The treatment of malignant tumors by repeated inoculations of erysipelas : with a report of ten original cases / by William B. Coley.

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THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

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In a paper published in the *Annals of Surgery*, in September, 1891, entitled "A Contribution to the Knowledge of Sarcoma," I referred at some length to the curative effect of erysipelas upon sarcoma, reporting the results of inoculation in three cases recently treated by myself.

At the time I began my investigations in this most interesting subject I had not read of Fehleisen's experiments in Germany. While collecting the cases of sarcoma treated at the New York Hospital during the past fifteen years, I found a case that, to my mind, had convincing evidence that erysipelas possessed a powerful curative principle antagonistic to sarcoma. (Fig. 1.)

Whether or not this principle could be isolated or utilized in the practical treatment of sarcoma was quite another question, yet one of sufficient interest and importance to lead me at once into making a thorough study of the subject.

Before going further it might be well to give a few points of interest in the case I have mentioned:

This was one of round-celled sarcoma of the neck, occurring in a German, aged thirty-one years. Five operations had been performed

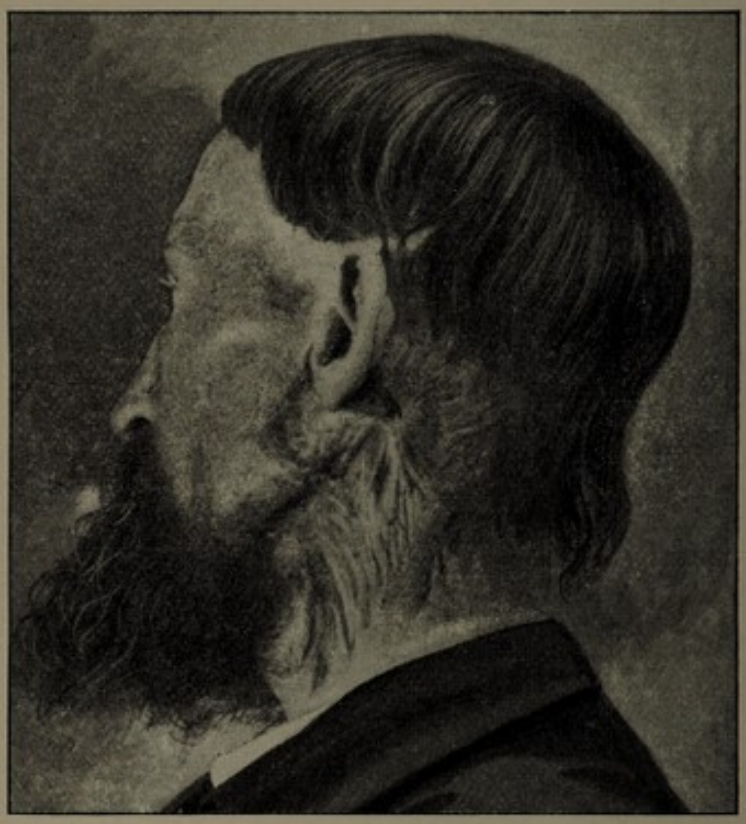
[1] Read (in part) before the Surgical Section of the New York Academy of Medicine, December 12, 1892.

by Dr. W. T. Bull within a space of three years. At the last operation it was found impossible to remove all of the tumor, and the case was considered hopeless.

Two weeks after the operation a severe attack of erysipelas occurred, followed by a second attack shortly after the first had subsided.

During the progress of the erysipelas the remains of the sarcoma entirely disappeared, the wound rapidly healed, and the patient was seen both by Dr. Bull and myself seven years afterward, at which time the photograph appended was taken.

FIG. 1.



Round-celled sarcoma of neck, cured by erysipelas. Photograph taken seven years after. (BULL'S case.)

The diagnosis in this case had been repeatedly confirmed by well-known pathologists, and there was no possibility of attributing the cure to any other cause than the erysipelas.

If erysipelas, a disease produced by a specific organism, could cure a case of undoubted sarcoma when occurring accidentally, it seemed fair to presume that the same benign action would be exerted in a similar case if erysipelas could be artificially produced.

Was it possible to produce an artificial erysipelas, and if so, what were its dangers and limitations? These were questions that immediately arose, and the answers to them, crude and imperfect though they be, I shall now endeavor to present.

In the course of a careful review of the literature of the subject I found that, aside from a vague and indefinite impression that tumors of doubtful character had been known to disappear after an attack of erysipelas, there was a certain amount of actual evidence. This evidence, though made up of facts few in number and scattered, was nevertheless strong.

It was made infinitely stronger by the publication of Fehleisen's paper in 1883, demonstrating the origin of erysipelas from a specific germ, and giving the results of a series of experiments upon five cases of malignant disease.

Having satisfied myself that the mortality from erysipelas uncomplicated was very small, I determined to inoculate the first case of inoperable sarcoma that should present itself.

I had but a short time to wait, and on May 2, 1891, I inoculated a case of sarcoma of the neck and tonsil (recurrent), which was kindly referred to me by Dr. Bull:

The patient was an Italian, thirty-five years of age, operated upon previously in Rome by Professor Durante, and in April, 1891, by Dr. Bull, at the New York Hospital. At the latter operation the growth was found too extensive to remove. At the time of my first inoculation the tumor of the neck was growing, and the right tonsil was the seat of a tumor the size of a hen's egg and almost completely blocking up the pharynx. Solid food could not be taken, and liquids frequently regurgitated through the nose.

The patient's condition was very bad. He was emaciated and cachectic. The dangers attendant upon an attack of erysipelas were explained to him, and in view of the hopelessness of his condition and the impossibility of obtaining further surgical relief, he consented to erysipelas inoculation.

The details of the earlier treatment are given in my former paper, and I will not repeat them here; suffice it to say that the inoculations were made by injecting small quantities of bouillon cultures ($\frac{1}{2}$ to 2 grammes) into the tumor itself, scarification (Fehleisen's method) having proved unsatisfactory.

The inoculations were continued at short intervals during May and a part of June. Slight local and constitutional reaction followed the inoculations, the tumor of the neck diminished in size, and the general condition improved. The tonsil tumor was also smaller and the voice much better.

During August and September the treatment was discontinued, and the tumors at once began to increase in size and the general condition to deteriorate.

October 1st they had reached their former size, and the patient's condition was little different from that at the time the inoculations were begun. At this time I succeeded in getting a culture of streptococcus erysipelatis kindly brought me by Dr. Farquhar Ferguson direct from Koch's laboratory, and I decided to make a further trial.

Five decigrammes of a fresh culture were injected into the tumor substance. Up to this time he had had no attack of true erysipelas, the

slight local reaction passing away in from twenty-four to forty-eight hours, and the temperature thereupon becoming normal.

Within an hour he had severe pain, nausea, vomiting, and a chill lasting forty minutes. His temperature rose to 105°, and within twelve hours a patch of perfectly typical erysipelas the size of the palm of the hand appeared upon the neck. This gradually extended over the face and head, and met upon the opposite side.

The disease ran the usual course, and I made little effort to check it, save to apply some ichthyol upon the forehead to prevent its extending to the scalp (which, I may add, it failed to do). At the end of ten days the pulse and temperature had become normal. The tumor of the neck began to break down on the second day, and discharged until the end of the attack. The discharge was not pus, but resembled the caseous material of a tubercular gland. The outlying nodules disappeared by absorption without breaking down. The tonsil tumor was smaller, but the diminution in size was not great. At the end of two weeks the tumor of the neck had disappeared, and there remained only the induration from the previous operations.

The appetite began soon to improve and he gained rapidly in flesh and strength. There has been up to the present time (twenty months) no return of the tumor in the neck, and although the tonsil tumor has remained about the same in size, its malignant character must have been greatly modified, as sarcoma of the tonsil is known to be rapidly fatal.

The patient's general condition at present (nearly two years) is very good, although he is suffering from a confirmed morphine habit which he had contracted previous to the inoculations.

My second and third cases were bone sarcomata (periosteal), one of the lower end of the femur and the other of the upper dorsal spine. These two cases are, as far as I have been able to ascertain, the only cases of bone tumors where inoculation has been tried; although Dr. Gerster reported at the Surgical Society, a year ago, a most remarkable case of sarcoma of the lower end of the femur, with amputation at the trochanter minor, followed by rapid recurrence in the stump. An attack of accidental erysipelas ensued a few weeks later, whereupon the tumor entirely disappeared, and the patient was seen by Dr. Gerster three years afterward, free from recurrence.

The results in my two cases, although temporarily beneficial, were not successful from a curative point of view. It is worthy of note, however, that in neither case was erysipelas obtained. The reaction, both local and constitutional, resembled exactly that which occurred in the early treatment of the first case; and the slight improvement compared with that which I have observed after true attacks of erysipelas, has led me to regard the presence of the streptococci themselves as a very important factor in destroying the neoplasm. My own experiments in the use of sterilized cultures of erysipelas, as well as the recent researches of Stronck, still further confirm this view.

My fourth case was a very large inoperable carcinoma of the face involving the entire left side and adherent to the bony structure. The patient was seventy-five years of age and had been treated at the New York Hospital for several weeks with pyoktanin injections (150) without any improvement.

