The tumor involved such a large segment of the mesentery that it was deemed unwise to attempt to remove it surgically, and the wound was closed.

Clinical Course: The patient was then referred to Dr. William B. Coley for toxin therapy. Physical examination on January 7, 1918, showed a recent cicatrix 10 cm. long over the left rectus muscle, the upper area of which was not entirely healed. Just under this was a large solid tumor, about 20 cm. in diameter, not deeply attached, but apparently connected with the mesentery or intestine. No enlarged nodes could be felt. The patient's general condition was good and there was no pain or any marked loss of weight. The blood examination was negative.

Radiation: The patient was admitted to Memorial Hospital January 8, 1918 and immediately received his first radium pack treatment (15,000 mch. at 10 cm. distance). He was made very ill by the radium and took two or three days to recover. He lost about eight pounds in weight in four or five days.

Toxin Therapy (Tracy XI): Injections were begun by Coley on January 15, 1918, the initial dose being 0.5 minim. This was increased very slowly, as the patient proved very susceptible, a dose of $2\frac{1}{2}$ minims caused a febrile reaction of 103°F . At the end of one week the tumor had decreased about one half, and became much more mobile. The patient's condition steadily improved.

Further Radiation: He was given a second radium treatment on February 7, 1918 (16,000 mch. at 10 cm. distance), and a third treatment on March 3, 1918 (10,000 mch. at 7 cm. distance).

Further Toxin Therapy: The patient then returned to his home on the West coast where the toxins were resumed by the family physician and given two or three times weekly. Some severe reactions with chills were elicited from doses of only 2 minims. On July 23, 1918, the patient again consulted Coley. Examination at this time showed a very small, hardly perceptible mass at the site of the original tumor.

Further Radiation: As a precaution he was given two applications of radium (18,000 mch. each at 7 cm. distance). During the year 1919 he received further applications of radium, totalling 44,283 mch.

Further Toxin Therapy: Injections were given spasmodically by the family physician (two or three a week) "in doses not sufficiently large to interfere with his daily routine of life." Coley again examined the patient in May 1920, at which time no definite mass could be found in the abdomen. There were, however, two very small nodes in both cervical regions.

Further Radiation: The lead tray was applied at 3 cm. distance to these areas (3,000 mch. each), and the radium pack was applied over the abdomen (17,000 mch.).

Further Toxin Therapy: Injections of the toxins were continued at home. The patient wrote Coley on October 22, 1920: "I have been getting along in

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fair shape but can see no appreciable change in neck except that the bump goes down a trifle when I have a high fever and then about as usual the next day or so. . . Have had some hard reactions three times in a week, the last of August up to 103°F. and two times in a week in September up to 101°F. with fever all the next day of over 100°F."

Further Radiation: Coley saw the patient next on November 25, 1920, when he again had the radium pack applied over the abdomen (6,344 mch.). Toxin therapy was also resumed (Parke Davis XIII). No details are recorded as a technic used or reactions elicited. He received no further radium treatment until August 8, 1921, when the lead tray (2,870 mch.) was applied over the supraclavicular region, and the pack (6,344 mch.) was applied over the abdomen. In January 1922, a small nodule was noticed on the left elbow. This was treated by roentgen rays and disappeared. In January 1923 he received another radium pack treatment (18,026 mch.) over the abdomen.

Further Toxin Therapy (Parke Davis XIII): The toxins were given in small doses with intervals of rest until November 1923, when the patient refused further injections.

Clinical Course: Two months after the toxins were stopped, a slight enlargement was noticed in the nodes of the left axilla, which steadily increased in size. Coley again saw the patient on January 20, 1925; he found enlargement at the site of the old intra-abdominal tumor, with apparent involvement of the retroperitoneal nodes. The cervical and inguinal nodes were normal. In the left axilla was a mass about the size of a small orange, soft in consistency, movable and extending for some distance beneath the edge of the pectoral muscle.

Further Radiation: The radium pack was again applied as follows: January 22, 1925: 12,000 mch. over the abdomen at 10 cm. distance; January 24, 1925: 10,000 mch. over the left pectoral region at 10 cm. distance; January 26, 1926: 10,000 mch. over the left axilla at 6 cm. distance.

Further Surgery: On February 4, 1926, Coley removed the tumor of the axilla surgically. It proved to be a "typical lymphosarcoma".

