A STUDY OF THE EFFICIENCY OF MIXED TOXINS (COLEY) IN INOPERABLE SARCOMA. A CRITICAL ANALYSIS OF 134 MICROSCOPICALLY PROVEN CASES.

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IN the BOSTON MEDICAL AND SURGICAL JOURNAL of August 13, 1914 (Vol. clxxi, pp. 253-261), I published a paper based upon observations made during the past five years upon 91 cases treated with mixed toxins of erysipelas and bacillus prodigiosus.* Some of these cases were under treatment too short a period to be of value in determining the efficiency of the toxins. Some were early cases in the series in which the doses were too small. Some cannot be traced by letters, visits to former homes, state or city records. Some were cases in which no pathological report was obtained. Some were cases of microscopically proven carcinoma. Some were cases of proven sarcoma in which toxins were administered as a prophylactic against recurrence after operations which might of themselves have cured (amputations without demonstrable metastases, etc.). Obviously in a critical analysis to determine the efficiency of toxins in the treatment of sarcoma such cases were excluded. There remained 32 cases. These were analysed; first, according to the type of sarcoma, and second, according to the anatomical situation and tissue of origin. These 32 cases were all primary or recurrent inoperable sarcoma, or cases in which the disease could not be eradicated by operation. All were proven by microscopic examination. All were under treatment at least three weeks. In all cases the results were free from vitiation by concurrent treatment (x-ray, radium, arsenical preparations, etc.). All living cases had been seen or heard from within three months.

The purpose of this study was to determine, if possible, the type or types of cases in which this treatment offered expectation of benefit. Obviously the answer to this question obtained by an analysis of so small a series of cases could be only suggestive. Despite many failures the most rigorous criticism of certain hopeless inoperable cases in which growths have permanently disappeared and no metastases have occurred must admit apparent cure attributable either to the toxins or to spontaneity. Factors are concerned of which we have no knowledge, and spontaneous cures have doubtless occurred. The percentage of apparent cures occurring with the use of toxins seems, however, too large to attribute to spontaneity. On account of a comparatively small percentage of most encouraging results an effort has been made in this paper

* I wish to express my appreciation to members of the staff of the Massachusetts General Hospital through whose courtesy this study was made possible.

to assemble a larger series of cases of sarcoma treated with the toxins in order to make more trustworthy deductions regarding their efficiency. To this end there have been added to my previously reported cases a few personally treated since the former publication and certain cases reported by Dr. Coley which have conformed to the criteria adopted in my earlier paper. Dr. Coley kindly sent me a copy of his address before the Third International Conference of Cancer Research held at Brussels in August, 1913. His monograph may be divided into five parts, viz.: the use of mixed toxins in inoperable sarcoma (81 cases), their use as a prophylactic after operations (9 cases), their use in inoperable carcinoma (8 cases), their use in the hands of other men (12 cases), and a tabulation of 125 cases also treated by other men. Our present inquiry is not concerned with use of the toxins in carcinoma nor as a prophylactic after operation. All of the other cases, 218 in number, have been abstracted and tabulated, as far as possible, after the manner of my own cases. Dr. Coley's recent paper on Sarcoma of the Long Bones in the *Annals of Surgery*, (1914, vol. lx, Nov., pp. 537-566) contains four cases not included in his Brussels address. These have been added, making a total of 222 cases. The data recorded has been, name or number of patient, age, sex, occupation, clinical diagnosis, duration of disease before operation or toxin treatment, history of trauma or irritation, nature of operation, interval between operation and toxins, size of growth before operation, size of growth when toxins started, site of injections, pathological diagnosis, tissue of origin, duration of treatment, maximum dose, character of reactions, effect of toxins on size and consistency of the growth and on pain, remarks of interest, and end result.

Only those cases in which data are given, which conform with the criteria adopted for an analysis of my own cases, have been selected for this series. In other words, all cases must have been proven by microscopical examination; all must have been primary or recurrent inoperable sarcoma, or cases in which the disease could not be eradicated by operation; all must have been under treatment at least three weeks; all must have been free from concurrent treatment (x-ray, radium, arsenical preparations, etc.). Of the 222 cases which have been abstracted 100 have been chosen as suitable for this analysis. Perhaps I have been very critical and have excluded cases which by others might have been judged worthy of consideration. The question is vital. The toxins have merit but the treatment is distressing. I believe, therefore, that conclusions furnished only by most rigorous criticism should be accepted.

Following the plan pursued in my previous paper I have arranged the cases in six groups determined by the effect of the toxins.

Group A includes those cases in which there was no appreciable effect. There were 12 cases.

Group B. includes those cases in which the growths softened but did not appreciably diminish in size. This softening may be fairly attributed to the toxins rather than to increased vascularity and cellularity associated with rapid growth; for it occurred at the site of the injections. There were 5 cases.

Group C includes those cases in which growths disappeared or practically disappeared, but returned. There were 20 cases.

Group D includes those cases in which growths disappeared but metastases simultaneously occurred. There were 10 cases.

