The treatment of sarcoma and carcinoma by injections of mixed toxins / by C. Mansell Moullin.

The Treatment of Sarcoma and Carcinoma by Injections of Mixed Toxins.

C. MANSELL MOULLIN.

on:
E, SONS
ON, Ltd.

The Treatment of Sarcoma and Carcinoma by Injections of Mixed Toxins

BY

C. MANSELL MOULLIN, M.D.Oxon., F.R.C.S.

Surgeon and Lecturer on Surgery at the London Hospital; Examiner in Surgery at the University of Oxford

Formerly Radcliffe's Travelling Fellow; Fellow of Pembroke College, Oxford; and Hunterian Professor of Surgery and Pathology at the Royal College of Surgeons

London

JOHN BALE, SONS & DANIELSSON, Ltd.

OXFORD HOUSE

85-89, GREAT TITCHFIELD STREET, OXFORD STREET, W.

1898

INTRODUCTION.

This little work, which has grown out of a paper that was read before the Harveian Society of London, contains a short account of the results that I have obtained thus far from the use of the mixed toxins of the streptococcus of erysipelas and the bacillus prodigiosus (Coley's fluid), in cases of malignant disease. I have added to it in an appendix brief particulars of all those instances that I can find in which malignant growths have disappeared after attacks of erysipelas, whether occurring accidentally or communicated, and of some of the most important of those in which a like result has followed the injection of the mixed toxins. I have done this partly in the hope that I might save others who are interested in the subject from the heavy labour of searching out references; but chiefly that the sceptical might learn that these results are by no means isolated or confined to a few observers.

C. Mansell Moullin.

69, *Wimpole Street, W.*

The Treatment of Sarcoma and Carcinoma by Injections of Mixed Toxins.

C. MANSELL MOULLIN, M.D., F.R.C.S.

THERE are, I imagine, few subjects in surgery more urgent at the present time than the treatment of malignant growths which have passed the stage in which they are capable of being removed by operation. For such cases there is nothing left. The patient may be young and in the full vigour of life, with in every other respect a prospect of a long career before him; or he may be old and fast breaking up; it makes absolutely no difference. The limits of operation have been reached, there is nothing more to be done. And the number of these cases is not only a very large one, but according to the Registrar-General's statistics shows very little sign of decreasing. It is possible that with improved methods of diagnosis, and as the not altogether unreasonable dread of operation grows less, it may fall to some extent. As matters stand, it is unfortunately only too true that hopeless recurrence is the fate of the greater number of those who suffer from sarcoma or carcinoma, whether they are operated upon or not.

Nor is this all. This subject does not concern those only who have passed beyond the limits in which removal is possible. It concerns no less all those who suffer from malignant disease of any kind, whether they are capable of being operated upon or not. Whatever may be said in favour of our present method of dealing with malignant disease, it is impossible to argue that, even when it is successful, it is an ideal one, or incapable of improvement. In the vast majority of in-

stances operation for malignant disease means mutilation, though from long habit we may not recognise it as such. Amputation is no remedy, though at present it seems to be the only method of treatment that holds out a prospect of saving life.

It would take far too long and would serve no useful purpose, were I to attempt to enumerate the different plans that have been proposed for dealing with these growths. Most of them have no scientific basis of any kind. Many of them are absurd at first sight, and very few have met with the slightest success even in their authors' hands. I shall leave all these on one side. One method, however, the injection of Coley's fluid, a mixture of the toxins of the streptococcus of erysipelas and the bacillus prodigiosus, stands out apart from the rest. It is founded upon well-authenticated clinical data. It has been elaborated by systematic scientific observation and experiment, and it has been proved to be successful in a certain proportion of cases. I have tried it myself in ten with varying degrees of success, and I propose first to describe the manner in which the method has been evolved step by step, and then to deal as impartially as I can with the results that have been obtained. I shall confine myself in the main to cases of sarcoma. In carcinoma it does not answer so well (although recently Dr. Coley has met with considerable success in the treatment of some forms of epithelioma), and I shall only allude to its influence upon this class of malignant disease when the cases serve to illustrate some of the points involved.

It has been known for many years, according to Fehleisen since the seventeenth century, that not only malignant growths, but chronic ulcers of the skin, lupus nodules, syphilitic sores and other affections, occasionally disappear with great rapidity after an attack of erysipelas. The number of cases that have been recorded with sufficient accuracy and detail is not a very large one, it is true. They are undoubtedly of exceptional occurrence. Many of them are of somewhat ancient date, as might be expected from the fact that erysipelas is much less common now than it used to be, and that the attacks are less severe than they were in pre-aseptic days ; but after making full allowance for all these defects there still remains a sufficient number of well authenticated instances to dispel at once the idea that the disappearance can be in any way due to mere coincidence.

Placing on one side other affections and cases of carcinoma, I have been able to find records of fifteen undoubted instances of sarcoma in which an accidental attack of erysipelas occurred; of these fifteen no less than nine were cured—if by cure is understood complete disappearance of the growth and no recurrence for a period of sometimes so long as seven years—and in five of the remaining six, the external aspect and the size of the tumour were profoundly altered for a time, although no permanent cure resulted.