I inoculated him in May, 1891, with a bouillon culture of the same stock that I had used in my first case. Slight local and considerable constitutional reaction followed, the temperature rising to 102½° and accompanied by some nausea and vomiting. The reaction occurred ten hours after inoculation, and subsided in forty-eight hours. The inoculations were discontinued after three injections, owing to inability to treat the patient at his home or to obtain a suitable place in a hospital.

The effect of the inoculations upon the tumor was not apparent beyond a slight softening. In this case, as in the two preceding ones, there was no real erysipelas produced.

CASE V. *Very large sarcoma of the back; recurrent; inoculation with erysipelas; failure to produce erysipelas.*—The patient was a man aged forty-five, a carpenter by trade, without history of hereditary taint, and who had always been well until three years before, when, without any injury, a swelling appeared over the right scapula. At the end of one and a half years it had reached the size of a cocoanut, and was removed at St. Luke's Hospital by Dr. Francis H. Markoe.

Recurrence took place four months later, but the patient delayed coming back to the hospital until February, 1892, at which time the tumor had become inoperable. It occupied the entire mid-scapular region, and its semi-circumference vertically and transversely was 17½ and 18½ inches.

Through the kindness of Dr. L. Bolton Bangs and Dr. Markoe, the case was referred to me with a view of trying erysipelas.

The cultures which I had used the previous fall had become too attenuated and I was unable to obtain any fresh ones. The patient was kept two weeks in the erysipelas ward of Bellevue Hospital, and although surrounded by patients in all stages of erysipelas, and inoculated repeatedly by direct means, it was found impossible to produce erysipelas, and he was discharged.

CASE VI. *Large sarcoma of back and groin; operation (groin tumor), recurrence in four weeks; erysipelas inoculation; entire disappearance of both tumors; recurrence three months later; second inoculation; second disappearance; recurrence in back, not in groin.*[1]—The patient, a German, forty-six years of age, cigar-maker, with a good family and personal history, applied at the Hospital for Ruptured and Crippled early in January, 1891, for treatment for a swelling in the right groin.

At that time there was a tumor the size of a goose-egg—hard, slightly nodular, deeply seated in the region of the inguinal glands without any signs of an inflammatory nature. Hernia could easily be excluded, and the usual causes of an adenitis were absent. The patient had first noticed the tumor five months before; it had slowly but steadily increased in size, and was slightly painful. I made the diagnosis of malignant disease, in spite of the fact that careful questioning failed to elicit any history of a primary tumor elsewhere. A few days later I operated

[1] As this is, perhaps, the most interesting and suggestive of my cases, I give it somewhat in detail.

upon the tumor of the groin, at the Post-Graduate Hospital. The tumor was found to consist principally of degenerated glandular tissue, but no pus was present. The microscopical examination was unsatisfactory. While putting on a spica bandage I discovered a large flat tumor in the lumbar region of the back, measuring six inches by four, elliptical in shape, and projecting from the normal surface about one-half to one-inch. It was very hard and nodular, presenting numerous tuberosities. Its color varied from a bright red to a plum color. It was freely movable, and was evidently situated entirely in the skin and subcutaneous tissue. The patient stated that it had been there five years, but having caused him little inconvenience, he had paid slight attention to it. In

FIG. 2.

Sarcoma of back and groin. Entire disappearance after erysipelas inoculation. (COLEY.)

fact, his knowledge of pathology was so crude that he had regarded it as "simple hemorrhoids," his idea of the latter disease having been gained from an afflicted friend.

Other than an indefinite history of injury in the army in 1870, no cause could be found for the tumor.

Soon after leaving the hospital Dr. Geo. H. Fox kindly saw the case with me, and his diagnosis was sarcoma of the skin. A photograph was taken at the time, February, 1891, shown in the accompanying cut.

Shortly afterward I removed two sections of the tumor under cocaine, for microscopical examination, and the diagnosis of sarcoma was confirmed by the careful examination of Dr. Farquhar Ferguson, the pathologist of the New York Hospital. At this date, February, 22, 1892, the tumor of the groin had already recurred and was growing rapidly. The tumor of the back was also increasing in size. In view of the rapid recurrence in the groin and the large size of the tumor of the back the patient was advised, both by Dr. Bull and myself, to have erysipelas tried. After some deliberation he consented, and on the 21st of April, 1892, I began inoculations.

I inoculated him, as in the preceding case, with bouillon culture injected into the tumor itself, using in this case a freshly prepared culture, kindly furnished me by Dr. T. M. Cheesman, of the laboratory of the College of Physicians and Surgeons of this city, from material which I had obtained from a recent case of erysipelas.

During the first three weeks of treatment the inoculations were made at intervals of two to three days. Well-marked constitutional reaction followed, accompanied by slight local redness at site of puncture; the condition returning to normal at the end of twenty-four to forty-eight hours. The effect on the tumor was a perceptible decrease in size; there was no formation of pus, nor was there any breaking down of the tumor tissue. At the beginning of the fourth week I used a new culture sent me from the laboratory of the Johns Hopkins Hospital. The first injection of 7 decigrammes produced a reaction quite similar to that obtained from the other culture. The second, of 1½ grammes, two days later, produced a perfectly typical attack of erysipelas, both in the back and groin (injections having been made in both places).

Four hours after the inoculation the patient had a very severe chill, with nausea and vomiting and marked prostration. The temperature rose to 105½°, and the pulse to 130°. The subsequent history was that of a typical but severe attack of erysipelas. The disease did not extend over a very large area, although no measures were taken to check it.

From the beginning of the attack the change that took place in the tumor was nothing short of marvellous. It lost its lustre and color, and had shrunk visibly in size within twenty-four hours. Several sinuses formed the second day and discharged necrosed tumor tissue. A few days later the tumor of the groin, which was about the size of a goose-egg, and very hard, when the inoculations were begun, broke down and discharged a large amount of similar material.

This continued for two weeks, after which time the sinuses gradually closed. The most projecting portion of the tumor of the back ulcerated over an area one and a-half inches in diameter, but this rapidly healed.

Three weeks from the date of the attack both tumors had *entirely disappeared*, and there was scarcely any induration remaining. His recovery from the erysipelas was retarded somewhat by an unusual complication.

During the early part of the inoculation treatment (before the attack of erysipelas) he received a blow upon the chest while scuffling with another patient. Four weeks later, when recovering from the erysipelas, he began to feel pain in the region of the injury, and soon after a diffuse swelling appeared.

The temperature ranged from 101° to 102½° for a week, and the swelling gradually increased in size. There was no redness, but fluctuation could be detected, and a needle introduced in the mammillary line between the fourth and fifth ribs drew thick creamy pus.

The following day I made an incision under cocaine anæsthesia, and found a large abscess connecting with the pleural cavity and lung itself, as shown by the passage of air through the wound, and the fact that the patient for several days (before and after operation) expectorated a large amount of purulent material, exactly like that found in the abscess. About ten ounces of pus was evacuated, the cavity washed out, and a drainage-tube inserted. The tube was withdrawn at the end of ten days, and the sinus had entirely closed two weeks later.

The patient's general condition improved rapidly. He gained seven pounds in twelve days. There was no recurrence of the tumors until July 1st, when a small nodule, the size of a pea, appeared at the site of former tumor in the back.

July 18th there were six small nodules within an area of from two to four inches, the largest of which was seven-eighths of an inch in diameter.

July 3d inoculations were begun again, but no reaction was obtained until July 19th, when one gramme of a culture sixteen days old, fifth generation, produced a chill eight hours later, followed by a rise of temperature to 103½°. After two days a small sinus formed and necrosed tumor tissue came away.

One nodule, which was seven-eighths of an inch in diameter when the injection was made, disappeared at this time, but the effect on the rest of the nodules was only a temporary check. They grew rapidly afterward, and by October 1st had coalesced, forming a flat tumor similar to the original one, and measuring two and a half by four and a half inches. The nodules had also reappeared in the right groin. The patient was sent to the New York Cancer Hospital Cottage in order to have the erysipelas inoculations more systematically carried out. He was given injections of $\frac{1}{12}$ to 2 grammes (of bouillon culture of the same stock as that used in the spring) every other day for two weeks. I could not produce an erysipelas, and the slight reactions failed to diminish the size of the tumor, although they checked its growth.

At this point I succeeded in getting a new and virulent culture from a case of uncomplicated facial erysipelas, seen on the day of its development, before treatment.

The fact that the temperature was 106½° the first day of the disease made me hopeful that could I succeed in isolating them, the streptococci would be virulent. I made cultivations upon five tubes of agar-agar, and succeeded in getting pure cultures in two of them. These I first tested upon rabbits, and then proceeded to use them in the case I am describing.

The first injection was made October 23, 1892; 7 decigrammes, second generation, six days old, of a bouillon culture were injected into the tumor. A severe chill occurred three hours later, and the temperature rose to 104½°. October 24th the temperature had fallen to 101½°, and as there was no evidence of erysipelas in the vicinity of the inoculation a second injection of 7 decigrammes was given October 25th. The temperature remained normal. November 5th, 2 grammes of a culture ten days old (second generation) was followed by a severe reaction, and a temperature of 104½°, which, however, fell to 100° in six hours.

From October 23d to November 14th the inoculations were kept up at short intervals, and followed by the results just described. The tumor was slightly diminished in size, but grew rapidly as soon as the inoculations were stopped.