Group E includes those cases in which growths diminished in size but still persisted. In this group have been included those cases in which inoperable masses have been so reduced that operations have subsequently been performed. A very few cases of this description have shown upon pathological examination no remaining trace of sarcoma. Such cases, in which the pathological reports have been made by pathologists of repute, have been included in Group F, apparent cures.

Growths treated with mixed toxins may disappear either by undergoing marked necrosis (becoming soft and fluctuant), by what appears to be simple absorption (probably the same process as the first but absorbing as fast as broken down so that no fluctuant tumor occurs), or by acute inflammation followed by resolution with a resulting fibrous mass. The latter process has been demonstrated microscopically in a series of photomicrographs in my previous paper.* A period of inflammation is followed by one of young connective tissue and blood vessels resulting eventually in fibrous tissue. The tumor in such cases is destroyed by an inflammatory process. With this microscopical evidence it seems fair to consider such cases apparent cures. All other cases with residual masses that have not been examined microscopically have been included in Group E. There were 14 cases.

Group F includes those cases which are apparent cures in which growths have disappeared and no metastases have occurred. There were 73 such cases.

Again following the plan pursued in my previous paper these 134 cases have been analyzed; first, according to type of sarcoma, and second, according to the tissue of origin or anatomical situation.

TABLE I.

ANALYSIS OF CASES ACCORDING TO TYPE OF SARCOMA.

Group	A	B	C	D	E	F	Totals
Spindle cell.....	2	1	5	1	1	22	32
Fibro-sarcoma ..	2				3	4	9
Round cell.....			4	1	4	14	23
Small	1	1	8	2	2	13	27
Large	3		1	1		1	6
Melanotic				5		1	6

* I am indebted to Mr. E. S. Brown of the pathological laboratory at the Massachusetts General Hospital for his care and skill in the production of these pictures.

Glant cell.....	1	1			1	11	14
Mixed cell.....	3	2	2		1	5	13
Leiomyoma					1	1	2
Angiosarcoma					1		1
Hypernephroma ..						1	1
Totals.....	12	5	20	10	14	73	134

In Table I* is shown an analysis according to the type of sarcoma.

Spindle Cell Sarcoma. It so happened in my previously recorded cases that the pathologists' reports indicated the type of spindle cell, small or large. This distinction was, therefore, made in the previous analysis. It was interesting to note that of the three cases of each type there were no apparent cures of the small cell type, whereas there was one of the large cell type. This distinction of the size of cell may not be important. It is seldom made in Coley's case reports. In this present analysis, therefore, both have been assembled under the head spindle cell. The term fibrosarcoma, however, has been retained. Of the former there appears 22 apparent cures, of the latter four; a total of 26 cases, that is, about 36% of the total number of apparent cures.

Round Cell Sarcoma. In my previously reported cases a differentiation between small and large round cell cases was made. This has been followed, as far as possible, in this series. In a considerable number this distinction is not made, so the general term round cell has been used. The apparent cures include 14 cases of round cell, 13 cases of small round cell, and one case of large round cell; a total of 28 cases or about 39% of the total number of apparent cures. I am interested to note only one apparent cure of large round cell type. In my previous paper I made the observation that of about an equal number of cases of each type there were no apparent cures of the large cell type, whereas there were two of the small cell type. This larger series apparently substantiates this observation. The treatment of inoperable round cell sarcomata with mixed toxins, therefore, offers reasonable expectation of benefit, especially the treatment of the small round cell type.

Melanotic Sarcoma. In the previous series of cases it was observed in cases with multiple melanotic growths that individual tumors might be destroyed but coincident with this local benefit untreated tumors were increasing in size and new metastases were forming. All cases fell in Group D. One case, however, in which the treatment of a single large melanotic growth was undertaken lived for two years and two months. This case was given the largest single dose I have seen recorded, 52 minims. He displayed great tolerance for the toxins. The prognosis appeared favorable, as previously reported, until a spree of nineteen days was indulged in. After

* In the tables both my successes and my failures have been recorded. The full title of Coley's Brussels address, however, shows that he wished principally to set forth cases successfully treated. Some failures, however, were included. These tables, therefore, cannot be accepted as showing the proportion of failures and successes.

this his tolerance was greatly diminished so that only a dose of 4 or 5 minims could be given and metastases in various tissues appeared in quick succession.* I was led to state that the toxins offered no expectation of benefit in cases of multiple melanotic growths but that they might be legitimately tried in cases with single melanotic growths. It is interesting to note in this larger series that five of the six cases fall also in Group D and that the other case, that of Dr. Greenwood of Leeds, England, was a single large growth. This case is an apparent cure, the only cure of a melanotic case that has come to my notice. These facts seem curiously to substantiate the conclusions previously made from observations of a smaller series of cases.