I must remark by way of parenthesis that no deduction can be drawn from these figures as to the proportion of cases in which cure takes place after erysipelas. There is a very obvious fallacy. Only successful cases have been recorded. No special attention has been paid until the last few years to the effect of erysipelas upon malignant or any other growths; and consequently no one, in days gone by, would have published or called attention to an attack of erysipelas occurring in a patient suffering from a malignant growth, unless some definite or striking event followed from it. This fallacy, however, as Dr. Coley has pointed out, is confined to reports of cases in which erysipelas has been caused accidentally. It does not apply to cases in which erysipelas has been communicated purposely by inoculation, or to those in which the toxins produced by the streptococcus of erysipelas have been injected. It is probable that all, or nearly all, of these have been recorded, whether successful or not; and the statistics that have been collected about them are only liable to the same fallacies as those that vitiate, more or less, the statistics of every other surgical operation. Some of these nine cases were of a very striking character.

Bruns, for example, has recorded a case of melanotic sarcoma of the breast, with enlarged glands in the axilla, which was excised in 1880. Recurrence took place long before the wound was healed. Four weeks after the operation erysipelas broke out; the tumour vanished entirely, and eight years later the patient was perfectly well, without recurrence of any kind. In a case published by Biedert—that of a girl eleven years of age—there was an enormous sarcoma of the tonsil protruding between the lips, projecting into the nose and orbits, and blocking the pharynx, so that tracheotomy was necessary. Three days later an attack of erysipelas broke out,

and in six days the tumour had disappeared, and the ulcerated surfaces were beginning to heal. Two years afterwards the girl was well, except for the stenosis due to the cicatrices. A third, a sarcoma of the hip, which disappeared almost as rapidly, is recorded by Wyeth. The patient was a child seven years of age. The thigh was amputated through its lower third for sarcoma. Recurrence took place. Disarticulation at the hip-joint was performed. The tumour returned in the stump almost at once, and formed a huge fungating mass. Erysipelas broke out. The growth sloughed away in a few days; the wound healed up, and seven years later the child was well. A fourth case, recorded by Dr. Coley, was one of round-celled sarcoma of the neck, operated upon five times by Dr. Bull, of New York. The patient was given up as hopeless. Two attacks of erysipelas occurred, one shortly after the other, and seven years later the patient was alive and well.

Such cases as these—isolated though they were—could not fail to attract attention, and even before the microbic origin of erysipelas was known several attempts were made at inducing an attack by means of inoculation. When Fehleisen discovered the streptococcus, and it was shown that pure cultures could be obtained by growing it upon suitable nutrient media, it was naturally not long before a systematic attempt was made. Fehleisen himself was the first. Seven patients—two affected with lupus, five suffering from hopeless malignant disease—were inoculated. One of these had recently had an attack of erysipelas, and the inoculation failed. The six others reacted, although in the case of one of them only the first inoculation was followed by any result.

Coley and others quickly followed suit; but two things very soon became apparent. First, that it was exceedingly difficult in many instances to induce an attack. (In no less than five out of thirteen recorded by Coley, and in one of Fehleisen's seven, genuine erysipelas never occurred at all.) Secondly, that it was still more difficult to limit the effect of the attack when it did occur. There are twenty-five cases recorded in which an attempt was made to induce an attack of erysipelas by inoculation. In nearly all pure cultures were injected or rubbed in after the skin had been scarified. In one the patient was placed in a bed which had a notoriously

bad history. Six of these, as already mentioned, never had a genuine attack, although in most of them many attempts were made. The patients were feverish ; there was a certain amount of œdema and redness around the point of inoculation, and they were ill for a few hours. But by the end of the first, or at the utmost of the second day, the symptoms had disappeared. No less than four of the remaining nineteen died as a direct result of the attack.

Fourteen of these cases were definitely sarcomata. One of them, under the care of Dr. Coley, a sarcoma of the neck, that had already recurred twice, was cured ; that is to say, four years and a half afterwards the patient was well in every respect. Another, a lymphosarcoma of the neck, which had resisted arsenic, under the care of Kleeblatt, disappeared entirely, but there is no record as to how long the patient remained well afterwards. In two others, under the care of Dr. Coley, after repeated inoculations with living cultures, each of which was followed by temporary improvement, a cure resulted from the use of the mixed toxins. (One of these Dr. Coley has since reported as having a recurrence in the abdomen, more than three years after the last trace of the original growth had disappeared.) Two others, an enormous sarcoma of the neck, under the care of Busch, and a lymphosarcoma of the tonsil, under the care of Kleeblatt, almost disappeared, but as soon as the effect of the erysipelas had passed off, began to grow again. Two of Fehleisen's diminished considerably for a time. Four were scarcely affected, and in the remaining two erysipelas never occurred at all.

It is worth noting that in every single case in which erysipelas occurred, the tumour showed some change, although in four of the twelve it was very slight. Only one was cured. In another the tumour disappeared, and there is no further record. A third remained free from recurrence for upwards of three years.

The next step was to utilise Brieger and Frankel's discovery, and employ the toxins produced by the streptococcus of erysipelas by themselves, without the germ.

Lassar was the first who did this. The case was one of epithelioma of the face supervening upon lupus. The toxins were separated by filtration, sterilised by steam and injected into the nodules. Some local redness and œdema, with

general discomfort, followed, but the tumour was not affected. In a little while, in spite of the dose being increased, tolerance was established, and the treatment was abandoned as unsuccessful.

Coley adopted the same plan in his earlier cases. The unmistakeable improvement that followed the repeated injections, even when no erysipelas was produced, leading him to believe that a portion, if not all, of the curative influence might be due to the toxins rather than to the action of the germ itself. He saw at once that this method possessed great advantages over inoculation with living organisms; it was much less dangerous; the dose could be regulated, and the effect would be proportionate to the amount injected.