November 14th. Careful measurements were taken of the tumor of the back, and were as follows: 5 by 3½ inches, with ½ by ¾ inch projection.

An injection of 1½ grammes two weeks old, of exactly the same culture tube as that used at the previous inoculation, was followed by a chill fourteen hours after, and a rise of temperature to 105°. A patch of

erysipelas soon appeared (some distance from the point of inoculation), and the disease ran a typical course, lasting a week.

The area of erysipelas never exceeded eighteen inches in diameter, and was chiefly confined to the right buttock. No attempt was made to limit it. The temperature, after the first day, ranged between 101° and 103½°, and at no time was the condition serious

The changes produced by this attack of erysipelas were no less remarkable than those that occurred during the former. Within twelve hours of the onset the tumor became dull and lustreless, and began to break down and soften.

Four or five sinuses formed, from which degenerated tissue escaped during the entire course of the erysipelas. At the end of thirty-six hours the tumor had diminished one-half, and at the end of a week there was nothing left save slight thickening and induration at the site of the tumor. The nodules in the groin had entirely disappeared.

Two weeks later (December 1, 1892), the induration in the back had perceptibly increased, and several suspicious-looking places had appeared on the surface, showing that the tumor had not been entirely destroyed.

December 7th. The nodules had increased rapidly in size, and injection of 1 gramme, second generation, twenty days old, was given.

Scarification and multiple punctures were also tried on the normal skin near the tumor.

The inoculation was done at 10.30 A.M. At 1 P.M. there was malaise and headache, nausea and vomiting at 2 P.M., and at 3 P.M. the temperature was 105.° At 8 P.M. it was still $105\frac{2}{10}$°, and pulse 140. It had fallen to 101½° the following morning (December 8th), and there was no evidence of a new attack of erysipelas, although the tumor was smaller.[1]

CASE VII. *Sarcoma of the breast; seven recurrences; inoculation of erysipelas; partial disappearance of the tumor; recurrence; operation; inoculation repeated. (Still under treatment.)*—F. P., thirty-eight years of age, single; first noticed a tumor in the left breast five years ago. Her family and personal history was good, and she had no recollection of having injured the breast.

It grew steadily, and was somewhat painful. Several physicians and surgeons were consulted, and all considered it a cystic adenoma, and advised letting it alone.

In September, 1889, it showed undoubted features of malignancy, and was removed by Dr. Webber, of Cleveland, Ohio. It recurred four months later, and in five weeks had reached the size of an orange. The subsequent history up to the time I first saw her (June 1, 1892) was simply a repetition of operation and recurrence.

The seventh operation was performed by Dr. Bull, at St. Luke's Hospital, in April, 1892, at which time a large tumor was removed. Recurrence took place before the wound had healed, and June 1st the growths had reached the size indicated in the figure. (Fig. 3.)

In view of the hopelessness of benefit from further operation, the erysipelatous treatment was suggested to her by Dr. Bull, and she decided to have it tried. She was transferred to the New York Cancer Hospital Cottage, which was kindly placed at our disposal by the board,

[1] A week later, a spontaneous attack of erysipelas occurred in the same region as the last; and during the three weeks following, two similar attacks occurred, though milder in type.

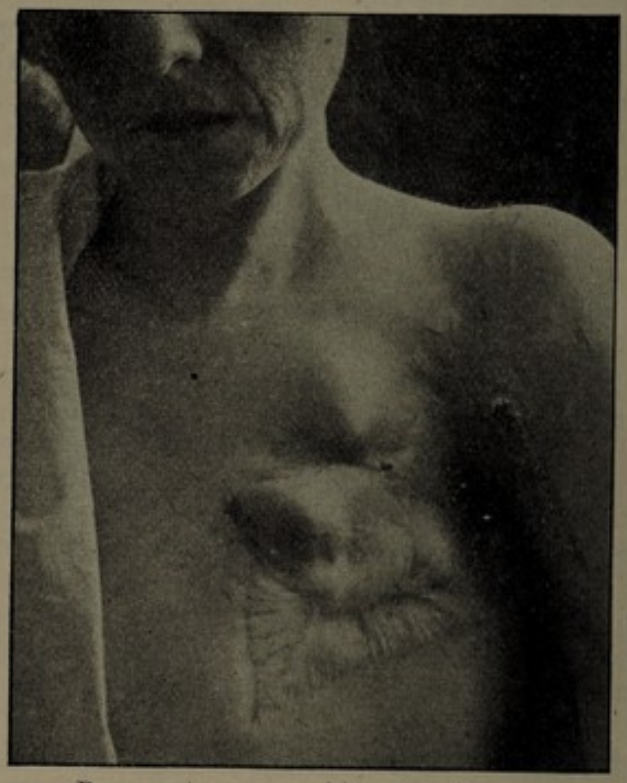
and June 2, 1892, the first inoculation was made by Dr. Bull and myself.

There were three separate tumors present in the left mammary region, 1½ inches, 2 inches, and ¼ inch in diameter, respectively.

The two larger ones were fixed to the chest-wall.

One and a half grammes of a culture five weeks old was injected into each of the two larger tumors, at 9 P.M., June 2, 1892. Temperature before injection was 98½° Two hours later there was intense pain, followed by a chill lasting more than an hour. At 3 A.M. the temperature had risen to 104.2°. The patient had severe vomiting and purging.

FIG. 3.



Recurrent sarcoma of breast. (COLEY.)

The next day, June 3d, there was an erysipelatous blush, extending seven inches across toward the right side. The disease ran the usual course, and at the end of a week the temperature had fallen to normal. The tumors broke down on the second day and discharged degenerated tissue, as in the preceding cases. The tumors decreased very much in size, one of them almost disappearing. They soon began to grow again, and others appeared in neighboring parts.

The inoculations were repeated, but a second attack of erysipelas was not produced until July 2d.

June 30th. At this time the lower tumor was scraped out with a sharp spoon under cocaine, and ten minims of culture, two weeks old, put into the wound. Twenty-six hours later she vomited and had chilly sensations, but no distinct chill. The temperature was 99.4°, and steadily rose until 12 M., July 4th, when it had reached 104°. It remained high for several days, reaching 105° in two days.

The erysipelas spread over a considerable portion of the back and down the left arm to the hand.

The temperature did not fall to normal until the eleventh day of the disease.

Although all of the nodules were diminished in size and some even disappeared, the check proved but temporary, and they soon began to increase in size.

Although the last attack of erysipelas was a severe one, the recovery was very rapid, and the general condition was soon as good, if not better, than before the attack.

The tumors grew very rapidly and were exceedingly painful. In October there were three distinct tumors, the largest of which was as large as a cocoanut, without ulceration, very soft, almost cystic in feel. There was a second tumor, as large as a large orange, a fungoid mass with a small pedicle.

Both of these were removed by operation in the latter part of October, and the large areas left uncovered by skin healed with remarkable rapidity.

She has gained considerable weight and strength, and there now remains a tumor the size of half an orange, which has been treated by repeated inoculation the past two weeks. The growth has been checked, but the tumor has not decreased in size.

I have not yet been able to produce a third attack of erysipelas in this case.

The general condition is better than last June, and there is no evidence of general dissemination.[1]

Case VIII. *Recurrent carcinoma of the breast; repeated inoculations of erysipelas; diminution in size of tumor; improvement temporary.*—The tumor occurred in a woman forty years of age, who was married and had had children. Predisposing causes were to be found in a family history of cancer, and also in a personal history of mastitis. The tumor was first noticed one and a half years before. Four operations had been performed within less than a year. The tumor at the time of inoculation was the size of a goose-egg, 5 by 3 inches, and occupied the upper part of the region of the left breast. The growth was markedly protuberant and ulcerated over an area the size of a silver half-dollar. A thin, serous discharge, very profuse, necessitated frequent dressings. There was also a hard tumor, the size of an egg, adherent to the skin on the right breast, which was unmistakably carcinoma.

Inoculations were begun August 1, 1892, and continued at short intervals for two months. Moderate constitutional reactions followed the injections, and there was partial degeneration of the tumor, and considerable diminution in its size. The general condition of the patient was perfect, and not perceptibly the worse from the treatment. The reaction usually passed away in twenty-four to forty-eight hours, and the patient was able to be up and out most of the time. I did not succeed in producing a true attack of erysipelas, although I used the same cultures as in the preceding case.

The inoculations were discontinued in the early part of October, and the tumor began soon to increase in size.

Case IX. *Recurrent carcinoma of the cervical glands; repeated inoculations; partial degeneration of tumor.*—The patient was a man, fifty-five

[1] March 8, 1893. The patient's general condition is about the same. She is being treated with injections of the toxic products of erysipelas.

years old, operated upon by Dr. Frank Hartley for a large carcinoma of the neck in July, 1892, with rapid recurrence following.

He was treated for three weeks in October, 1892, at the New York Cancer Hospital Cottage, with repeated inoculations of a pure culture of erysipelas.

Marked reaction followed, but erysipelas was never produced.

The larger tumor (small egg) broke down, and for several days there was considerable discharge of degenerated tissue, and the tumor decreased in size about one-third. Failing to produce erysipelas, I advised further operation with a view of trying the erysipelas from new virus in the event of recurrence.