Giant Cell Sarcoma. There is much disagreement at present regarding the nature of these growths. Certain pathologists and surgeons maintain that they are true malignant tumors, i.e. capable of forming metastases (Coley, Eve, Maybury). Others admit that such growths are prone to recurrence but deny them malignancy in the sense of forming metastases. The name giant cell tumor (Bloodgood), instead of giant cell sarcoma, has, therefore, been suggested. Again Barrie, of New York, believes that the process is only inflammatory, an osteomyelitis. Without discussing these opinions it is true that many cases of this condition can be cured by one or more curettings or resection. Other cases on account of size or situation may require amputation. Still others, probably the smallest group, cannot be cured by surgery alone. I refer in particular to more or less extensive involvement of the vertebrae. In considering growths originating in the medullary cavity of bone it is to be remembered that some may arise from endosteum and others from marrow elements. It is to be remembered that osteoclasts are present and these, I believe, may be regarded as foreign body giant cells of endothelial origin. The presence of some giant cells in medullary tumors is, therefore, to be expected. It is to be remembered that some of these tumors remain limited to bone. They may be expansile but for a long period remain localized. Spontaneous fractures may occur and heal. This class may be regarded as one type of bone cyst and considered myxomata. We are all familiar with another type which more quickly ruptures the bone, invades the soft parts, grows with great rapidity, often to considerable size, and not infrequently causes death. In selecting cases for this series I have had this type of case in mind. The term giant cell sarcoma has, therefore, been retained. Finally these medullary growths do not, in the majority of cases at least, conform with the condition commonly called osteomyelitis.

In my previous series were reported four cases which it seemed fair to regard as giant cell sarcomata. Two of these were apparent cures.

* A detailed account of this case with photographs and photomicrographs is given in the *Boston Med. and Surg. Jour.*, 1914, Vol. clxxi, No. 7, August 18, 1914.

There have been added in this series ten cases including nine apparent cures, making a total of eleven apparent cures. The character of these cases, as shown in the case epitomies at the end of the paper, will, I believe, justify the use of mixed toxins in selected cases. Certain cases are appropriately treated by one or more curettings, others by resection, and still others on account of their size or situation by amputation. The records seemed to justify a preliminary trial of toxins in carefully chosen cases in which slowly growing tumors have ruptured more or less extensively into the soft parts rather than the immediate sacrifice of the limb. If such treatment is practised, the patient should understand that amputation may ultimately be necessary, and it should not be long deferred in the advent of increased rapidity of growth, repeated hemorrhages, considerable absorption, or superimposed infection. By this method with skilful judgment a few limbs apparently have been saved.

A small group on account of anatomical situation (more or less extensive involvement of the vertebrae) defy surgical eradication. These, I believe, should be submitted primarily to surgical attack, followed immediately by toxin treatment. The records justify the use of the toxins in such cases.

Mixed Cell Sarcoma. Under this head have been assembled cases with pathological returns of osteosarcoma, spindle cell osteosarcoma, chondrosarcoma, osteochondrosarcoma, etc. It has never been my good fortune to benefit with the toxins any cases of this class. This series, however, shows five apparent cures, viz: mixed cell tumor of the parotid, round and spindle cell sarcoma of the uterus, chondrosarcoma of the ilium, round cell osteosarcoma of the humerus and scapula, and spindle cell osteosarcoma of the superior maxilla.

There remain in Table 1 three cases, a leiomyoma, an angiosarcoma, and a hypernephroma, epitomies of which appear at the end of the paper. The first case (No. 56) was a leiomyoma of the uterus for which hysterectomy was performed. Within a few months the entire pelvis was filled with an inoperable recurrence of hard consistency and irregular outline, apparently involving the bladder. Mixed toxin treatment was instituted. The mass became smaller, softer, more movable, and pain ceased. Treatment was continued with periods of rest for about three years. Three years, eleven months later the patient was in excellent health and local examination showed only slightly more scar tissue than would be expected after an hysterectomy. This was apparently a case of malignant leiomyoma. I have at present under treatment a somewhat similar case referred by Dr. W. J. Mixer. A hysterectomy had been performed for fibroids. Tumors subsequently appeared on the back and paralysis of the legs ensued. Dr. Mixer removed as far as possible a growth involving the vertebrae, complete eradication was impossible. The patient is now able to walk with assistance.

Toxin treatment was instituted immediately after operation and has been continued for two months. Pathological reports: 1. Tumor over sacrum, probably leiomyoma; 2, Tumor on right shoulder, leiomyoma; 3, Specimen removed at operation on spine, spindle cell sarcoma. It is too early to predict the outcome but the course has been so far favorable.

The second case (No. 33) was a thrice recurrent angiosarcoma of the breast. Toxin treatment was instituted when the mass extended laterally from the sternum to the anterior axillary line and from the clavicle above nearly to the costal border below. It was fixed to the chest wall and composed of markedly protuberant nodules and considerably ulcerated. Mixed toxin treatment for eight months caused softening and progressive decrease in size. The mass was then operable and was excised. No pathological report is given but the patient was seen eight years later without evidence of recurrence. This case has been recorded in Group E.