Coley soon found that bouillon-cultures sterilised by heating to 100° C. were too feeble. The effect was the same as in those cases in which living cultures were injected without causing erysipelas, but much less severe. Filtration through a Kitasato's filter made them weaker still. Accordingly he made use of the fact discovered by Roger, of Paris, that the bacillus prodigiosus, a non-pathogenic organism, has the power of intensifying the action of certain pathogenic germs, and among others the streptococcus of erysipelas.

Two solutions were prepared, one containing the toxic products of the streptococcus of erysipelas (from a fatal case), the other those of the bacillus prodigiosus. These were mixed, sterilised by filtration without the use of heat, and preserved by the addition of a few thymol crystals. The proportion in which they were used was about one part of the bacillus prodigiosus toxin to four or five of the other.

Injections of these mixed toxins caused a much greater effect. The reaction was more marked; a rigor was not uncommon; sometimes there was an outbreak of herpes labialis, and the effect upon the tumour was unmistakeably greater. Later, at the suggestion of Mr. Buxton, a further improvement was made, and the germs were grown together in the same fluid. Shortly afterwards, in order to preserve whatever value might exist in the bodies of the germs themselves, the mixed cultures were heated to a temperature of 58° or 60° for an hour (this, according to Coley, being sufficient to render them sterile), and then used without filtration.

The following is the detailed account of the method at present employed :—

Ordinary peptonised bouillon is put into small flasks containing 50 to 100 cc., which, after proper sterilisation, are inoculated with the streptococci of erysipelas, and allowed to grow for three weeks at a temperature of from 30° to 35° C. The flasks are then inoculated with the bacillus prodigiosus, and the cultures allowed to grow for another ten or twelve days at room temperature. At the end of that time, after being well shaken up, the cultures are poured into sterilised, glass-stoppered, half-ounce bottles, and heated to a temperature of 50° to 60° C. for an hour, sufficient to render them perfectly sterile. After cooling a little powdered thymol is added as a preservative, and the toxins are ready for use. The toxins, when prepared in this way, are very much stronger than when filtered through a Pasteur-Chamberland or Kitasato filter, the active principles contained in the germs themselves being preserved. If, as is sometimes the case, the preparation is found to be too strong to be used with safety, it can be diluted with glycerine or sterilised water.

The best method of making the bouillon is to soak a pound of chopped lean meat over night in water. In the morning strain it through a cloth, make up to 1,000 cc. and boil for one hour. Then filter through a cloth, add peptone and salt, neutralise and boil again for an hour. The bouillon will then pass through filter paper perfectly clear, and be ready to put into the flasks. It is not, however, necessary to neutralise the bouillon, as the streptococci will grow even more readily in acid bouillon, and the resulting preparation is, if anything, stronger than when neutralised bouillon is used.

In order to keep up the virulence of the cultures they are put through rabbits in the following way:—The hair of the ear is clipped close with a pair of scissors, and the skin washed with weak carbolic acid, and then sterilised water. A minute quantity of a bouillon culture, forty-eight hours old, is then injected subcutaneously in four or five different places in the ear. Forty-eight hours later, after again washing the ear with carbolic acid and sterilised water, a flat needle sterilised in the flame is inserted under the skin at or near the point of inoculation, and the layer of skin cut off with a sharp sterilised scalpel. The piece of skin is then rubbed well over the surface of an agar tube with a thick platinum wire needle. After twenty-four hours in the incubator, the colonies of strepto-

cocci will show as minute white specks, and from them a pure culture can be obtained. If the agar is made with 75 per cent. of bouillon and 25 per cent. of urine, the streptococci will grow more freely than if bouillon only is used. The dose of this preparation varies from one to eight minims. I have had a temperature of 105° F. follow the injection of two minims. I usually begin with the minimum dose, and gradually increase until the desired reaction, *e.g.*, temperature 103° to 104° F. is reached.

Coley lays great stress upon the necessity for employing virulent cultures only. In the successful cases the toxins were all made from cultures obtained from fatal cases of erysipelas. He also points out that much larger quantities can be borne when injected subcutaneously than when injected directly into a vascular tumour, the difference being due in all probability to the more rapid absorption in the latter instance.

Coley recommends that a very small dose should be used at the beginning—one minim of the filtrate, for example, or half a minim of the unfiltered toxins, and that the dose should be gradually increased until the reaction temperature reaches 103° or 104°. Very little benefit has been noticed in cases in which no reaction has been obtained. Usually injections are given daily, aiming to get two or three well marked reactions during the week, but this must depend upon the general condition of the patient, and the rapidity with which recovery sets in. If well borne, the treatment has been continued two or three weeks, and if at the end of that time no improvement has taken place, it has been discontinued. In some of the successful cases it has been kept up for three or four months, occasional intervals of a few days' rest having been allowed. In several instances, in spite of the reaction and the depressing effects, the patients have steadily improved in general condition, and have gained markedly in weight.

In the summer of 1895, Dr. Coley, of whose kindness I cannot speak too highly, sent me over some fluid prepared by him, and took the trouble to write to me on several occasions a long account of the results at which he had arrived. Since then I have received several more samples from him, and I have used these and also the fluid prepared

under similar conditions, at the British Institute of Preventive Medicine.

I have tried these fluids in ten cases in all, with two deaths. The first of these two fatal cases, undoubtedly at the time the injection was made, was not a suitable one. The patient was a man over 70 years of age, with an enormous and very vascular sarcoma of the femur, whom I saw in consultation in the country. His condition was very feeble; and during the month that elapsed before the fluid could be procured, he became much worse. The first injection was not followed by any conspicuous result. The second, two days later, caused a rigor, which was followed by such prostration that the patient never rallied. The tumour was a very vascular one, pulsating freely, and the injection on the second occasion in all probability entered directly into a vein. Under such conditions there is no doubt it would be better to inject the fluid into some other part of the body, and not into the tumour, unless the patient has already become habituated, so that some degree of tolerance is established.