Clinical Course: The disease was not controlled and the patient finally died in September 1928, 11½ years after onset. Autopsy revealed a tumor 15 x 18 cm. in diameter at the original site, directly on top of the abdominal vessels between the two kidneys, but more to the left. The liver and lungs revealed no metastases, nor were there any in the left axilla. The growth was entirely retroperitoneal, and rather firmly attached to the vertebrae but not involving them. (46)

Comment: In analyzing this case Coley stated that he believed it to be of interest for the following reasons: "First, it shows that a rapidly-growing lymphosarcoma of the small intestine has been almost completely controlled for a period of ten years, the patient remaining in good health during most of this period. Second, it shows that even when metastases had developed, one should not abandon treatment. In this case the metastatic tumor in the cervical nodes completely disappeared under further treatment. The latest and most extensive metastasis in the axilla did not occur until November 1923, some time after the toxin treatment had been discontinued." (44) Analysis of all the cases of various types of cancer treated by toxins combined with radiation clearly indicates that where radiation is given first, the patient may tolerate smaller doses of toxins and suffers more from adverse radiation effects. It is also more difficult to gain permanent control of the disease. Note that in this case no toxins were given until the patient had received a massive radium

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pack treatment, which made him very ill and caused him to lose eight pounds in five days. No intravenous or intratumoral injections were given. The patient received a great deal of radium over the next eight years (210,000 mch.). It would appear that toxins were not administered during 1918 sufficiently aggressively to completely destroy the growth and increase host resistance enough to prevent recurrence or metastases. In this case the combined toxin and radium treatments, given between 1918 and 1923, succeeded in holding the growth almost at a standstill with certain periods, such as July 1918, when the original tumor was barely palpable, and there was no evidence of disease elsewhere. The autopsy findings indicate that the prolonged toxin therapy in this case (intermittently for $5\frac{1}{2}$ years) may have protected this patient against the deleterious tissue changes usually produced by such heavy radiation.

References: 44; 46; 85.

CASE 30: Lymphosarcoma or Hodgkin's disease of the left cervical nodes and mediastinum was the clinical diagnosis of Dr. William B. Coley and the Memorial Hospital staff. No microscopic examination was made in this case until after the toxins had been given for several months. (See below, report of Dr. James Ewing).

Previous History: B.H., male, aged 46, of Carlisle, Kentucky, a farmer. One brother had died of cancer of the stomach, another of pellagra, the father of apoplexy. The patient had always enjoyed very good health until January 1917 when he had an attack of grippe. He never fully recovered his health after this, and a bronchial cough remained all spring. In April 1917 he developed what was diagnosed as typhoid fever by the local physician, who stated that there were several chills and sweats during this illness. Onset, in the middle of June 1917, the patient noticed that the lymph nodes on both sides of the neck had suddenly swollen to a considerable size. At this time the patient had completely recovered from the fever. In about three weeks the swelling receded until only one or two small lymph nodes were palpable. These remained stationary. About November 10, 1917, the nodes on the left side swelled again and slowly increased in size. Pain developed in mid-December, but was not very severe except at times. The patient was referred to Dr. William B. Coley and was admitted to Memorial Hospital on January 21, 1918. Examination at this time showed the whole left supraclavicular region from the mastoid to the clavicle occupied by a mass of enlarged nodes. These extended beneath the sternomastoid muscle, projecting more from the posterior than the anterior edge. They were firm but not hard in consistency. A few were discrete, most of them being loosely fused together. The skin was normal in appearance and was not adherent to the underlying nodes. On the right side there were a few enlarged nodes behind the sternomastoid, and above the clavicle, and a few below the angle of the jaw. The spleen was not enlarged. The nodes in both axillae appeared normal in size. X-ray examination by Dr. Douglas Quick showed slight increase in the width of the mediastinal area and moderate thickening at the right lung roots.