The last case (that of Mr. Cornell of Sheffield, England) was a woman of 37 upon whom a transperitoneal nephrectomy was performed for hypernephroma. In four months toxin treatment was started for a huge recurrence and continued for four and a half months with entire disappearance of the tumor. A year later she was seen in excellent health without evidence of recurrence.

TABLE II.

ANALYSIS OF CASES ACCORDING TO ANATOMICAL SITUATION AND TISSUE OF ORIGIN.

Group	A	B	C	D	E	F	Totals
Nose and sinuses...			2			6	8
Tonsil	1	4				2	7
Parotid		1		1		3	5
Pharynx	1	1					2
Cervical glands....	(1)	4	(6)	1	(2)	7	(4) 12
Chest wall.....	(1)	(1)		1		1	2
Breast		1		1		1	3
Abdominal wall....						7	(2) 7
Axilla				1	(1)	1	(3) 2
Groin				(1)	1	2	3
Intra-abdominal ..	(7)	1			1	4	(2) 6
Pelvis	1	(1)				1	(2) 2
Uterus				2		3	5
Ovary		2		1		1	4
Kidney				1		2	3
Bone (not giant cell)	5	2	2	2	3	(1) 13	27
Giant cell	1	1			1	10	(1) 13
Fascia and muscle.	3	1	2	(1)	1	5	(2) 12
Skin and subcu.....				5		3	8
Nerve sheath						1	1
Orbit				1			1
Sperm. cord	1						1
Totals	12	5	20	10	14	73	134

ANALYSIS ACCORDING TO ANATOMICAL SITUATION AND TISSUE OF ORIGIN.

In Table 2 is shown an analysis of cases according to anatomical situation or tissue of origin. It was rather striking in my previous analysis to note that five of six intranasal and nasal accessory sinus cases were apparent cures.

The others fell in Group C, the growth practically disappearing but recurring. Two cases have been added in this series and it is interesting that one is an apparent cure, and the other falls in Group C. These six apparent cures include fibrosarcoma of the septum and ethmoid, giant cell sarcoma of the antrum and superior maxilla, large spindle cell sarcoma of the ethmoid, small round cell sarcoma of the antrum and ethmoid, small round cell sarcoma of the antrum, ethmoid, superior maxilla, posterior septum and nasopharynx, and spindle cell sarcoma of the ethmoid, superior maxilla and frontal sinuses. The case epitomies show the extent of these growths. I must conclude, as previously, that the toxins are apparently of value in sarcomata arising in the nose and accessory sinuses, whether round cell, giant cell, or spindle cell.

Of the Cervical Gland cases it will be noted that there are seven apparent cures of primary growths and four of metastatic extensions from disease of neighboring structures. The latter are indicated in parentheses. This plan has been followed throughout the paper. Only primary growths are considered in this analysis but, believing that the effect of toxins on direct extensions or metastatic growths might be of interest, I have represented such secondary processes in parentheses. The apparent cures of primary sarcoma of the cervical glands are cases 18-24 inclusive, all reported as round or small round cell type, and composing about 10% of the total number of apparent cures. Add to this number four apparent cures of metastatic involvement. It seems fair to regard the toxins worthy of trial in inoperable cases of this type.

The Abdominal Wall cases are seven in number, 5 of spindle cell type, 2 of round cell type, and all apparent cures. Two extensions to the abdominal wall from sarcoma of the ilium were also apparent cures.

The intra-abdominal cases show four apparent cures including three spindle cell and one round cell. These were all inoperable growths involving in one case the ascending colon, small intestine, omentum, and liver border, and in another case the cecum, omentum, and mesentery. In the previous series were recorded seven cases of intra-abdominal sarcoma, all failures. These however, were extensions from thigh, true pelvis, or spermatic cord, or metastases from distant tumors. The apparent cures noted in this table were all primary growths. The two apparent cures recorded in parentheses were spindle cell sarcomata of the abdominal wall involving the bladder.

Of the Bone cases (not giant cell) thirteen apparent cures are recorded; five spindle cell, five round cell, and three mixed cell. The bones involved included two cases of the maxilla, two of the vertebrae, two of the ilium, and one each of the radius, humerus, sternum, metatarsal, tibia, femur, and lower jaw. The results of surgical treatment of periosteal sarcoma of the

femur and upper humerus (including hip joint and interscapulo-thoracic amputations) are notoriously poor. An apparent cure of each is here recorded. It need not be stated that sarcoma of the vertebrae often defy surgical cure. Partial operations are necessarily followed by recurrence and subsequently by death. The case epitomies at the end of the paper are, I believe, sufficiently convincing to justify the use of toxins in these inoperable bone cases. The number of apparent cures, furthermore, comprises over 18% of the total number of apparent cures here assembled.

Of the Giant Cell Bone cases the series shows ten apparent cures including three cases with involvement of the vertebrae, two of the superior maxilla, and one each of the sacrum, ilium, inferior maxilla, radius, and femur.