The second case that was fatal died of acute pyæmia, under conditions curiously like those of a case recorded by Mr. Marmaduke Sheild, in the *British Medical Journal* of January, 1897. In both cases the fluid was carefully tested by a thoroughly competent observer (in mine Dr. Bulloch), and proved to be absolutely sterile. In both instances another patient who was being injected from the same bottle, at the same time, and even on the same day, experienced nothing more than the ordinary reaction. In both full precautions were taken to sterilise the syringe. In Mr. Sheild's, there was some sloughing of the growth. In mine there was some necrosis of bone with suppuration. In Mr. Sheild's, the secondary deposits were proved to be due to a staphylococcus, and not to a streptococcus. In mine, unfortunately, no examination of the micro-organism in the secondary deposits was made, but it was proved that there were no organisms in the fluid injected, so that they must have come from somewhere else. The explanation is, I think, fairly clear. In both cases the wounds were full of pyogenic organisms, probably, in both, staphylococci. It is well-known that micro-organisms that are comparatively harmless, either from the conditions under which they have been

living or from the smallness of their number, may become intensely dangerous if they are associated with or aided by the presence of other organisms, or the injection of other toxins. Animals, for example, that normally are unaffected by the tetanus bacillus, lose their immunity if the bacillus prodigiosus or its toxins are injected at the same time; and I have no doubt that this was the case in my patient. The staphylococci were there, inert or almost inert. The injections of the toxins, either by increasing their virulence, or by diminishing the resistance of the tissues, or by both, changed the condition of things and pyæmia followed.

The natural deduction is, that strict asepsis is absolutely essential, and that there is danger of pyæmia (which in both instances was of a very rapid type) if injections are made in cases in which a sloughing or a suppurating wound is already present.

Of the eight remaining cases, one was a carcinoma of the breast and axilla, which showed no change. A second was a lymphosarcoma of the groin in a young man, who after one or two injections declined further treatment. A third was a similar growth in the neck in a man 65 years of age, which was not affected in the least, although the toxins were injected in considerable doses. Two improved slightly; and in three the tumours disappeared.

The following are very briefly the chief particulars of these five cases :—

(1) H. K., aged 28, admitted into the London Hospital November 27, 1895, for a swelling in the groin, which he had first noticed four weeks before after a heavy day's work. He had continued at work for some days, but then felt ill and had laid up at home.

On examination there was a swelling in the right iliac fossa, extending deeply on the inner surface of the pubes, reaching to within an inch of the middle line; fixed, firm, not fluctuating; rather tender on pressure; lying underneath the iliac vessels and lifting them up so that the artery could be felt more distinctly than its fellow on the opposite side.

There were four enlarged glands lying over the swelling. The innermost, which was about the size of a walnut, was the largest, and was the swelling that had attracted the patient's notice. The skin was not red or fixed, and it did not pit upon pressure.

The patient looked ill, and his temperature was very irregular. During the week that followed his admission, before any treatment had been adopted, it rose to 101° F. on two evenings. For the most part it kept slightly above normal.

Treatment was commenced on December 4, half-minim of Coley's fluid (it had been kindly sent over by Dr. Coley) being injected into the tissues over the swelling. That evening the temperature fell to normal. The next morning it reached 100·5°. A second injection of one minim was made that afternoon without any immediate result beyond reddening of the skin; but on the evenings of the 6th and 7th the temperature rose to 102° F., falling afterwards to normal.

Without entering into wearisome details, I may say that the injections were continued every second or third day, gradually increasing the amount up to six minims, with occasionally, in the most capricious manner, a rise of temperature. Thus, on December 21, 24 and 27, six minims were injected without any result; while the same quantity on the 28th was followed by a shivering fit and a temperature of 102° F. Again, on January 18, 20 and 22, six minims were injected without result; while on January 30, February 3 and 10 there were three rigors, with a temperature on one occasion of 102·8° F., although the dose had been reduced to five minims after the first rigor, and the intervals were longer. Finally, at the end of February, the dose was raised to eight minims, and as this had no effect, the treatment was discontinued.

So far as the patient was concerned, the treatment did not appear harmful, in spite of the rigor, for his weight went up from 9st. 12lb. to 10st. 5lb.

The tumour at first increased rapidly in size. The skin over it became red and tender, so that at last the injections had to be made by the side of it instead of over it, and the outline of the deep swelling became vague and indistinct, extending below as well as above the pelvic brim. About the middle of January it was noted that the tumour was certainly smaller and the glands less apparent. At the end of the month, at the same time as the three rigors, it was larger again, and had all the appearance of being acutely inflamed. Then from that time until the date of his discharge at the beginning of March, 1896, it began to shrink and grow hard and irregular

in outline until there was very little of it to be felt. Since then it has scarcely altered.

(2) F. D., aged 48, was admitted into the London Hospital on November 10, 1896, for an abdominal tumour.

One month before, patient had been seized with a sharp pain in the left flank. Shortly afterwards he noticed that there was a swelling there. He had been constipated of late, and had suffered much from flatus. There were no urinary symptoms.