CASE X. *Large carcinoma of inguinal glands following amputation of carcinomatous penis one year before; repeated inoculations; temporary improvement.*—The history of this case, as far as the erysipelas is concerned, is almost exactly parallel to the one just described. The tumor was the size of an orange, in the right inguinal region. The patient was seventy-five years of age, and very feeble, having chronic bronchitis and a weak heart. I did not succeed in giving him erysipelas, yet partial degeneration of the tumor followed the repeated injections of the streptococci.

The treatment was discontinued, owing partly to his weak condition and to the attenuated condition of the virus.

In addition to these cases of my own, I have collected and tabulated all the reported cases of carcinoma and sarcoma in which erysipelas, either spontaneous or artificial, intervened. It is upon a careful study and analysis of these cases, as well as upon the more practical experience derived from my own cases, that my conclusions are based.

Time will not permit me to go into these cases in detail, and I can do nothing more than give a brief summary of the results.

We find a total of 38 cases of malignant disease in which an erysipelas has occurred, either by accident or intent.

Of these 38 cases the erysipelas occurred accidentally in 23 cases, and was the result of inoculation in 15 cases (including my own); 17 cases were carcinoma, 17 cases were sarcoma, 4 either sarcoma or carcinoma.

The immediate and final results were as follows:

Carcinoma. Of the 17 cases, 3 were permanently cured. In addition, 1 case of probable carcinoma (Hutchinson's) was well five years after the attack of erysipelas. Of the remaining 13, 10 showed improvement, which, although temporary, undoubtedly added to the life of the patient in most cases. One case (Janike's) died, as a result of the erysipelas, on the fourth day.

Sarcoma. In turning to sarcoma we find the curative action of the erysipelas even more marked. Of the 17 cases of sarcoma we find 7, or 41 per cent., well and free from recurrence from one to seven years after the attack of erysipelas. Nearly all of these 7 cases have a remarkable history. The cases of Dr. Bull, Dr. Gerster, and my own have already been described.

The remaining 4 were as follows: The first (Biedert's) was a

very large round-celled sarcoma, involving mouth, face, nose, and orbit of a child ten years of age. The features were greatly distorted, and the general condition so bad that death from exhaustion was anticipated soon. While in daily expectation of being obliged to do a tracheotomy, a severe attack of facial erysipelas occurred. The tumor disappeared, as if by magic, during the course of the erysipelas. The child recovered, and at the end of a year was perfectly well, with no trace whatever of recurrence.

The next case (Brun's) was a melanotic sarcoma of the breast, with entire disappearance, and no recurrence.

The sixth case (Busch's) was a multiple sarcoma of the face that entirely disappeared after an attack of facial erysipelas, and did not return.

The seventh case (Kleeblatt's) was a lympho-sarcoma of the neck, very large; the erysipelas in this case being the result of inoculation.

In addition to these seven cases there is one other, a probable sarcoma of the breast, that was cured.

Ten of the remaining eleven showed more or less marked improvement; in some cases the tumor entirely disappearing, and not recurring for several months.

One case died as a probable result of the erysipelas, which was in this instance accidental.

To put the result still more briefly: In carcinoma, 17 cases, 3 cures, 17.6 per cent.; 1 death, 5.9 per cent. In sarcoma, 17 cases, 7 cures, 41 per cent.; 1 death, 5.9 per cent.; 4 sarcoma or carcinoma, 2 cured.

These cases have been in no way selected, and I have made every effort to include all cases resting upon competent authority, yet it might be urged as an objection to accepting these figures as representing the true percentage of cures, that cases have probably occurred which, owing to no marked improvement following the erysipelas, naturally failed to be reported. This objection, though valid as far as the accidental cases are concerned, would cease to hold in the cases of inoculation for the reason that, being so few in number, all, or nearly all, have probably been reported.

Grouping by themselves, then, the cases where the erysipelas was artificially produced, we find 7 cases of carcinoma, 1 cure, or 14.3 per cent., and 8 cases of sarcoma, 2 cures, 25 per cent. These cases were as follows: Fehleisen, 2; Kleeblatt, 2; Busch, 1; the remaining 3 cases being my own.

These figures may then be taken to fairly represent the curative effect upon carcinoma and sarcoma in the worst cases; and when we reflect that in nearly every instance the tumor was not a primary growth, amenable to operative treatment, but either a recurrence after operation had been tried and failed, or from its nature inoperable, then and then

only are we in a position to fully estimate the importance and value of erysipelas as a *curative* agent.

I have purposely excluded in the foregoing analysis 8 cases of my own treated by *repeated injections* of erysipelas cultures, which, without producing erysipelas, caused marked improvement in the tumors. These cases should be grouped by themselves, and they bring us back to the question regarding the nature of this *curative principle*, which, however variable its action, must be regarded as having a constant relation to erysipelas.

In my former paper I referred briefly to the different theories offered in explanation of this benign action, and even then I was inclined to believe it due to "antagonistic bacterial action," the neoplasm being regarded as dependent upon some unknown micro-organism.

Since that time the evidence in favor of the micro-parasitic origin of cancer has been steadily and rapidly accumulating until at the present moment it rests little short of absolute demonstration. Time will not permit more than a brief mention of the more salient points of this evidence, yet since a proper appreciation of its character and strength is necessary to anything like a clear understanding of the probable action of erysipelas upon malignant tumors, we cannot pass over it unnoticed. We shall consider:

1. *The close resemblance of cancer to other diseases known to be of bacterial origin.* The striking analogy between cancer and tuberculosis was noticed long before the tubercle bacillus was discovered. Sir John Simon in 1877 clearly pointed out this analogy, and in fact even then argued very strongly in favor of a micro-parasitic origin of cancer. His paper states the points at issue so clearly and briefly, and moreover the facts adduced and the conclusions drawn—showing as they do an almost prophetic insight—make it a paper that can be read with the greatest interest and profit to-day. He pointed out the error in the earlier investigations in allowing the "anatomical forms," interesting enough in themselves, to obscure the more important "property of infectiousness," which he regarded as the "real puzzle" of the disease. "The anatomical forms are matters of mere local accident, but the infectiousness of cancer represents its very cause." He showed that the element of heredity plays an entirely different rôle in cancerous and non-cancerous tumors; that while in the latter the hereditary influence often seems to be the *entire* cause of the tumor, an "embryonic fault" belonging to the same pathological class as supernumerary toes and fingers—in *cancer* it supplies only that portion of the cause which, as in tuberculosis, is familiarly known as *predisposing conditions*. This opinion we know is generally accepted at the present day. There is, moreover, a growing tendency to no longer adhere to the stereotyped classification of "tumors," and we venture to predict that in the near

future, instead of "tumors," a class at present embracing elements without the remotest analogy either in their etiology or mode of development, we shall have two main groups—the first of which might be designated as *congenital hypertrophies;* the second, *neoplasms,* etiologically dependent upon infection from without.

This statement may seem a trifle strong, since Cohnheim's embryonic theory of the origin of cancer is not only still held by the larger body of medical men, but has quite recently been championed by Baumgarten in Germany as well as by distinguished pathologists in this country. In spite of all the objections and criticisms, the micro-parasitic theory has steadily gained ground, and just now the confirmations are rapidly outnumbering the objections. These objections, the most of which were formulated by Cohnheim himself, ten years ago, have nearly all been answered. He argued that cancer could not be of microbic origin, first, because it was neither epidemic nor endemic. Tuberculosis is neither epidemic nor endemic, yet due to Koch's bacillus. Malaria is neither contagious nor epidemic, yet is caused by an intra-cellular parasite; again, tetanus is not contagious, and hardly more endemic than cancer itself, as shown by the researches of Haviland, and confirmed by recent investigations.[1] The second objection was that cancer could not be inoculated from one individual to another or to animals.

Cancer has been transferred from one part of the body to others in the same individual (Hahn and Von Bergmann) by inoculation, and moreover, it has been transferred from one animal to others in a few cases. That most of the experiments in inoculating animals have failed is really no objection to the theory. We know that there are many vegetable and animal parasites whose life history embraces a long cycle of changes in form and development, only a brief portion of which is found in the "host."

The *evolution* of *parasites* is a subject of great interest and importance, yet one that, as yet, has been but little investigated by the trained naturalist and biologist.

For a clearer understanding of the "laws of parasitism," and their relation to specific diseases, we are much indebted to the recent and valuable contribution of Dr. Joseph Frank Payne, of London. If his view, that there is a definite relation between the contagiosity of a specific disease and its chronicity be correct, we at once see a striking analogy between cancer on the one hand, leprosy and tuberculosis on the other, and there is no need to go further for an explanation of the slight contagiosity of cancer. Ballance and Shattuck go so far as to assert that "there is no fact in the etiology or life history of carcinoma or sarcoma that has not its counterpart in tuberculosis."

[1] The researches of Gueilliot prove cancer to be mildly contagious.

2. *Analogous diseases in animals and plants known to be of parasitic origin.* In the vegetable kingdom we find a large variety of "tumors" known as "galls." One by one these have all been proven to be of parasitic origin. If we turn to the lower animals, we find in "coccidial infection" an analogy so striking, that many observers have considered it identical with cancer. Without entering into any discussion of this question, this much may be regarded as proven: That certain low organisms or protozoa known as coccidia, have been found in animals, chiefly rabbits; that they possess the very *rare* property of being able to set up a proliferation of epithelium; that in the animals in question, and at least in one case (Leuckhart's) if not in two cases in man, they have produced multiple tumors associated with the same clinical symptoms and pathological changes that are found in true cancer.