Toxin Therapy (Tracy XI): Injections were begun by Coley on January 21, 1918, and were given daily. The first two of 0.5 and 1 minim each, produced no reaction. The third, of 1.5 minims, caused a febrile reaction of 102°F. , eight hours after injection. Coley reported on January 24, 1918: "Has had four doses of toxins . . . without any other treatment. Very susceptible, marked reaction after dose of $1\frac{1}{2}$ minim. Decided decrease in size of nodes after first two doses. Today after four doses mass has decreased about $\frac{3}{4}$ of original size." (85) The following day after a dose of $1\frac{1}{2}$ minims had caused

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a slight chill and fever of 103°F., Coley added: "Examination today, January 25, shows tumors have almost entirely gone and contour of neck is normal. Nodes the size of walnuts in mid-cervical region January 21, have entirely disappeared, and now only a few small nodes above the clavicle about the size of small beans can be felt. General condition normal." Injections were continued daily, gradually increasing the dose. The average febrile reactions were 100° to 102°F., on one or two occasions 103° to 104°F. After the first 10 days the frequency was reduced from 24 to 48 hours. On February 14, 1918 Coley reported: "The neck remains normal. No nodes can be felt. He has lost 14 pounds in weight, which is no more than usual with severe toxin treatment. He feels fine and has a good appetite." (85) The patient was discharged home on February 15, 1918, less than a month after the toxins were begun. On March 14, 1918, Dr. B. Frank Reynolds, the family physician, reported: "On his return home I found that the enlarged nodes in the neck had entirely disappeared and there is no evidence of their returning so far. He has gained in weight about 15 pounds and feels well. I have been using toxins in 0.5 minim doses increased to 1 minim, every other day for two weeks. He has had no chills or fever following any of the treatments. . . injections do not seem to be absorbed extra well." Intramuscular injections were continued until about March 25, 1918. Against Reynolds' orders the patient returned to work: he was a farmer and it was spring.

Clinical Course: By April 10, 1918, enlarged nodes were apparent in both axillae and both inguinal regions. These increased rapidly in size.

Further Toxin Treatment (Tracy XI): Injections were resumed by Reynolds at this date, increasing the dose by 0.5 minim each time to the point of giving him a chill and a febrile reaction of 101° to 102°F. They were given every other day intramuscularly in the arms. A few hours after injection the patient was able to be up and around. Reynolds advised him to return to New York and he did so and was readmitted to Memorial Hospital on April 24, 1918. Examination at that time showed the cervical nodes entirely free from recurrence. However, the left axilla contained a mass of enlarged nodes varying in size from a hickory nut to a pea, more or less loosely bound together and freely movable. They were moderately firm in consistency but not hard, typical of Hodgkin's disease. The left axilla had a similar slightly smaller mass of nodes. The right groin contained enlarged nodes in both the inguinal and femoral regions similar to the axillary masses, varying in size from a hickory to a hazel-nut. Some projected beyond the normal surface and formed distinct tumors easily seen. These nodes were loosely held together by connective tissue and were fairly movable. The left groin showed a similar condition though the nodes were slightly smaller.

Surgery: On April 25, 1918, the larger and more superficial nodes in the groin were removed under novocaine by Coley and examined by Dr. James Ewing. His diagnosis was: "Simple inflammatory lymphoma. Has some characteristics of lymphosarcoma." (85 Path. Report #486. 1918.)

Further Toxin Therapy: Injections were continued by Coley, the initial dose in this series being 2 minims on April 20, 1918. This caused a febrile reaction of 101.6°F. and a chill lasting 10 minutes. Injections were also given on April 24, 26, 27, 28, 1918 in doses of 2 or 3 minims, the febrile reaction gradually diminishing to 100°F. Four injections were given during the week of May 1, 1918. Beginning May 7, the Parke-Davis XIII preparation was used, the dose being 5 minims. This caused a temperature of 102.8°F. Two more injections were given at Memorial Hospital. Examination on May 14, 1918 showed very little change in the axillary nodes. Those in the right groin were

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slightly smaller. The general condition was about the same. An x-ray examination of the chest on May 16, 1918 showed an extensive mediastinal mass displacing the heart to the right.

Radiation: Beginning on May 15, a total of 13 x-ray treatments were given, lasting $3\frac{1}{2}$ or 4 minutes each, to the right and left axilla, the neck, the right and left groin and the posterior chest. Another roentgenological examination of the chest on May 30, 1918 showed a very marked improvement in the mediastinal mass reported two weeks before. The patient was discharged home on May 30, 1918.

Clinical Course: No further toxins were administered. Apparently the improvement was only temporary. The disease progressed causing death on October 24, 1918, 16 months after onset.

Comment: This case indicates the dangers of reducing dosage and frequency too soon, thereby losing control of the disease. (Compare with the case of Dr. P. V., see above Series C, Case 18, also reported in 95, Case 21, p. 61-63.)

References: 46, 85.