On examination the left flank was occupied by a large swelling of irregular shape, hard, not fluctuating, and not connected with the skin or the abdominal muscles. It appeared to be fixed. Below it descended into the iliac fossa. Above it reached under the false ribs. In front it came nearly to the middle line, pushing the colon in front of it. There was no glandular enlargement, and very little pain.

During his stay in the hospital the tumour enlarged rapidly. Patient went out and was re-admitted on December 12. The tumour had increased considerably in size, but there was less trouble with the bowels.

On December 14, half a minim of Coley's fluid was injected over the tumour, and the temperature rose that evening to 100° F. On the 16th, two minims were injected, and the injections were continued every two or three days, the amount being increased gradually to six minims. As a rule there was no rise of temperature. On December 29, however, when four minims were used, there was a rigor with a temperature of 102° F. On January 24, seven minims were injected. The same evening the temperature rose to 101·8°, and the patient complained of headache, cold shivers, sweats and throbbing. The next day, without anything further being done, it rose again to 103·6°, and for a fortnight it continued very irregular, and persistently above normal. No further injections were made.

The tumour continued to increase in size until at last it pressed upon the colon to such an extent that obstruction seemed imminent. At the time of the rigor in the middle of January it became acutely inflamed, the skin being red and œdematous, so that there was some fear of suppuration setting in. Under the influence of rest and lead lotion this slowly subsided, and after the inflammation had gone the shrinkage continued until scarcely anything of the original swelling could be felt.

The patient was discharged in the middle of March, in much better condition than when he came in.

These two cases were shown at the Medical Society in November, 1897. In each there was still a certain degree of resistance over the seat of the swelling, but there was no tumour, and the patients were both in perfect health.

(3) I. V., aged 38, was admitted into the London Hospital October 3, 1895. There was a history of his having fallen upon his hip some months before. In June he was attacked with severe pain down the back of the left leg. After continuing for some weeks this disappeared, but a few days later, after being subjected to some manipulation, it returned with much greater severity, and at the same time a swelling made its appearance in the region of the hip. On admission it was noted that the deep iliac glands were greatly enlarged; that there was an irregular swelling moving with the thigh, and occupying all the space between the anterior superior spine and trochanter; and that the limb was inverted and apparently shortened. There had also been a recent attack of phlebitis of the opposite femoral vein. The thigh could be flexed to an angle of 135°, and there was no pain on manipulation or movement. Injections of Coley's fluid were begun on October 14, and in the course of six days the dose was increased to nine minims. This was followed by a rigor. Another rigor occurred on the 22nd, after the same dose; and then after several more injections of the same amount without any effect, a rigor, with a temperature of 103°, was caused by one of only five minims. After this the treatment was suspended, as the patient complained of feeling weak and prostrate.

The swelling of the thigh diminished very considerably in size, and continued to do so for some time after the patient left. The glands completely disappeared, so that they could not be felt; and the movement of the hip-joint became more free. Two months after discharge I heard that an abscess had formed in the region of the hip, but that the patient was in other respects well and able to get about. A year later there was no recurrence.

(4) M. H., married, aged 29, was admitted into the London Hospital on October 7, 1896, suffering from a tumour of the right temple.

Six years before a swelling had been noted over the root of the right upper canine tooth. This gradually increased in size until the cheek became much distended by the growth. The right superior maxilla was removed at the London Homœopathic Hospital on December 31, 1894. The tumour on microscopic examination proved to be a mixed round- and small spindle- celled sarcoma.

Three months before admission the patient noticed a swelling in the right temporal region. This has gradually increased in size, and become the seat of shooting pains.

At present the right cheek has fallen in, and the line of the scar left by the previous operation is plainly visible. The external angular process of the frontal bone on the right side is replaced by a rounded swelling about 1½ inches in diameter, rendering the upper and outer part of the bony margin of the orbit indefinite in outline. Behind, the swelling shades off gradually. Below it reaches to, and is apparently connected with, the zygoma. Consistence is very firm and uniform. There is no fluctuation.

Injections were commenced on October 9, with fluid obtained from the British Institute of Preventive Medicine. They were made into the arm, and were continued almost daily, the dose rising from half a minim to twelve minims. Sometimes there was slight reaction, the temperature rising to 101°; but there was no rigor or headache, and the tumour continued steadily to increase in size.

On November 7 three minims of some fluid kindly sent over by Dr. Coley were injected into the tumour. The temperature rose to 101° F.; the feet felt cold, and the patient vomited. The next day, after five minims, there was a distinct rigor in the course of an hour, with headache, vomiting, and pain in the back. The injections were continued daily until the dose reached eight minims, each injection being followed by a rigor. On November 15 it was noted that the tumour had definitely altered in shape. The margin of the orbit can be felt. The eyebrow is no longer raised up over the tumour. But, on the other hand, over the zygoma, where the injections are made, the swelling is greater than it was before, but softer and semi-fluctuating.

The following day, as the patient strongly objected to the injections into the tumour, nine minims were injected into

the arm, without result. The next day, as the lower eyelid was œdematous, the patient declared her conviction that the swelling was increasing, refused further treatment, and went out.

The subsequent history, as sent to me by Mr. Gordon Brown, of Finsbury Circus, is worth recording. Mr. Gordon Brown writes that after the patient left the hospital the tumour increased in size, affecting the malar bone, causing considerable swelling in the zygomatic fossa, and leading to exophthalmos. There was intense pain in the head. The eyeball protruded and sloughed away. In June she became pregnant, and the head symptoms got better. In November the tumour had diminished in size very greatly, but there was a recurrence in the left tibia, just below the head of the bone, and the inguinal glands were enlarged.