We must further admit that several independent observers, notably Sawtschenko on the Continent, and Ruffer and Walker in England, by the use of improved methods of staining have been able to demonstrate the constant presence of protozoa in a very large number of specimens of carcinoma. That these are true parasites and not "invaginated cells" or "degenerated metamorphoses," as many have been inclined to regard them, has been very recently confirmed by the testimony of Metschnikoff, the highest living authority in micro-zoölogy.

These protozoa are so similar to the coccidia already referred to, that they can scarcely be differentiated. Whether or not they are identical, seems to me a matter of indifference; that they are very closely allied forms seems more than probable. That they have not yet been cultivated outside the body is no evidence against their being the cause of cancer, when we consider how much time it has taken to discover their mere presence.

If, with a distinguished authority, we admit that "for the development of cancer it is necessary that there should be a continuous irritation, and one capable of multiplication," and knowing as we do that the irritants capable of fulfilling these conditions are limited almost entirely to the animal and vegetable parasites, we can scarcely fail to accept the micro-parasitic theory. The great merit of this theory, as Ballance and Shattuck have pointed out, is that "it not only offers a working hypothesis for further investigation with which none other can compare, but it holds out the hope that it may one day admit of scientific treatment based on the same lines as other micro-parasitic diseases." Having endeavored to make clear the grounds for believing in the parasitic origin of cancer, the explanation of the action of erysipelas is not difficult. If a small quantity of blood-serum of an animal rendered immune to tetanus is capable of destroying or rendering inert the virulent bacilli in a fresh case, it is quite as easy to understand that the toxic products of the erysipelas streptococci might bring about such changes in the blood-

serum as to destroy the parasite of cancer. The parasite having been destroyed, the irritation would consequently cease, and this would lessen the hyperæmia of the parts, upon which factor the life of the tumor-cells of low vitality largely depends.

This theory, if it may be called such, has occurred to me as offering the best explanation of all the phenomena observed. It explains the rapid degeneration, with a breaking down of the tumor tissue, as well as the slower disappearance by absorption. It also explains those interesting cases, several in number, where an erysipelas remote from the tumor has caused a disappearance in precisely the same way as a local attack. These latter cases, it would seem, prove the phagocytosis theory insufficient to explain the action of erysipelas. It is worthy of note that the action of erysipelas upon lupus and the secondary and tertiary lesions of syphilis (see Mauriac) is similar to that in malignant tumors, and this fact, joined to the fact that erysipelas has never been known to affect non-malignant tumors, is another point in favor of the parasitic origin of cancer.

The attempt to explain its action on the theory of a mere local irritation, classing it with the various caustics, needs only to be mentioned to be disproved.

The clinical facts already mentioned, that a number of malignant tumors have disappeared as a result of an erysipelas in another region of the body, coupled with the very recent experiments of Prof. Spronck and his co-workers in Leyden, settle the point beyond dispute. In the experiments referred to, twenty-six cases of malignant disease (eight sarcoma, eighteen carcinoma) were injected subcutaneously with the toxic products of the streptococcus of erysipelas, the germ itself having been destroyed and removed.

In every case the injections were made in parts remote from the tumor, usually the gluteal region. Nearly all of the cases of sarcoma showed marked improvement, and in some cases the tumor entirely disappeared. It is true recurrence usually took place, yet in one case (Remsen's), a large inoperable sarcoma, the primary growth entirely disappeared, the secondary growths were reduced to very small size, and there had been no recurrence up to the publication of the paper.

The effect upon carcinoma was very slight, and only in one case was the beneficial action marked.

It should be noted that very small doses were used in these cases, one-half to one gramme.

In no case was the reaction very great, 103° being the highest temperature recorded, the condition usually becoming normal at the end of twenty-four hours. Spronck himself admits that better results might have been obtained from larger doses, yet he preferred to err on the side of safety.

Treatment by repeated injections of fluid cultures. As far as I know, my cases are the only ones that have been treated by repeated injections of the pure fluid cultures of erysipelas.

I began this method more than eighteen months ago, and have used it in nearly all my cases. I have in most cases made the injections deeply into the tumors themselves. The doses employed have varied with the age and virulence of the cultures, but I have aimed to obtain a good reaction, a temperature of 104° or 104½° frequently following. The reaction has usually subsided within thirty-six to forty-eight hours after the injection, unless erysipelas was produced. The effect upon the tumors was more marked in the cases of sarcoma than carcinoma, but all cases showed a cessation of growth and a more or less marked diminution in size. Several sarcomatous nodules, some nearly one inch in diameter, disappeared entirely. It is evident that in these cases the effects produced were chiefly due to the toxic products of the streptococci.

In view of these results, as well as those of Spronck, it may be considered definitely proven, that a portion, if not all, of the benign influence rests in the toxic products of the erysipelas germ, rather than in the germ itself. The fact that, thus far, the results from an attack of true erysipelas have been far more brilliant and permanent, prove that either the germ itself or its continued action plays an important rôle, or, what is quite as probable, we have not yet learned how best to isolate the toxic principles and to use them in the most efficacious doses. It is more than probable that sterilizing cultures by heat changes the chemical relations of the toxalbumins. I am at present, with the assistance of Dr. Alexander Lambert, making experiments with *filtered cultures*, the germs having been removed by means of a Kitasato filter, without subjecting the fluid filtrate to heat. If the virtue of the erysipelas lies entirely in these toxic principles, the treatment of malignant disease will be much simplified, as there will be neither the danger from the erysipelas nor the necessity for isolation.[1]

Dangers associated with erysipelas. I have endeavored to ascertain as far as possible the actual mortality of uncomplicated erysipelas. Nearly everything that has been written upon the subject is of little value in determining this point, because the term "erysipelas" has been used in a very loose way, including many cases of cellulitis and septic infection. I do not believe in the identity of the streptococcus of erysipelas and the streptococcus pyogenes, although I am aware that the opposite opinion is held by many of the leading bacteriologists. Those who hold to the identity of the two germs, base their opinion largely upon the close

[1] Since the above was written, the very valuable researches of Roger have been published in the Revue de Méd., December, 1892. They go far toward proving that the virtue of the erysipelas rests in the toxic products, which can be easily isolated and used in much larger doses than by Spronck.

resemblance, morphologically and biologically, and they claim that the clinical differences are due to the different sites of infection and variations in virulence of cultures; that the same germ in the outer layers of the skin will produce true erysipelas, that injected deeply into the tissues will cause cellulitis and multiple abscesses. I believe this explanation entirely theoretical and not supported by facts. During the course of these experiments I have injected, upward of one hundred and fifty times, pure cultures of the streptococcus of erysipelas, of almost every degree of virulence, into the (human) tissues, superficially and deeply. In but two cases did I see an abscess, and in one of them a careful bacteriological examination was made of the pus (before it had become contaminated), and mixed cultures were found, the staphylococcus aureus being present with the streptococcus.

There appears to be good ground for believing that when suppurative processes are associated with erysipelas, a mixed infection is present, and that there is a real and important difference between the germ of erysipelas and the streptococcus pyogenes, in spite of their close resemblace.

The fact that they are pathogenic for different animals respectively, and also their different action with reference to lactic acid, are other points against their identity.

If we include the cases of diphtheria inoculated with erysipelas (Babtschinski), we have a total of 40 cases where erysipelas has been artificially produced, with but one death—2½ per cent. We know that the virulence of the germ varies within wide limits, and that it can be modified at will by passing it through animals, therefore it seems reasonable to assume that with proper precautions its mortality in inoculation can be made trifling or *nil.*

Conclusions.—1. The curative effect of erysipelas upon malignant tumors is an established fact.

2. The action upon sarcoma is more powerful than upon carcinoma, in about the ratio of 3 to 1.

3. The treatment of inoperable malignant tumors by repeated inoculations of erysipelas is both practicable and not attended with great risk.

4. The curative action is systemic, and probably due chiefly to the toxic products of the streptococcus, which products may be isolated and used without producing erysipelas.

5. This method should *not be employed indiscriminately* until further experiments have proved its limitations.

In concluding, I wish to express my great indebtedness to Dr. Wm. T. Bull for the advice and assistance frequently and generously given, without which much of the work would have been impossible. I am also under deep obligations to the authorities of the New York Cancer Hospital, to Drs. Prudden and Cheesman of the College of

Physicians and Surgeons, and to Drs. Ferguson and Biggs of the New York Hospital Laboratory, for kind assistance and laboratory facilities.

[NOTE.—Since the above paper went to press I have continued my experiments, with the following results: I have had one fatal case of erysipelas inoculation—a large inoperable sarcoma of the neck. The patient was sixty-five years of age, and his general condition had been greatly impaired, both by the disease and by a very extensive operation a short time before. Attenuated cultures having failed to produce any reaction, a fresh culture from a virulent case was used. A severe attack of erysipelas followed, to which the patient succumbed on the fifth day. In this short period a marked change had taken place in the tumor. No breaking down had occurred, yet it was less than half its former size.

Toxic products. During the past month I have been using a preparation of the toxic principles of erysipelas in four cases of inoperable sarcoma. The injections have been made into the tumor itself, and repeated every forty-eight hours. The reaction has been almost identical in character with that produced by true erysipelas, though milder in degree, and it has always passed away within twenty-four to forty-eight hours.