CASE 38: Inoperable lymphosarcoma, involving the cervical, supraclavicular and axillary nodes and the mediastinum, confirmed by microscopic and x-ray examinations at Memorial Hospital and at the Mayo Clinic.

Previous History: M. A., female aged 18, of Ishpeming, Michigan. The patient had always been in good health, except for measles and rheumatism at the age of 11. She had not been subject to frequent colds or sore throats. Onset, in October 1919, she noticed an enlarged node on the left side of the neck. The first lesion was treated with iodine salve for two weeks.

Tuberculin Therapy: Tuberculin injections were given subcutaneously for a year. The swelling diminished suddenly in size seven months after onset, but about this time a similar enlargement was noticed on the right side. The patient stated that the latter "started like a pimple" in the upper mid-supraclavicular region and steadily increased in size until it was as large as an orange when first seen by Coley. Shortly thereafter, a huge mass developed on the left side. Examination on admission to Memorial Hospital, October 16, 1921, revealed that the nodes in both axillae were distinctly enlarged. The mass just to the right of the mid-sternum extended over half of the sternum and the whole anterior and posterior supraclavicular region, being 11 x 12 cm. in diameter. It was firmly fixed to the chest wall, smooth and symmetrical in outline and projected 5 cm. beyond the normal surface of the chest. On the left side was a similar but smaller mass extending out to the left of the sternum about $1\frac{1}{4}$ cm., but apparently connected with the larger mass by a narrow prolongation. Both were firm in consistency, the overlying skin being normal and not adherent. The inguinal nodes were not involved. The menstrual cycle was normal, although on two occasions the patient had missed a period altogether. She felt as well as usual, and in the preceding two years had gained rather than lost weight. She had been seen at the Mayo Clinic and had been referred to Coley by the Doctors Mayo.

Surgery: A node was removed from the shoulder for biopsy by Dr. Bradley L. Coley on November 16, 1921.

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Radiation: X-ray therapy was begun the next day and eight exposures were given in 10 days (two to the right and left axilla, two to the right and left chest posteriorly). The radium pack was applied on October 19, 1921 over two areas on the chest (1,610 and 8,670 mch. each). Radiation caused a definite skin reaction which subsided in a month.

Toxin Therapy (Parke Davis XIII): Injections were begun about October 28, 1921, following radiation. The dose was increased very slowly to $3\frac{1}{2}$ minims which caused a chill on November 23, 1921. Steady improvement occurred during toxin therapy and x-ray examinations on November 3 and 10, 1921 showed marked diminution in the size of the shadow in the mediastinum.

Further Radiation: On November 10, 11 and 15, 1921 three more radium treatments were given, two to the right and one to the left cervical region (4,204, 4,213 and 8,073 mch.) By December 1, 1921 the radiation reaction on the neck and proximal chest was subsiding, and steady decrease in size of the involved nodes was observed.

Clinical Course: The patient was allowed to go home for Christmas on December 20, 1921. She returned on January 8, 1922. Chest films taken January 12, 1922 revealed further diminution in the size of the mass in the mediastinum.

Further Radiation: Two more x-ray treatments were given on January 11 and 18, 1922, to the chest. One more radium pack was given on January 29, 1922 (6,703 mch.)

Clinical Course: On February 15, 1922, the condition was reported as follows: "Steady, progressive improvement both in disappearance of the sternal mass, and axillary and cervical swellings, and also in general condition, as evidenced by increase of 26 pounds in weight." By March 9, 1922, the patient weighed 130 pounds, a gain of 31 pounds in a little over four months, and there remained only one small node in the left axilla.

Further Radiation: Another x-ray treatment was given on March 13, 1922 to the left axilla.

Clinical Course: The patient was discharged in excellent condition on March 30, 1922. The x-ray examination at that time was reported as follows: "although there is considerable widening of the mediastinum, marked improvement is noted when compared with previous plates."

Further Radiation: She was readmitted on July 31, 1922, and on August 4, received a radium pack over two areas of the sternum (3,544 and 14,384 mch. each). X-ray examination on August 10, 1922 showed considerable diminution in the size of the mass in the mediastinum, but an extensive infiltration remained along the bronchi out into the parenchyma of the lungs on either side. Another radium pack was applied over the sternum on August 23, 1922 (16,000 mch.) High-voltage x-ray therapy was administered on August 8, 1922 over the entire chest.