Under heading *Fascia and Muscle* have been assembled all cases originating from these tissues except those specially listed under headings *Chest Wall* and *Abdominal Wall*. There appear five apparent cures of primary growths and two of secondary growths from the spine and metatarsal. Five of the seven are of spindle cell type, including two of the buttock, and one each of the thigh, knee, and calf. The remaining two are growths of the back, both round cell. Cases of sarcomata of the upper extremities appear among the failures in this series but not among the apparent cures.

Skin and Subcutaneous Tissue cases include sarcomata arising from cutaneous and subcutaneous benign growths (pigmented naevi, etc.). The apparent cures include a melanotic sarcoma of the neck, a spindle cell degeneration of a pre-existing benign tumor of the shoulder, and a round cell sarcoma of the lip.

In reviewing both tables the type of growth most benefited is seen to be the round cell, 39% of the total number of apparent cures. Of this type the small round cell responds very much more favorably than the large round cell type. The percentage of apparent cures furnished by other varieties is spindle cell 36, giant cell about 15, and mixed cell about 7. It is seen that primary growths of bone (not giant cell) furnish the greatest number of apparent cures, over 18%, the giant cell cases furnish about 15%, cervical gland cases about 10%, and nose and accessory sinus cases about 8%. It has been stated that the spindle and round cell cases were evenly divided in bone and intranasal and sinus cases. The cervical gland cases are all round cell.

Very striking relief of pain is occasionally observed with the use of toxins. Coley makes particular mention of this in cases 85, 104, 55, and 56, namely, periosteal spindle cell sarcoma of the humerus, giant cell sarcoma of the sternum, round cell sarcoma of the pelvis, and malignant leiomyoma of the pelvis. The most remarkable cases in this respect which I have observed are a spindle cell sarcoma of the pelvis, and a tumor of the upper jaw encroaching on

the mouth, nose and orbit, both kindly referred by Dr. S. J. Mixter. The first case (No. 54) prior to the institution of toxins suffered such agony that doses of $\frac{1}{2}$ to $\frac{3}{4}$ of a grain of morphine were necessary every two or three hours. During the twenty-four hours he would also receive phenacetin, aspirin, codeia, and cannabis indica. Shortly after the treatment was started only occasional small doses of morphia were necessary, some days none at all. The other case although evidently a very vascular sarcoma of the superior maxilla cannot be included in this series because no pathological report was obtained. This man, who had been accustomed to considerable doses of morphia, entirely omitted the drug after the toxins were started.

CONCLUSIONS.

1. From this critical survey it seems fair to conclude that mixed toxins of streptococcus and bacillus prodigiosus (Coley) are of value in certain cases of inoperable sarcoma.

2. The treatment of primary or recurrent inoperable sarcoma with mixed toxins must be intensive. The increment of the dose and the interval between injections requires some experience. This method of treatment is distressing and is never certain. This analysis has been undertaken, therefore, in the hope of ascertaining the types of case which offer reasonable expectation of benefit.

3. The institution of this treatment is unjustifiable in cases in which operative measures of reasonable safety offer possible hope for removal. A frank statement of the nature and the severity of reactions, and the probability of benefit should be made to the patient or some responsible person before the treatment is undertaken.

4. Seventy-three cases after most rigorous criticism have been regarded as apparent cures.

5. The small round cell type apparently offers the greatest expectation of benefit followed closely by the spindle cell type (excluding fibrosarcoma). Only a relatively small number of mixed cell type have been benefited. The use of toxins in cases with multiple melanotic growths does not seem justifiable but their use in single melanotic growths is legitimate.

6. Regarding the tissue of origin the greatest number of apparent cures have occurred in bone sarcomata (exclusive of giant cell cases) over 18% of the total number of apparent cures, with an equal division of round cell and small cell types.

7. Giant cell cases (as defined in the text) furnish about 15% of the total number of apparent cures. The records seem to justify preliminary trials of toxins in carefully chosen cases in which slowly growing tumors have ruptured more or less extensively into the soft parts rather than immediate amputation. With skilful judgment a few limbs have apparently been saved. If such treatment is practiced, the

patient should understand that amputation may ultimately be necessary, and it should not be long deferred in the advent of increased rapidity of growth, repeated hemorrhages, considerable absorption, or superimposed infection.

A small group on account of anatomical situation, viz., extensive involvement of the vertebrae, defy surgical eradication. These, I believe, should be submitted primarily to surgical attack followed immediately by toxin treatment. The records justify this practice.

8. Primary inoperable round cell sarcomata of the cervical glands compose about 10% of apparent cures.

9. Sarcomata arising from fascia and muscle, which have been apparently cured, have been situated in the lower extremity, abdominal wall, and back. They compose about 16% of the total number of apparent cures. Nine of twelve are of spindle cell type.

10. In a small number of cases the toxins produce striking relief of pain.

REFERENCES.