The temperature has never risen above 103½°, and has usually dropped to normal the following day. I have frequently made use of the toxic products of the *bacillus prodigiosus* in combination with the products of the erysipelas coccus, to intensify the action of the latter, and always with the desired effect. (This peculiar action of the one germ upon the other, I may add, was noted by Roger in his recent experiments on rabbits.)

Every one of my four cases of sarcoma has shown a marked and progressive decrease in the size of the tumor, and in one case (*vide* paper, Case VI.) a sarcoma of the back and groin, the tumor has entirely disappeared, and the injections have been stopped. The patient has regained his normal weight (one hundred and sixty-five pounds) and has returned to work.

These results have been so encouraging that, for the present at least, I have decided to use the toxic products of erysipelas in preference to inoculating the germ itself. The advantages of so doing are very great. The necessity for isolation is avoided, and the action of the products can be so carefully regulated that the danger element can be entirely eliminated.]

Reference.	Surgeon.	Age	Date.	Character of tumor.	Erysipelas, accidental or inoculated.	Immediate results.	Final results.
1. Berlin. klin. Woch., 1866, 23; 1868, 32.	W. Busch	43 F.	1866	Multiple sarcoma of skin (face).	Erysipelas, facial, accidental.	Large tumor broke down; smaller ones disappeared by absorption.	Permanent cure.
2. Ibid.	Ibid.	28 F.	1868	Very large lympho-sarcoma of neck, size child's head.	Erysipelas, facial, accidental.	Tumor diminished in size one-half in eight days.	Died on eleventh day, collapse.
3. Ibid.	Ibid.	19 F.	1868	Large inoperable sarcoma of neck.	Erysipelas, produced by putting patient in bed near case of erysipelas.	Tumor greatly diminished in size in two weeks; began to grow again.	Improvement temporary.
4. Archiv f. klin. Chir., Bd. xii. S. 18	Mosengeil	50 F.	...	Carcinoma of face; partial excision; recurrence.	Erysipelas, accidental; slight attack lasting two days.	Cessation of growth; patient discharged at end of three weeks.	Not traced.
5. Inaugural Dissertation, Bonn, 1870.	Hahn	...	1870	Carcinoma of face.	Erysipelas, accidental, several attacks.	Temporary destruction of tumor.	Recurred soon after.
6. Archiv f. klin. Chir., Bd. xii. 111.	Mosengeil	...	.....	Epithelioma of ear.	Erysipelas, accidental.	Disappearance.	Cure.
7. Schmidt's Jahrbucher, Bd. cxlvi. 345	Lusana	52 F.	.....	Epithelioma of temporal region.	Erysipelas, facial, accidental.	Disappearance in five weeks.	?
8. Vratch, 1882, S. 262.	Stein	F.	.....	Large tumor of breast, skin adhesion, axillary glands involved; carcinoma with little doubt.	Erysipelas of back, accidental.	Almost entire disappearance of tumor, only two small nodules size of nut left.	Not traced.
9. Bull. de la Soc. de Chir., t. viii. 302.	Nélaton	...	.....	Large tumor of lower jaw (sarcoma probably).	Erysipelas, accidental, facial.	Entire disappearance.	Recurred.
10. Ibid.	Pamard	M. ad't	.....	Carcinoma of submaxillary glands following excision of tongue.	Erysipelas, accidental.	Completely disappeared	Recurred.
11. Ibid.	Delens	F. ad't	.....	Very large tumor of breast.	Erysipelas, accidental.	Total disappearance.	Recurred.
12. La Union Médicale, 1882, 136.	Dauchez	F. 52	.....	Carcinoma of temporal region ulcerating; enlarged glands.	Erysipelas, facial, accidental.	Tumor reduced in size one-half; glands entirely disappeared.	Recurred.
13. Gaz. hebd., 1885, 26.	Ricochon	F. 52	1885	Very large lympho-sarcoma of neck; large tumor of tonsil.	Erysipelas, facial, accidental(sev're attack).	Very great decrease in size of tonsil and neck tumors.	Later grew again
14. Deut. med. Zeitung, 1886, 4.	Biedert	F. 11	1886	Large sarcoma; round-celled sarcoma involving mouth, nose, and throat; tonsil tumor size of goose-egg	Erysipelas, facial, severe attack, accidental.	Entire disappearance of all tumors in one week.	Child perfectly well and free from recurrence one year later.
15. Beiträge z. klin. Chir., 1888, 445.	Bruns	47	.....	Melanotic sarcoma of breast.	Erysipelas, accidental.	Entire disappearance.	Permanent cure.
16. Centralbl. f. Chir., 1884, 44.	Neelsen	F. ad't	.....	Carcinoma of breast.	Erysipelas, accidental, severe; three weeks later 2d attack.	Tumor greatly diminished in size.	Recurred later; new tumor.
17. Ibid., 25.	Janike	F. ad't	.....	Carcinoma of breast, recurrent.	Erysipelas inoculation	Tumor much softer and smaller.	Death fourth day from erysipelas.

Reference.	Surgeon.	Age	Date.	Character of tumor.	Erysipelas, accidental or inoculated.	Immediate results.	Final results.
18. Erysipelas. Monograph, Fehleisen. Berlin, 1883.	Fehleisen	F. 58	1882	Multiple fibro-sarcoma of skin (gluteal region).	Erysipelas, inoculation (scarification).	Reaction in 61 hours; course 14 days; small tumors disappeared; main mass partially degenerated.	Temporary improvement.
19. Ibid.	Ibid.	F. 49	1882	Carcinoma of breast recurrent (2 x 3 inches diameter).	Erysipelas, inoculation.	Reaction 30 hours; two weeks' course; entire disappearance of tumor.	No relapse nearly one year.
20. Ibid.	Ibid.	F. 8	1882	Sarcoma intra-ocular; secondary in submaxillary glands.	Erysipelas, inoculation.	Reaction 23½ hours; little change in primary growth; glands diminished one-half.	Temporary improvement.
21. Ibid.	Ibid.	F. 52	1882	Carcinoma of breast, disseminated.	Erysipelas, inoculation.	Reaction 19 hours: two weeks' course; tumor reduced one-half in two weeks.	No further decrease.
22. Ibid.	Ibid.	F. 40	1882	Carcinoma of breast, recurrent; axillary and cervical glands involved.	Erysipelas, inoculation.	Reaction 15 hours; one nodule softened and broke down, others not greatly diminished.	Temporary improvement.
23. Inaugural Dissertation, Berlin, 1889.	Weichel	M.	1889	Carcinoma of penis and ing. glands (recurrent).	Erysipelas, of scrotum, accidental.	Three weeks' course; entire disappearance of carcinomatous masses.	Patient died later from sudden hemorrhage from surgical wound. Autopsy: all organs normal.
24. Reports of N. Y. Surg. Soc., 1892; N. Y. Med. Journ., 1892, i. 641.	Gerster, A. G.	F. 16	1884	Sarcoma of femur; amputation of trochanter minor; recurrence in stump.	Erysipelas, accidental: five weeks after recurrence.	Entire disappearance of tumor.	Patient alive and well three yrs. after.
25. Annals of Surg, Sept. 1891, Coley	Bull, W. T.	M. 30	1884	Large round-celled sarcoma of neck; five operations; recurrence.	Erysipelas, accidental, two attacks.	Entire disappearance.	No recurrence in seven years.
26. Vratch, 1882, 16; Lond. Med. Record, 1884, 11.	Winslow	M. ad't	1882	Sarcoma of neck; clinical diagnosis	Erysipelas, accidental.	Total disappearance.	One year later a sarcoma of breast developed.
27. Münch. med. Woch., 1890, No. 7.	Kleeblatt	M. 54	1888	Sarcoma of neck following removal of sarcoma of tonsil.	Erysipelas, accidental; second attack three months later by inoculation.	Diminution in size from child's head to pigeon's egg in ten days.	Temporary improvement Recurred two months; erysipelas inoc. Complete disappearance. 2d recurrence one month.
28. Ibid.	Ibid.	M. 52	1888	Sarcoma of neck (microscopic).	Erysipelas, inoculation.	Entire disappearance.	No recurrence 1890 (2 years).
29. N. Y. Cancer Hospital Records, 1883.	Powers and Dowd	F. 52	1892	Sarcoma sup. maxilla.	Accidental.	Diminished one-half in two weeks.	Recurred.
30. Annales de l'Institut Pasteur, 1888, 223.	Holst	F. 40	1887	Carcinoma of breast, recurrent.	Erysipelas, inoculation.	Reaction 20 hours; nine days' course; recurred three times; marked decrease in size.	Relapsed four months later.
31. Archiv. of Clin. Surg., July, 1892.	Hutchinson, Jonathan	F. ad't	.....	Probable carcinoma of breast.	Erysipelas, accidental.	Entire disappearance.	No recurrence in five years.
32. Personal communication.	Finney, J. M. T. (Baltimore)	...	.....	Epithelioma of nose, size of silver quarter.	Erysipelas, accidental.	Entire disappearance.	No recurrence in two years.
33. Ibid.	Ibid.	...	.....	Double carcinoma of breast, recurrent; axillary glands involved.	Erysipelas, inoculation.	Diminution in size; general improvement; had two spontaneous attacks later.	Died five months later from metastasis.
34. Ibid.	Starr, C. L.	F. ad't	1892	Carcinoma of breast and axillary glands; several nodules in arm; breast incised.	Erysipelas produced by direct inoculation from fresh case.	Severe attack of erysipelas extending over breast and down arm; nodules in axilla and arm disappeared.	Temporary improvement. Nodules in arm and axilla entirely disappeared.