Further Toxin Therapy: The toxins were again administered during the summer of 1922, but the site, frequency and duration are not recorded.

Clinical Course: The patient continued to gain and by October 13, 1922 the x-ray examination showed that the mass in the mediastinum had practically disappeared, although there remained considerable infiltration along the bronchi into the lungs.

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Further Radiation: Two x-ray treatments were given, one to the left neck and one to the left axilla, on October 2, 1922.

Further Toxin Therapy: Injections were given during February 1923, but the technic is not recorded.

Clinical Course: During the early summer of 1923 a swelling of the left arm developed. The patient was readmitted to Memorial Hospital on August 14, 1923. X-ray plates showed no bone involvement and x-ray examination made on August 23, 1923 showed very little mediastinal involvement.

Further Toxin Therapy: Injections were resumed by Coley on September 12, 1923 and 23 were given during the next 49 days. The febrile reactions ranged from 100.6°F. to 104°F., but there were only three or four marked reactions. On October 31, 1923, it was noticed that the patient had improved, but there was still a swelling of the left arm and hand, more pronounced below the elbow. The patient was discharged on November 1, 1923.

Clinical Course: The disease was not controlled and death occurred on March 5, 1924, 4½ years after onset.

References: 46; 85.

CASE 39: Generalized pseudoleukemia, confirmed by microscopic examination at Memorial Hospital by Dr. James Ewing who reported: "The sections of lymph node in the case of Dr. A. show a peculiar picture which one very seldom sees and which it is difficult to classify among the recognized types of lymph nodes. The sections show marked enlargement of the node, with some infiltration of the capsule by medium sized round cells. The follicles of the node are increased both in size and number. The lymph cords are increased in bulk. The blood vessels are not much compressed and are not at all obliterated. The sinuses are obliterated by the growth of cells. The cells are everywhere distinctly hyperchromatic, and give the impression of definite but moderate malignancy. There are none of the features of Hodgkin's granuloma. The usual features of diffusely growing lymphosarcoma, of lymphocytic type or reticulum cell type are missing. The blood shows no leukemia. I would therefore class the case as belonging in the group of generalized pseudoleukemia. Histologically it is lymphadenoma. The prognosis is better than with true lymphosarcoma or Hodgkin's granuloma, but it is still grave."

Previous History: J.G.A., male, pathologist, aged 62, of Liverpool, England. There was a definite predisposition to malignancy on the maternal side: the great-grandmother had a tumor of the neck, the grandfather died of cancer of the liver; while the patient's mother died of cerebral apoplexy, she was suffering from a progressive growth of the liver. There was no similar history on the paternal side. The patient's father died of Bright's disease and uremia. Both he and the maternal grandfather suffered from gout. The patient had had the usual childhood diseases. He had appendicitis twice at the age of 19, but recovered without operation. He enjoyed "singularly robust health" all his life, with only one day away from work (in 1904 from pertussis). Through an accident at the age of 11 he had a deviated nasal septum and a tendency to chronic nasal catarrh which became accentuated on his return to England (he lived in Canada from 1892 to 1915). In 1899 he had a mild tendonitis of the Achilles tendon, diagnosed as gouty. He enlisted in World War I in 1914 at the age of 57, with larger chest capacity than any of the 30 or so other officers

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of his unit, all his juniors. He went through four years of war without a single day off duty. In 1923 he had two attacks of typical Sydenhamian gout. Onset, the patient noticed during the first World War that his shirt collars were becoming increasingly tight. Before the war he could wear 17½ inch collars comfortably, but by 1919 he had to get 18½ inch. In the autumn of 1920 he noticed that the contour of his neck was abnormal and on manipulation detected symmetrically disposed swollen lymph nodes in the anterior triangle. A few weeks later noting that he had an increasing jowl, he found a palpable swollen lymph node behind the angle of the jaw on either side, also some swollen nodes in the axilla. His health was quite good at the time, but he consulted Sir Humphrey Rolleston in London early in 1921. Blood examinations at this time were negative. The inguinal nodes were so indurated and coalesced that the individual nodes could not be felt. There was also some enlargement of the prostate. Acting on the experimental observation of Layton of Leeds, on the effects of minute doses of thyroid, he took thyroid, with apparently good effects as regards the prostate and the lymph nodes; i.e. if there was any increase in size in the nodes in the next three years, the increase was so slow as to be imperceptible. The patient was vice chancellor of a large university and in December 1923, "at the end of the term, after a very strenuous year of work he found himself thoroughly worn out and took to his bed over the week-end for a complete rest." His wife called Dr. Murray Cairnes who got Sir Humphrey Rolleston to come down to Liverpool in consultation. Further blood tests showed no material change from 1921. The teeth were then x-rayed and three were removed. On Rolleston's advice he spent from January 24 to May 17, 1924 in Sicily and Italy.