In December, 1897, when Mr. Gordon Brown very kindly sent the patient to see me, the sarcoma at the outer angle of the orbit had disappeared completely. There was a deep hollow in the temporal fossa. The eyeball was gone and the orbit empty, and the margins of the bones were quite distinct. The left leg was very much swollen, and there was evidently a large tumour in the upper part of the tibia.

This case is too complicated and involved to be of much use as evidence one way or the other. That the original fluid tried did no good is certain. It is equally certain that very rapid change ensued in the tumour after the fluid sent over by Dr. Coley was injected. This, however, when it was injected, as the former was, into the arm, did not seem of any avail ; but it was only tried twice under these conditions. Whether the subsequent disappearance of the tumour after it had become so swollen (perhaps from the inflammatory changes induced in it by the injections) as to cause sloughing of the eyeball, is to be laid to the credit of the toxins, or of the pregnancy, or of both, cannot be said. In either case, whichever was the cause, it was not sufficient to prevent a recurrence making its appearance in another locality.

The fifth case was that of a man 64 years of age, suffering from fibro-sarcoma of the back. It had begun to grow sixteen years before, and had been removed on three occasions. The latest period of immunity was, as usual, much the shortest. The tumour itself was very irregular in shape, adherent to the

skin and the fascia beneath; firm in consistence and about the size of the palm of the hand. Around were a number of smaller nodules. Injections were made into it three times a week for more than a month. Each injection was followed by a certain amount of reaction, but it was never very intense, although other cases in which the same fluid was used reacted on several occasions very severely. This may have been due to the density of the tumour, for it was almost as firm and as elastic as cartilage. There was a definite effect, but it was not sufficient. The tumour altered in size and in shape. Portions of it became flatter; some disappeared entirely. But taking it as a whole it did not decrease in size. At one period it looked as if it were going to diminish rapidly, but the change was only of a temporary character. After five or six weeks the injections were abandoned.

Of these five cases, therefore, three were apparently cured; in one the original tumour disappeared, though the fact of pregnancy occurring at the same time must not be forgotten; and in the fifth there was only a temporary diminution affecting one portion. It is true that in the three instances in which the tumours disappeared there was no microscopic examination. I am unable to prove that they were sarcomata. All I can say of them is that they were diagnosed as such by others, independently of myself, and that if they were not sarcomata it is impossible to say what they could have been. They were certainly not gummata or tuberculous deposits; and equally certainly they were not the product of any infective or pyogenic organisms. Had such been present, the result of injecting such powerful toxins would undoubtedly have been the intensification of their action, not its abolition.

The cases that have been reported by Dr. Coley, who has been working at this subject for many years, are very much more numerous and more important. In the *American Journal of Medical Sciences* for September, 1896, Dr. Coley has published an account of ninety cases of sarcoma that have been treated by him. In thirteen of these the tumours entirely disappeared; and in nine of these thirteen there has been no recurrence, although in one case four years have elapsed, in two cases over three years, and in three cases more than two years. Thirty-three in all improved; forty-five—exactly one half—showed no change, and three died.

All these cases, with one exception, were verified and the diagnosis confirmed by microscopic examination, carried out by thoroughly competent and independent observers. They were all inoperable, and many of them had been given up as absolutely hopeless.

Dr. Coley has been very much more successful with spindle-celled sarcomata than with any others. Out of fourteen, five disappeared entirely under his treatment, two disappeared completely for a while, and all the rest improved. Round-celled sarcomata are much less fortunate. Only two were cured out of fifty-two; and although sixteen improved, the treatment failed completely in no less than thirty-one. The numbers of the other varieties of sarcomata were too small to justify any definite conclusions. The melanotic sarcomata, of which there were seven in all, were failures, only two showing any improvement. This is a little singular when it is remembered that out of the comparatively small number of cases in which sarcomata disappeared after an accidental attack of erysipelas, no less than two were melanotic.

There have not been many opportunities for ascertaining the character of the changes that are produced in sarcomata by attacks of erysipelas or the injection of toxins. When there is an ulcer or a fungating sore, inflammation and sloughing appear to be the rule. In one or two instances the whole tumour has been thrown off in this way. On the other hand, with an unbroken surface, sloughing is the exception. The skin becomes red and tense: at first the swelling increases in size; then it becomes softer, so that it may even fluctuate; the colour fades away; the skin becomes loose and falls into folds and wrinkles; and in a little while the whole mass flattens down and disappears. If the normal tissues have been destroyed, a hollow may be left in place of a prominence. In one or two instances an incision has been made and several ounces of a yellowish-white puriform fluid have been evacuated. The difference seems to depend upon whether pyogenic organisms are present or can gain access through some accidental abrasion. If they are present, the tumour sloughs; if they are not, it undergoes a process which for rapidity and thoroughness can only be compared with acute yellow atrophy of the liver.

So far as I am aware there is no record of any case of

sarcoma treated by the mixed toxins in which a thorough microscopic examination of the tumours was made during the process of absorption. In Mr. Sheild's it is merely stated that the change produced in the tumour seemed to be due to inflammatory action in a soft neoplasm, and that the growth in one part was necrotic, with some purulent infiltration of the muscles underneath. The only definite description that I can find is in the accounts of three cases, one of sarcoma and two of carcinoma, in which the tumours were in process of disappearing during an attack of erysipelas, when it proved fatal. The streptococcus of erysipelas of course was present, whereas it would not be if the toxins only were used; but making allowance for this, it seems probable that the essential tissue changes would be the same whether the toxins were injected or produced on the spot.