Reference.	Surgeon.	Age	Date.	Character of tumor.	Erysipelas accidental or inoculated.	Immediate results.	Final results.
35. Ibid.	Eliot, E., Jr.	F. ad't	1892	Carcinoma of breast, recurrent.	Erysipelas, accidental.	Marked decrease in size of tumor, and general improvement.	Subsequent increase; attempt to inoculate unsuccessful.
36. Ibid.	Morris, R.I.	F. 26	Dec. 1892	Carcinoma of breast, recurrent.	Erysipelas, accidental.	Ten days' course; marked decrease in size of tumor.	Again grew.
37. Münch. med. Woch., July, 1890.	Kleeblatt	F. 23	.....	Tumor the size of pigeon's egg under eyelid.	Erysipelas, accidental.	Entire disappearance.	Cure.
38. Ann. Surg. Sept. 1891 (Coley). Reported in part.	Coley, W.B.	M. 31	May, 1891 Oct 1891	Sarcoma of neck and tonsil, recurrent.	Repeated inoculation; first real attack of erysipelas Oct. 1891.	Diminution in size; subsequent increase; after attack in October almost entire disappearance of tumor of neck and decrease of tonsil tumor.	Patient in good health March, 1893; no return in neck; tonsil tumor smaller.
39. Ibid.	Ibid.	F. 16	May, 1891	Sarcoma of femur size child's head; periosteal round-celled.	No attack of erysipelas produced; repeated injection of pure culture	Slight decrease in size; marked local and constitutional reaction.	Died 3 months later from exhaustion.
40. Ibid.	Ibid.	F. 26	July, 1891	Sarcoma of vertebræ, spindle-celled; recurrent.	Repeated inoculation; no attack of erysipelas; cultures attenuated.	Slight softening of tumor; reaction 103½°.	Effect temporary, injections continued but short time.
41. Unpubl.	Ibid.	M. 44	Feb. 1892	Sarcoma of back (17 in. in diam.), spindle-celled.	Repeated inoculation failed to produce erysipelas	No effect on tumor.	Injections discontinued, as cultures were too weak.
42. "	Ibid.	M. 76	June, 1891	Carcinoma of face.	Inoculation failed to produce erysipelas.	Reaction 102½°; no effect on tumor.	But three injections made; cultures poor.
43. "	Ibid.	M. 40	April, 1892	Sarcoma of back and groin, recurrent.	Inoculation, severe attack of erysipelas; 2d attack Nov. 1892; 3d attack Dec. 1892; 4th attack Dec. 1892.	Tumor of back 7 x 4 inches entirely disappeared in two weeks, tumor of groin as well.	Recurred July. Reinoculated Oct and Nov. Tumor again almost disappeared. Recurred in back. Mar. 1893, condition excellent. Entirely disappeared after toxic products injections
44. "	Ibid.	F. 40	June, 1892	Sarcoma of breast, recurrent; eight operations.	Inoculation erysipelas; first attack June, second July.	Tumor much diminished in size; general health improved; small tumor of vagina disappeared.	Subsequent relapse and growth; treated by repeated injections of pure cultures. Subsequent operation and injection; still under treatment.
45. "	Ibid.	F. 42	Aug. 1892	Carcinoma of breast, recurrent; four operations; size of goose-egg.	Repeated inoculations eight weeks no attack of erysipelas	Tumor diminished in size one-half; general health not affected; Reaction 101 to 104°.	Subsequent growth.
46. "	Ibid.	M. 54	Oct. 1892	Carcinoma of cervical glands; recurrent.	Repeated inoculation; no attack of erysipelas.	Tumor softened and broke down in part; reaction 100–103½°.	Subsequent operation.
47. "	Ibid.	M.	Oct. 1892	Carcinoma of inguinal glands; recurrent.	Repeated inoculation; no erysipelas produced.	Reaction 103½°; partial degeneration of tumor.	

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DIFFUSE TUBERCULAR HEPATITIS WITH TUBERCULAR PERICARDITIS.[1]

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The following case is worthy of being placed on record, both on account of the rarity of the disease and the unusual character of the symptoms.

Ellen S., aged twenty-eight years; married; husband and one child dead of tuberculosis; four children living and healthy; family history unimportant. Since her husband's death, two years ago, she has been in domestic service. She enjoyed good health until early in December, 1891, when she began to feel epigastric distress after eating, and a short time later vomited almost as soon as food was taken. The vomited matter became increasingly bile-stained, whilst strength failed and thirst was prominent. About January 1, 1892, she noticed a jaundiced hue which soon became quite marked. The bowels had become loose in December,

[1] Read at the Meeting of the Canadian Medical Association, Ottawa, September, 1892.

and now a troublesome diarrhœa set in. She frequently had chilly sensations, but no rigors, and was confined to bed during most of January.

When admitted to Toronto General Hospital, on January 27, 1892, she was considerably emaciated, and her face had an anxious, pained expression. The conjunctivæ and body surface generally were deeply jaundiced and the skin moist. Her temperature was 99.5° F., pulse 108–120 beats to the minute. Distress was still felt in the epigastrium, and also in the right hypochondrium, but there had been no vomiting for two weeks. The bowels were constipated and stools clay-colored.

Inspection showed the abdomen to be decidedly full in its upper part, and the lower border of the liver was easily traced across a level three-quarters of an inch above the umbilicus; it was even and somewhat rounded, the surface of the organ being smooth and tender. In the left side the hepatic dulness was continuous with that of the spleen, the lower end of which extended one inch below the border of the ribs. There was considerable tenderness all over the liver and spleen, and continuous pain in these regions was complained of.

There were signs of pleural effusion in the right side, dulness extending as far forward as the mammary line, and as high as the fourth rib in that line and the fifth dorsal vertebra behind. Over this area respiratory sounds were audible, but weak, and occasional friction sounds were present with both inspiration and expiration.

The apex beat of the heart was displaced a little outward and was somewhat diffuse, a high-pitched systolic sound, probably pericardial, being heard over the fourth and fifth costal cartilages to the left of the sternum, almost disappearing with inspiration.

The urine, specific gravity 1015, contained much bile-pigment but no albumin. No signs of disease could be found in the lungs, nor in the abdomen or pelvis, except those already spoken of.

February 8. Signs of pleurisy in left side.

13*th*. Pericardial friction fremitus felt in the third intercostal space; auscultatory signs very distinct. A week later the whole pericardium became affected, with considerable effusion, precordial dulness extending to the third intercostal space.

20*th*. Some coarse liquid crepitation present in lower parts of both lungs; this was found to vary in abundance from day to day. There was slight cough with occasionally some thick, dark sputum, mostly blood. The sputum disappeared entirely after a few days, and the cough subsequently abated so much as to give scarcely any trouble. Jaundice had begun to lessen perceptibly.

March 1. The pericardial effusion had begun to absorb; the right pleura showed no change, but the effusion in the left had gradually increased. The abdomen was extremely tender and diarrhœa troublesome, the stools being liquid and offensive. Some effusion into the peritoneal cavity was noted. The urine was less pigmented than at first, and contained a small quantity of albumin. Microscopic examination discovered the presence of pus corpuscles and crystals of tyrosin. The crystals were small, abundant (four or five in a field) and always adherent to pus corpuscles. The size of liver and spleen remained unaltered.

7*th*. Diarrhœa had become profuse and bowel motions involuntary; patient appeared *in extremis*.

10*th*. The bowels now became constipated and patient began to improve.

20*th*. She was quite hopeful and taking nourishment fairly. She slept better, had less pain, and the temperature was less disturbed, and finally sat up for an hour or two daily. This improvement lasted for only a few days, and then she grew rapidly worse again, the temperature varying from 96.5° to 103° F. There were profuse perspirations, but no chills. Jaundice was now completely replaced by a dusky livid hue. Fine liquid crepitation was heard in the lungs, more abundant and generally distributed than before. No signs of pericarditis were present, and no change was noticed in the condition of the right pleural cavity; the effusion in the left was increasing however, as was that in the peritoneal cavity. The urine still contained tyrosin crystals, pus, and a small quantity of albumin.

The patient's condition continued much as above during April, her strength gradually failing, although she had sat at the window of the ward almost daily. The liver showed no change in its condition, but tyrosin crystals were not found in the urine after April 10th. Death took place April 28th.

Report of post-mortem examination—made at the Toronto General Hospital, April 29, 1892:

Inspection shows the body of a woman of apparently forty years of age; emaciation extreme; skin dark and somewhat yellowish in color, black hair on chin and abdomen; rigor mortis and post-mortem staining poor; bedsores over sacrum.

Section shows subcutaneous fat almost none; muscles thin and black; omental fat much wasted; three pints of bright yellow slightly fibrinous fluid in abdomen.