Vaccine Therapy Combined With Arsenic: Dr. Cronin Lowe made a polyvalent vaccine from the mouth and nasal organisms and this together with open air treatment and minute doses of arsenious acid constituted the only therapy. Under this regime the lymph nodes at the angle of the jaws very noticeably diminished in size until they were just perceptible, and the group of enlarged nodes in the lower anterior triangle of the neck underwent such marked regression "as to seem well on the way to disappearance." The group in the right anterior triangle, which in December 1923 had been larger and firmer than the other side, had not undergone such marked reduction but had materially decreased. For the first time since early manhood it was possible to wear size 17 collars (a reduction of 4 cm.). The axillary nodes were softer, and those in the left axilla were definitely smaller. Instead of forming diffuse indurated masses, it was now possible to distinguish on palpation the individual nodes in the groin. The patient lost 21 pounds in weight under this treatment, but his weight was still much above normal for his height.

Clinical Course: Between May 17 and July 13, 1924, in addition to feeling and looking materially improved, he gained one pound in weight and by late July 1924 weighed 180 pounds. Early in August 1924 he was referred to Dr. William B. Coley by Rolleston who stated that recently the liver and spleen had become enlarged. A biopsy was performed at the Hospital for Special Surgery and reported by Ewing on August 6, 1924. X-ray examination of the chest was negative for mediastinal involvement.

Toxin Therapy (Parke-Davis XIII): In early August 1924 injections of Coley toxins were begun, and were continued for six weeks in doses up to 5 minims, with maximum febrile reaction of 102°F. By August 29, 1924 after only three weeks' treatment the patient stated that "I can feel nothing in the groins and right axilla, nothing in the left supraclavicular and cervical areas, nothing behind the angles of the jaw. The only indurated mass, and that now

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the size of a pea, is in the right lower cervical region. The continued reaction is most striking, the glands have virtually disappeared; and the hemoglobin has increased from 75 to 94%". The general condition was good. The patient returned to his duties as vice chancellor. His wife reported on November 16, 1924: "He is a different man. He eats, sleeps and wakes well. He is cheery and bright in spirit and seems to find it quite possible to get through his day's work; he has shown no sign of special or undue fatigue. . . Everyone is amazed at his changed appearance. . ." By December 11, 1924, he had relapsed of hepatic character. A low fat and carbohydrate diet was suggested and a course of pancreatic extract was prescribed. He therefore went on a diet of meat and green vegetables and he took "Pan-Secretin". During February only one injection a week was given and these caused febrile reactions of 101.8° from a 2½ minim dose. He also took a minute dose of arsenic once a day during the middle of the week, not near the time of his toxin injection. His spirits and energy began to improve markedly about February 1, 1925. By March his wife reported that there had been gradual steady improvement in his morale and his general condition. There was no sign of recurrence of the nodes. They went to Rapallo for a month that spring. There was a slight decrease in the rbc. and hemoglobin noted in the blood counts taken in April, but the wbc. was also lower. His weight remained constant, there was no lymphadenopathy, and the spleen was not felt. The liver was just as enlarged as in 1920. He felt well. "He finished a very busy term at the University in grand style and was not a bit over-tired," his wife wrote on April 20, 1925; she added: "He is in better received two courses of injections thrice weekly, in doses of 0.5 to 5 minims given intramuscularly. These produced no febrile reactions over 100°F. An interval of one week's rest was given between courses.

Concurrent Infection and Duodenitis: During December the patient developed a very heavy cold, with a good deal of expectoration and much nasal discharge, also a slight chill. This pulled him down. He also suffered from what he believed was delayed gastric indigestion. He then started taking Kruschen Salts regularly and had no further symptoms in the duodenal area. No injections of toxins were given for about two weeks.