One of these was a round-celled sarcoma of the neck, recorded by Busch. At the *post-mortem* examination it was found that the structure of the tumour had been reduced to a framework of connective tissue containing a large amount of yellowish fluid in its meshes. The sarcoma cells had undergone fatty degeneration, and formed a yellowish white emulsion containing numberless fat granules. By injecting water into it, the growth could be filled out again to its former size. Here and there, around the outskirts, portions of the growth that were still unaffected allowed its character and the nature of the changes it was undergoing at the time of death to be ascertained with certainty.

Very much the same appearance, making allowance for the difference in structure, was presented in the two cases of carcinoma. In Neelsen's it is recorded that the contents of the alveoli had undergone complete fatty degeneration. The alveoli themselves were in many places dilated into cysts, or were filled merely with *débris*. In places the old, empty alveoli were crushed together by the pressure of newer growth. In Janicke's more attention was paid to the invasion of the streptococci, which had penetrated in columns between the cell nests and had surrounded them. Whether they had actually penetrated into the cells could not be ascertained. The carcinomatous cells did not show any definite change. In places they were paler and less distinct, as if undergoing coagulation necrosis. Nowhere was there any sign of inflam-

mation. Neisser, who made the examination, came to the conclusion that the carcinoma nests corresponding to the invading micrococci were destroyed by the direct action of the organisms without any inflammatory process; but that the destruction was only partial. Fatty degeneration was also found by Spronck in the case of tumours removed from dogs while under treatment with erysipelas toxin; and on several occasions on which tumours have been incised under similar conditions large quantities of yellowish-white fluid, with numberless fatty granules suspended in it, have been evacuated.

It must be acknowledged that the results obtained by other observers vary a good deal. Some have failed altogether; many have not succeeded in obtaining any positive result, good or bad.

Friedrich, for example, after trying the toxins on nineteen cases, came to the conclusion that they had no specific effect of any kind, and that the changes the tumours sometimes undergo are merely the expression of the cumulative action of a number of injurious influences working together. Of the nineteen cases, however, that he records, four only were sarcomata and two lymphosarcomata. The rest were carcinomata, and are, therefore, outside the present inquiry. Moreover, though the streptococci were taken from many different cases, it is by no means certain that the growths were sufficiently virulent. None of the cases from which the cultures were taken had proved fatal. In most instances no attempt was made at intensifying the action of the toxins, and, as a natural consequence, when the unmixed toxins of the streptococcus were injected, very little reaction followed.

Spronck again, using erysipelas toxins alone, experimented on twenty-five cases without success. But it cannot be said that the injection had no effect upon the tumours. Eight only of the twenty-five were sarcomata. In one of these a large growth disappeared, and in some of the others there was a distinct improvement, though it was only of a temporary character. In some experiments performed on dogs who were suffering from tumours, very definite changes followed.

Répin also, although he used an intensely virulent preparation of the erysipelas toxins, and made injections twice a day, so as to get the maximum effect in the shortest time, met with very qualified success. Only one case out of four

showed any result. In that one, a recurring sarcoma of the shoulder, a large portion of the tumour sloughed away, but the patient became so ill, and lost so much weight that the treatment was abandoned. It is noteworthy that in many of the cases recorded by Coley, and in two at least of my own, the patients improved in weight and strength during the treatment, in spite of the frequent attacks of fever.

Three cases, published by Butlin, were also failures. In one part of the tumour sloughed, but the rest continued to grow. In another the fluid (which in this instance had not been prepared by Dr. Coley) may have hastened death; and in the third, a case of lymphosarcoma or lymphadenoma that had already disappeared once under the administration of arsenic, it had no effect at all.

In America the evidence is very conflicting. Many successful cases have been published by other surgeons. Dr. Johnson, of New York, for instance, has recorded a case of spindle-celled sarcoma of the pharynx of enormous size, which disappeared completely, and although upwards of three years have passed, shows no sign of recurrence. Dr. Mynter has published another—in which there was a huge sarcoma of the abdomen. But naturally in most of these sufficient time has not elapsed to show whether there will or will not be recurrence of the disease.

On the other hand Senn failed completely. In not one of the nine cases in which he tried the toxins was there any improvement. But, as Coley remarks, the cases were unhappily selected. Three were carcinomata. One was a melanotic sarcoma, a tumour of notoriously malignant type, and two others were periosteal sarcomata, a class which Coley admits are unusually refractory.

The most sweeping condemnation, a condemnation that impelled the editor of the *Journal of the American Medical Association* to reverse his opinion absolutely within the space of a few months, came from a Committee of three Surgeons appointed by the New York Surgical Society. Dr. Stimson, Dr. Gerster and Dr. Curtis found—

(1) That the danger to the patient from this treatment is great.

(2) Moreover, that the alleged successes are so few, and so doubtful in character, that the most that can be fairly alleged

for the treatment of toxins is, that it may offer a very slight chance of amelioration.

(3) That valuable time has often been lost in operable cases by postponing operation for the sake of giving the method of treatment a trial.

(4) Finally, and most important, that if the method is to be resorted to at all, it should be confined to the absolutely inoperable cases.

The point, of course, is in the second finding. No one, so far as I am aware, has ever advocated or practised this method of treatment for cases which were suitable for operation. And with regard to this finding, I would only remark that Dr. Coley's cases (to take his alone) have been thoroughly verified and authenticated in every way, and that they are neither few nor doubtful. It is no small achievement to have saved the lives of nine patients who had been given up as hopeless, and condemned to almost immediate death by every other surgeon who had seen them; and one single positive result is worth any amount of negations.