Pleuræ: Diffuse adhesions on both sides; loculi containing fluid formed by adhesions also on both sides; loculus on left side large, reaching from second rib to base and limited by nipple line in front; both pleuræ greatly thickened by layers of plastic lymph, only that immediately next the serous membrane being replaced by fibrous tissue; the adhesions appear old and are about one-half inch in thickness, but break down readily, being nearly pure fibrin. The pleuræ are found, when stripped, studded with miliary tubercles. The inflammatory process has spread from right side into the anterior mediastinum, and plastic material is thickly deposited on right half of inner surface of sternum.

Pericardium: Complete fibrinous adhesion exists between the parietal and visceral layers; thick, but readily broken down, except over the surface of the right ventricle, where, on a spot the size of a 25-cent piece, it is firm and fibrous. The lungs overlap the pericardial sac, almost hiding it, and are glued to it by fibrin.

Lungs: Milliary tubercles scattered through both, by far most densely in and just beneath the pleuræ; caseating glands at root of lungs; no consolidation; œdema and hypostasis.

Abdomen: Perihepatitis and perisplenitis of some standing, and with adhesions similar to those found between the pleuræ, fixing the liver and spleen to diaphragm, and spleen to liver.

Spleen: Weight twenty-three ounces; diffuse perisplenitis, adhesions; reaches forward and to right till its border is attached closely to the left lobe of the liver by plastic lymph; miliary tubercles scattered widely through the organ and plainly visible beneath the capsule; consistency, firm; pulp, increased.

Kidneys: Taken out with difficulty on account of density of the peri-

nephric areolar tissue; capsules peel fairly readily; scars as from old infarcts; tubercles in both cortex and medulla, but not in large numbers.

Ureters and bladder: Healthy.

Uterus and ovaries: Healthy.

Supra-renal capsules: Post-mortem softening.

Appendix vermiformis: Four and one-half inches; healthy.

Intestines: Large and small intestines empty, thin, pale; nothing specially noticeable excepting adhesions (old) between the colon, omentum, and gall-bladder.

Stomach: Shows catarrh.

Liver: Large, sixty-two ounces; smooth; cuts hard, as though cirrhosed; of "nutmeg" appearance; miliary tubercles beneath capsule and throughout liver substance; gall-bladder, ducts, and veins healthy.

Pancreas: Soft; post-mortem changes.

Head: Not opened.

Microscopic examination. Miliary tubercles are demonstrated in the lungs, pleuræ, pericardium, diaphragm, liver, spleen, and kidneys.

Liver: Sections of the liver show miliary tubercles, though not in large numbers, from one to three in a section being common. They are scattered widely through the substance of the liver, and tend to be intra- rather than interlobular. In addition to the tuberculosis there is a *diffuse* interstitial hepatitis, which is largely of the intercellular variety, and which is accompanied by little or no alteration of the capsule from within. The interlobular tissue is widely infiltrated with inflammatory cells, and the inflammatory process has spread into the lobules, causing an intralobular cell-infiltration, in many places quite dense, and a considerable new formation of connective tissue along the lines of the capillaries. This process has extended in many instances through quite a fourth of the distance between periphery and centre of lobule. The capillaries are in parts apparently occluded by the new tissue formation, and numerous leucocytes are to be seen in some, occasionally completely plugging them. The liver cells have undergone marked changes. Fatty infiltration is prominent in parts, whilst cell-atrophy is very conspicuous in the peripheral areas of lobules, where the pressure of the new tissue and cell infiltration is felt. Deposits of brownish-yellow pigment, apparently bile-pigment, are seen here and there in cells, but not in abundance. In very numerous spots a curious hyaline-looking necrosis of the liver cells has occurred. This is noticed both in single cells and in groups of cells, and presents an appearance as though the cell protoplasm had become coagulated and broken up into a large number of roundish particles, some larger than a red blood-corpuscle, but many much smaller. These particles stain strongly with eosin. In most instances the remains of at least one nucleus are distinctly visible amongst the necrosed protoplasm. The nucleus may remain intact, showing large nucleoli, or may be split up into fragments. These necrosed cells are in some cases infiltrated with leucocytes. The nuclei persisting in the broken-up cells are mostly very large, and stain darkly and sharply with hæmatoxylin, and the necrosed cells are also increased in size. Their limits are very definite. Scattered throughout the liver are enlarged cells with gigantic nuclei, corresponding closely to those of the necrosed cells; these are probably going through previous degenerative stages. In some parts numerous small branching bile-ducts are to be seen, such as are noticeable in so-called hypertrophic cirrhosis.

This woman presented a most rare and interesting pathological condition, the true nature of which could be only partly understood from the post-mortem examination. It was thought at first that we had to do with a case of pylephlebitis, with much more than the usual jaundice. There were serious difficulties to be explained, however, if this diagnosis were to be accepted—*e. g.*, the absence of a primary suppurating focus or ulceration in the pelvis, cæcal region, or elsewhere; the absence of chills; the signs of perihepatitis and perisplenitis, together with the affection, one after another, of the several serous cavities, and the long duration of the case. Pyæmia, probably more frequently than any other affection, gives rise to inflammation in such various parts, but its course is usually terminated much earlier. Bright's disease was excluded as a cause, by the condition of the urine, heart, and circulation. That there was sepsis in the case was quite evident from the temperature chart, the sweats, the dusky discoloration of the skin, the tumefied spleen, etc.; the source and nature of the poison were not so readily to be gotten at. When several parts are simultaneously the seat of inflammatory lesions, our minds naturally turn to tubercle as a possible cause; but it seemed just as difficult to explain many of the observed phenomena, especially those pointing to the liver, if this etiology were accepted, as with any other. Few pathologists refer at all to tubercle as a cause of diffuse hepatitis, and those who make reference to it say that it gives rise to no symptoms. Ziegler describes one form of tuberculous liver as exhibiting a general connective-tissue hyperplasia, the parenchyma being traversed by bands of fibrous tissue, in which are lodged gray or yellow tubercles (*Path. Anat.*, 1890, Band ii., p. 599). Saundby, in 1890, said that he had seen two cases of tubercular cirrhosis in which there was a tubercular network surrounding the lobules, and in the lobules a remarkable development of biliary canaliculi (*Brit. Med. Journ.*, 1890, vol. ii. p. 1459). Delafield and Prudden, speaking of tubercular hepatitis, say that it may be *associated* with cirrhosis (*Handbook of Path. Anat. and Hist.*, 1889). Coats, in his latest edition, makes no mention of the condition. Osler states that with eruption of miliary tubercles in the liver there may be a slight increase of connective tissue, which is, however, overshadowed by fatty change. "Practically," he says, "it is very rare, except in connection with chronic tuberculous peritonitis and perihepatitis, when the organ may be much deformed by a sclerosis involving the portal canals" (*Practice of Med.*). Pepper records a case following measles, in which jaundice was occasional; the liver was hobnailed. No history of syphilis could be obtained. Klein has described *acute* interstitial hepatitis as he found it in eight cases of scarlatina. R. P. Howard, of Montreal, in a paper on "Cirrhosis of Liver in Children," reports seven or eight out of sixty-three as being coexistent with tubercle.

Having been unable to find anything in the history of our case or in

the post-mortem appearances apart from the tuberculosis that would account for the occurrence of an interstitial hepatitis, we are constrained to believe that it resulted from irritation caused by the specific poison of the tubercle germs circulating in the blood. It could not have been the result of irritation by the localized tubercular nodules, since these were too few in number and too widely separated to account for a general hepatitis. The condition of the stomach and intestines was not such as to lead one to suppose that any fault in them was the cause. The points in the microscopic appearances which seem to add special strength to the view taken are: 1st, diffuseness of the process; 2d, large amount of cell infiltration present; 3d, necrotic condition of liver cells.

With regard to the first point nothing need be said, but of the second we may remark that such an inflammatory process is what one might expect where the poisoning was as acute as in this case. The comparatively small development of fibrous tissue is not what one would naturally look for were the process caused by prolonged absorption of irritative matters from the digestive tract or by retention of bile by obstruction. Alcoholism was excluded from the history of the case, and the liver had none of the characteristics of an atrophic cirrhosis; the deposit of bile-pigment was extremely small and confined to a few cells, none of the bile capillaries being plugged and dilated with it as so commonly seen in obstructive cirrhosis. A catarrh spreading from the duodenum might, of course, account for the passing jaundice, but not for the persisting hepatitis. The presence, moreover, of necrosed liver cells points rather to a toxine effect than otherwise. It has been shown that the toxalbumins of diphtheria and typhoid fever give rise to such a necrosis as described (*Johns Hopkins Hospital Bulletin*, March, 1892) and (Osler's *Practice of Med.*, art. "Typhoid Fever"). One of us has also observed a similar cell necrosis, with leucocytic infiltration, in a case of syphilitic cirrhosis.

The occurrence of tubercular pericarditis is worthy of note, since so few cases of this disease are on record. When she first came under observation there were signs of old pericarditis; these signs underwent no change and at the autopsy they were found to be due to old adhesions. Later, signs of fresh inflammation developed over the base of the heart and gradually extended downward to the apex. The moderate effusion that resulted was fairly rapidly absorbed and in five weeks after the first signs of pericardial disease showed themselves, all traces of the attack had disappeared. The history of the pericarditis contained nothing distinctive in itself; its tuberculous nature could be surmised only from the associated conditions.