- Coley: *Annals of Surgery*, 1891, xiv, 199-220.
 Coley: *Amer. Jour. Med. Sciences*, 1893, N. S., cv, 487-511.
 Coley: *Amer. Jour. Med. Sciences*, 1894, cviii, 50-66.
 Coley: *Amer. Jour. Med. Sciences*, 1896, cxii, 251-281.
 Coley: *Johns Hopkins Hosp. Bull.*, 1896, vii, 157-162.
 Coley: *Jour. A. M. A.*, 1898, ii, 389-395; 456-465.
 Coley: *Annals of Surgery*, 1907, xlv, 321-359.
 Coley: *BOSTON MED. AND SURG. JOUR.*, 1908, cxviii, 175-182.
 Coley: *Surg., Gynec. and Obstet.*, 1911, xlii, 174-190.
 Coley: *Annals of Surgery*, 1913, lvi, 97-108.
 Coley: *The Treatment of Malignant Inoperable Tumors*, Brussels, 1914.
 Coley: *Annals of Surgery*, 1914, lx, 537-566.
 Coley: *Annals of Surgery*, 1914, lx, 772-774.
 Barrie: *Annals of Surgery*, 1913, lvii.
 Barrie: *Surgery, Gynec. and Obstet.*, 1914, xix, 42-52.
 Barrie: *Annals of Surgery*, 1915, lxi, 129-141.
 Czerny: *Munch. med. Wochenschrift*, 1895, xlii, 833-835.
 Harmer: *BOSTON MED. AND SURG. JOUR.*, 1914, clxxi, 253-261.
 Johnson: *N. Y. Med. Record*, 1894, xlv, 616-617.
 Moulin: *Lancet*, London, 1898, i, 354-359.
 Shield: *British Med. Jour.*, 1897, i, 193-194.
 Thomas: *BOSTON MED. AND SURG. JOUR.*, 1901, cxlv, 367-373.
 Tosler: *Vermont Med. Monthly*, 1909, xv, 217-218.
 Warren: *BOSTON MED. AND SURG. JOUR.*, 1896, cxxxv, 665-667.
 Whitman: *Jour. Med. Research*, 1914, xxix, 465-472.
 Winberg: *N. Y. Med. Record*, 1902, lxi, 681-684.

CASE REPORTS.

These reports are arranged in groups according to anatomical situation or tissue of origin of the growths. Under these various headings the arrangement is: first, apparent cures, followed in order by cases which have been classed in Group E, Group D, Group C, Group B, and Group A. Personal cases are recorded in detail. Other cases appear in abstract. Reference to de-

tailed reports of such cases appears in parenthesis after the case number in this series. Unless otherwise stated the number in parenthesis indicates the case number in Coley's Brussels Address. When the number is preceded by the word Table, it indicates the case number in the table at the end of Coley's Brussels Address.

INTRANASAL AND ACCESSORY SINUSES.

CASE 1. Personal Case. Referred by Dr. Scudder. Twice recurrent round cell sarcoma of antrum, ethmoid, superior maxilla, posterior septum and naso-pharynx. L. P. Italian woman of 32. House records E. S. vol. 676, p. 221; vol. 702, p. 37; vol. 716, p. 159; vol. 722, p. 57.

March 2, 1910. Operation, Dr. Scudder. Ether. Resection of right superior maxilla for sarcoma of the antrum. Ethmoid cells curetted out. Frontal sinus not involved. Sphenoidal sinus opened, contained pus, curetted.

Pathological Report by Dr. James Homer Wright. Malignant Lymphoma. "Specimen consists of the greater portion of the right superior maxilla. Tumor mass 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 homogeneous tissue. Microscopic examination (paraffin section). 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."

Oct. 20, 1910. Operation. Dr. Scudder. Ether. Partial removal of the septum for recurrent sarcoma.

Pathological Report. (1010-69.) Dr. Whitney. Malignant lymphoma. "A few bits of tissue showing on microscopical examination growth of lymphoid cells, in places slightly elongated and spindle-shaped."

May 11, 1911. Moved to operating room. Seen by Dr. Scudder. "Radical operation with enucleation of eye intended, but impossible to pass Crile ether tube on account of obstruction. Piece of growth removed with tube, evidently sarcoma. Process had extended to left side of nose and face. Only hope lay in attack of both sides of face. Deemed inadvisable."

Pathological Report. (Pieces of tissue removed with Crile tube) (115-42) Dr. Whitney. "Round cell sarcoma. Small pieces of tissue from the nostril, showing upon microscopic examination a small round cell tissue with new-formed blood vessels and remains of small glands scattered throughout it."

May 11, 1911. Toxin treatment instituted and continued three weeks. Maximum dose 3 minims. Reactions severe. Patient followed five months outside hospital, then referred to Boston Dispensary for consolidation in right lung. Later treated at Burroughs Place Clinic, at Long Island, and at Middleboro for tuberculosis of lung.

Feb. 28, 1914. Seen at her home. Still thin but of good color, has done her own housework for the past year, and expects to be confined in a few days. Examination through nose and mouth and opening beneath right eye, which exposes whole nasopharyngeal cavity, shows no evidence of recurrence.

March 26, 1914. Normal child born March 5. Mother still well.