Further Toxin Therapy: They were resumed on January 10, 1925 and were given twice weekly. Rolleston examined the patient in January 1925 and was specially impressed by the continued absence of the axillary and groin tumors and the softness and smallness of the one mass still palpable in the right lower cervical region. In February 1925 his gastric contents were analysed and glucose tolerance, blood sugar, etc. were tested. The findings suggested some evidence of endocrine deficiency of a pancreatic and possible also spirits and energy, mental, and physical than I've seen him since late 1922 or early 1923. He has been walking in the mountains anything from five to ten miles a day, painting, sketching. . . The weather was ideal so he was out all day long. The blood counts taken in early May and early June were excellent. The injections of toxins were continued once a week (Sundays) in doses of four minims." His wife wrote again on June 8, 1925, "He is looking splendid and getting through term in excellent spirits and form. We had a reception for about 200 at our house on Friday night, on the occasion of our Honorary degree function and everyone was full of admiration for his splendid appearance. To me it seems almost too wonderful to be true." The patient wrote on June 29, 1925 that he felt himself again in every respect save that he tired more easily at the end of a busy day than he used to — but he felt that at 63 one might be prepared for that. He added: "I am so fit and immune that not since the autumn has there been any proper temperature reaction, not even when the dose is increased to 6 minims. At this time the only node that he could

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still detect remained small and showed no obvious increase. (It was the one first detected in the right supraclavicular region.) The blood counts for June, July and August remained excellent but the ones in September and October 1925 were not quite as good. His weight remained constant. He ate well and slept well. Toxin injections were continued each Sunday, in doses which caused minimal febrile reactions: 99°-100°F. These did not "pull him down at all." He also took iodine and small doses of arsenic. By November 11, 1925, a large, fairly hard node in the right groin developed, much as it had been two years previously.

Radiation: A radium pack treatment was given to the mass in the right groin on December 23, 1925 (a total of 30 hours over a 48 hour period) followed by very marked decrease in size and hardness. There remained only a "soft layer." The radium made him feel very tired, however, but there was no other symptom except fatigue; his morale was good and his mind was working better than it had for two years.

Further Toxin Therapy: Five days after the radium treatment injections were resumed and were kept up steadily twice weekly. During December 1925 Rolleston found evidence of involvement of the abdominal nodes behind the liver. Therefore, the injections which all during the previous year had been given only once a week, were given twice weekly, or once every five days, but it was difficult to get good reactions even with doses of 5 to 6 minims. His temperature never rose over 101°F. In February 1926, a reaction of 101.6° occurred after a dose of 4 minims from a fresh bottle of toxins. This was followed by a chill and the reaction lasted five hours.

Further Concurrent Infection: During late January he had an attack of bronchitis and was in bed five days but recovered and returned to work, however, he continued to have the cough which had begun in the spring of 1925. His family physician, Dr. William Murray Cairnes, wrote on March 23, 1926 that "he had been doing wonderfully well and this in spite of a good deal of stress and strain inseparable from the responsibilities of the high office he holds." His wife wrote: "He has done a much bigger winter's work than last, and has come out of it in better spirits and with more energy."

Further Radiation: The patient returned to New York in late March 1926 for two weeks. A radium pack treatment was given to the nodes in the groin, by Coley.

Clinical Course: No details are available as to how long the injections were continued, if at all, after his return home. The patient, due to his indomitable will, was able to carry on his arduous duties in spite of daily weakness and rapidly failing strength. During July 1926 the exhaustion and anemia progressed at an alarming rate. Death occurred on August 29, 1926, approximately eight years after the cervical and supraclavicular lymphadenopathy had first developed. He was only bedridden the last month of his life.

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Comment: The record of blood counts taken from October 1924 to December 10, 1925 showed the following:

DATE	HEMOGLOBIN	RED CELLS	WHITE CELLS
10/3/24	84%	4,488,000	6,500
1/11/24	90%	4,528,000	4,200
12/5/24	86%	4,576,000	3,600
1/12/25	76%	4,224,000	4,200
2/16/25	75%	3,852,000	2,700
3/6/25	82%	3,860,000	4,700
4/30/25	92%	4,928,000	9,500
6/5/25	95%	5,240,000	5,300
7/3/25	96%	6,432,000	7,800
9/7/25	88%	4,368,000	5,000
10/9/25	90%	4,528,000	4,200
12/10/25	88%	4,123,000	5,700

The only significant finding in the differential counts was a persistent relative increase in the number of large lymphocytes. The marked improvement seen on April 30 and June 5, 1925 occurred following the four weeks' holiday in Italy.

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