Nov. 2, 1914. Operation, Dr. Scudder. A skin flap swung from forehead to cover defect in cheek following operation March 2, 1910. No evidence of recurrence found at plastic operation.

Criticism. A small round cell sarcoma of the nasopharynx, nose, and left side of face after radical attack of right side. Considered inoperable. No evidence of malignant disease 3 years 5 months after toxin treatment. Recorded in Group F.

CASE 2. Personal Case. Referred by Dr. H. A. Barnes. Small round cell sarcoma of antrum and ethmoid. Throat records, vol. xiii, p. 297. L. A. W., male, 55.

Oct. 14, 1910. Admitted to Ward G. For three months difficulty in breathing through nose. For two months epistaxis twice a week lasting one to six hours. For two months frontal headache, especially on the right, and nasal discharge.

Oct. 14, 1910. Operation, Dr. Barnes. Cocaine. Two large pieces of tissue snared from nose followed by profuse hemorrhage. Ether necessary to check bleeding by packing.

Pathological Report. Small round cell sarcoma. "A small piece of tissue showing upon microscopical examination a solid growth of round and slightly elongated cells infiltrating the tissue in all directions."

Nov. 28, 1910. Operation, Dr. Barnes. Ether. One and one-fourth inch incision on right side of the nose. Nasal process chiseled away and sarcomatous tissue exposed. Posterior nasal plug inserted. Mass scooped out with finger. Antrum then opened through canine fossa and found filled with growth, which was scooped and curetted out. The whole naso-antral wall was found to be destroyed. Antrum and right naris packed with gauze.

Dec. 5, 1910. Toxin treatment started and continued five and one-half months (May 23, 1911). Forty-nine injections. Maximum dose 10 minims. Reactions often severe. During this time the appearance of septum became suspicious and a small piece was removed which showed small round cell sarcoma. Toxins continued two and one-half months longer, at which time a note in the throat department states, "Nose clean; everything in fine condition." Patient had gained 25 pounds.

Dec. 12, 1911. (Seven months since toxins discontinued.) My record reads, "looks well, good weight and color. Working as janitor. No symptoms of recurrence. No evidence of same. Seen by Dr. Mosher who finds no evidence of recurrence."

Last seen Dec. 24, 1913 (two years, seven months since toxins discontinued). In excellent health, good weight and color, working steadily as janitor.

Criticism. A small round cell sarcoma of the antrum and ethmoid. Seems quite improbable that curetting eradicated such an infiltrating process, as recurrence showed. Seems fair to attribute apparent cure in part, at least, to toxins. Recorded in Group F.

CASE 3. Personal Case. Referred by Dr. Crosby Greene. Large spindle cell sarcoma of ethmoid and frontal bone. L. E. F., a woman of 46. House No. 180998.

Feb. 12, 1912. Admitted to Ward G with following history: Eight years ago first noticed movable

mass inside the nose, which was partially removed. Recurred one year later. At second operation (Dr. Greene) under ether a considerable quantity of tumor tissue and ethmoidal bone removed with cutting forceps. Pathological report, spindle cell sarcoma. No evidence of recurrence until last year when began to experience frontal headache and frequent epistaxis, and lately dizziness, nausea, and throbbing in head.

Feb. 12, 1912. Operation, Dr. Greene. Ether. Through an incision at side of nose and beneath eye the antrum opened. Its inner wall and middle turbinate removed. Ethmoidal region found filled with vascular growth which was evacuated with curette. A large portion of the right nasal bone was removed and cribiform plate exposed. Brain pulsation visible.

Pathological Report. No. 122-45. Spindle cell sarcoma. "A piece of growth from ethmoid showing upon microscopical examination bundles of large spindle cells interlacing irregularly. Blood vessels in many places with distinct walls."

Treatment with mixed toxins instituted in one week and continued six weeks. Reactions moderate. Maximum dose 4 minims.

Dec. 2, 1913. A letter from Dr. Greene states that one year after operation (Feb., 1913) no subjective or objective evidence of recurrence.

March 6, 1914 (two years since toxins discontinued). A letter from patient states that her health is very good and there is no indication of old trouble.

A letter received from patient May 29, 1914, states she is still in excellent health, two years, two months since treatment discontinued.

Criticism. An extensive infiltrating spindle cell sarcoma. An extensive operation by Dr. Greene. It may be argued that all of the growth was eradicated at operation. This is possible but at the time it did not seem probable. Perhaps this case should be excluded. It has been recorded in Group F.

CASE 4. Personal Case. Referred by Dr. Mosher. M. L., age two. Throat records, vol. xiv, p. 245.

Dec. 3, 1910, admitted to House with history of appearance of sore in the nose accompanied by much discharge and passage of pieces of tissue. The nose appears flattened and one-fourth inch of the anterior end of the septum has disappeared. The exposed septum is much thickened. Tuberculin skin test and Wassermann test negative. December 8, specimen removed for examination.

Pathological Report by Dr. Whitney: fibroma or fibrosarcoma.

Jan. 20, 1911. Operation, Dr. Mosher. Ether. Septum and thickened ethmoidal region removed as far as possible and packed with gauze.

Jan. 24, 1911. Treatment with mixed toxins instituted and continued five months. Reactions slight, rarely severe. Maximum dose three and one-half minims.

Patient has since been seen by me with rhinologist every few months. Now two years, eleven months since toxins discontinued, there is no subjective or objective evidence of recurrence.

Jan. 29, 1915. Patient still free from recurrence. (3 years 9 months since toxins discontinued.)

Dr. Whitney kindly re-examined the sections in March, 1914, and reported, as previously, fibroma or fibrosarcoma.

Criticism. Owing to the pathological report it may be argued that this case should be excluded. It has been included because the process involved not only the septum but extended up into the ethmoid cells. Recorded in Group F.

CASE 5. (Table, Case No. 88.) Case of Dr. J. C. Whitley of St. Louis, Missouri. Sarcoma of superior maxilla, frontal sinuses and ethmoid.

Pathological Report. Spindle cell sarcoma with giant cells. Toxin treatment instituted immediately after an incomplete operation. Maximum dose, 20 minims. Remains of growth sloughed out. Patient in excellent health without signs or symptoms of recurrence two years later. Recorded in Group F.

(To be continued.)

THE STUDY OF DISTURBANCES OF THE STOMACH.

By H. F. HEWES, M.D., BOSTON.

[From the Clinic of the Massachusetts General Hospital.]

(Continued from page 292.)

All physicians are familiar with the fact that stomach symptoms are perhaps the most common, at all events one of the most common, attributes of the human race. In the study of these manifold stomach conditions he must discriminate as far as possible, by his history record and physical examination, and tube examination in the cases not obviously cases of disease outside of the stomach, whether they are real stomach diseases, or part of a general condition, of debility, or nerve instability, or intestinal atony and constipation, and use the x-ray for their study where his judgment decides for it.

A third special method of investigation of much use in connection with the study of stomach cases is the examination of the feces for blood by the chemical blood test.

A constant or frequent blood finding in the feces in cases with symptoms pointing to stomach trouble is good evidence of the existence of ulcer of the stomach, or duodenum, or cancer. In some cases of duodenal ulcer it is our only means of making a definite diagnosis. Of course blood in the feces may come from hemorrhoids, or intestinal lesion, as intestinal cancer, or ulcer, or colitis. And some of these conditions may give apparent stomach symptoms. But often, as stated, this blood finding taken with other factors of the cases is of much value for the diagnosis of a stomach lesion.

This concludes the review of the methods of clinical study which are utilized in the investigation of cases with symptoms suggesting stomach trouble.

The exact method of procedure of clinical examination for diagnosis differs, of course, with individual cases.

It may happen that the first method of study, the record of symptoms as given by the patient, is sufficient for absolute diagnosis, and further investigation by special methods may be deemed unnecessary. This, for example, is the fact in some cases of bleeding ulcer having a clear record of recent vomiting of blood. Or it may be that this record with the record of physical examination gives a definite diagnosis of some disease outside the stomach, as appendicitis or tuberculosis, which may be deemed a sufficient cause of symptoms.

In all other cases, making the majority of cases with stomach symptoms, it is necessary, however, to go further and make at least a tube examination, and often an x-ray examination also. If the tube examination plus the record previously obtained makes a diagnosis, we may stop here. This is the fact in cases showing twelve-hour food stasis, for example. Such a finding means always obstruction of the pylorus, with rare exceptions due to ulcer or cancer, and often the tube examination tells which of the two, ulcer or cancer.

If with the record and tube examination, diagnosis is not clear, we may resort to x-ray examination. This may show definite evidence of disease, when tube examination is merely suggestive, or when it is entirely negative, or it may exactly locate a lesion already diagnosed by the examination.

The following records of cases taken from my own clinical records, will illustrate the method of procedure followed in the study of stomach cases, and the variation in this procedure according to the character of the particular case in hand. Special cases have been selected also to illustrate some of the most important points already reviewed in regard to the value of the various data obtained by the several methods of examination, for drawing conclusions for diagnosis.

CASE 1. R. L., age 30, Aug. 1, 1911. One week ago the patient, who had had no previous dyspepsia, began to have distress in the epigastrium, coming, perhaps one hour after meals and lasting one to two hours—there was raising of gas and sometimes sour regurgitation, but no vomiting. This has continued to the present time.

Yesterday the patient vomited a quart of red blood. The specimen was seen by her physician.

Examination: Patient rather pale. Hemoglobin, 65%. Physical examination otherwise negative. A diagnosis of bleeding ulcer of the stomach was made without further investigation. It was not considered desirable to use the tube and x-ray examination seemed unnecessary. In fact all that the tube could show would be blood, of which we had evidence in the history, and the x-ray examination would very likely show nothing, as is often the case with fresh bleeding ulcers. The feces examined on the first and second days of observation showed a strong positive blood test. This case could have been one of bleeding from esophageal varix but a diagnosis of ulcer seemed reasonable,