With such conflicting evidence it is not an easy matter to form a definite opinion. There are, however, certain conclusions which, though some of them may require modification later on, appear to me to be justified at present.

(1) It cannot be denied that there is a considerable number of cases in which sarcomata, that had been given up as hopeless, often after repeated operations, have absolutely and entirely disappeared under this method of treatment. There is no other method of treatment (except inoculation with the streptococcus of erysipelas itself) of which this can be said.

(2) Some of these cases have remained free from recurrence for upwards of three years, the period which, in the case of excision of the breast for scirrhus, is regarded by many operators as justifying the use of the term cured.

(3) Several of the cases in which sarcomata have disappeared after an attack of erysipelas have remained free from recurrence for seven years and upwards.

(4) The fact that there may be a few—a very few—cases recorded in which sarcomata have disappeared, either spontaneously or after such diseases as acute specific fevers, has nothing to do with these conclusions. (The statement that sarcomata do occasionally disappear is repeated with great

regularity, but well authenticated cases in which this has taken place, verified in the way in which Dr. Coley's have been verified, are very difficult to find.)

(5) Nor are the conclusions in any way invalidated by the fact that injections of the mixed toxins are sometimes followed by the disappearance of other growths, such as lupus, keloid, syphilitic deposits, carcinomata, &c. It may make the disappearance of sarcomata more difficult to understand, but it in no way disproves it.

(6) The proportion of cases of sarcomata that are cured by the injection of the mixed toxins depends, among other things, upon the histological character of the growths. Spindle-celled sarcomata are by far the most successful. This suggests the conclusion that the mixed toxins have a selective action, even if it is not specific.

(7) The disappearance of sarcomata is not due to inflammation, but to an intensely rapid form of fatty degeneration, comparable only to that which affects the hepatic cells in acute yellow atrophy of the liver. Inflammation and sloughing, when they do occur, are septic complications.

(8) Degeneration and absorption may occur, whether the toxins are injected directly into the tumours or into some distant part of the body. In the former case, however, the constitutional symptoms are more severe and the effect more rapid.

(9) The method is attended by a considerable degree of danger. It should therefore only be adopted in those cases in which there is no other remedy. The chief risk appears to be from collapse and pyæmia. There must always be danger of the latter if there is a suppurating or a sloughing sore. It may be argued that patients whose lives are immediately threatened by a malignant growth will never be cured by any remedy that does not involve some degree of risk.

(10) The toxins are of no use unless the cultures are taken from a virulent case of erysipelas, or are made virulent by passing the streptococcus through rabbits.

(11) The bacillus prodigiosus, in spite of theoretical objections, has the effect of immensely increasing the reaction.

(12) The effect is most striking in the case of rapidly growing sarcomata. Slowly growing ones appear to have much more resistance. Probably this merely means that

masses of embryonic cells with little organisation, give way to injurious influences more readily than those that are more closely knit together.

(13) Patients often gain in weight and strength while under treatment.

(14) Treatment should be continued until the whole growth has vanished, or has become so small that it can be removed.

(15) If there is a recrudescence of the disease, it does not follow that the toxins will be as efficacious the second time as they were the first. Whether this is the result of tolerance being established cannot be said.

(16) Growths of a similar character may spring up in other parts of the body after many years.

(17) The severity of the reaction is very variable. Probably this depends upon the rapidity with which the injection is absorbed, rather than upon any cumulative action it may possess.

The disappearance of the growths is not the result of the high temperature. High temperatures due to other causes, such as specific fevers, are not followed by this result.

Coley suggests that injections of the mixed toxins may be useful in preventing recurrence after sarcomata have been removed by operation.

Incidentally it may be mentioned that injections of the streptococcus of erysipelas apparently never cause suppuration. If, therefore, the streptococcus of erysipelas is identical with the streptococcus pyogenes, the name of the latter had better be changed.

APPENDIX I.

Cases of Sarcoma and Carcinoma in which Erysipelas has broken out accidentally.

Busch, *Berl. Klin. Woch*, 1866, No. 23, p. 245.

Sarcoma of Face.

Woman, aged 43, who had in previous years suffered several times from attacks of erysipelas. In August, 1863, the patient noticed numerous red spots around the left eye, and on the left side of the nose. In December there was an attack of erysipelas, after which the spots became larger and more prominent, while others formed on the right side as well. Soon some of these grew out into prominent tumours, and in June, 1864, the lymphatic glands became involved. In July it was noticed that there was a prominent tumour extending across the face under the left eye, with many smaller ones. The tumours were reddish-brown in colour, vascular, of the consistence of a sarcoma, and movable in the skin. The ducts of the gland follicles caused little depressions on the surface. The glands of the neck were swollen, and there were indurated patches in many other parts of the neck and face. The growth under the left eye was partly excised and proved microscopically to be a rapidly growing sarcoma.

On the fourth day after the operation the temperature rose, and the wound was attacked by erysipelas. The upper eyelid became partly gangrenous; the wound suppurated freely, and the tumours became very much swollen. On the eleventh day the erysipelas began to subside, leaving the nodules softer and smaller. On the nineteenth there was a fresh outbreak. The nodules became more tense again, and part of the one beneath the left eye sloughed away. Then the rest began to shrink. An attack of diarrhœa came on, and the patient slowly recovered. In November the nodules were flat. In December there was no trace of them left. They had swollen up and disappeared—all with the exception of the one operated upon—without suppurating.

BUSCH. *Loc. cit.*

Sarcoma of Neck.

Woman, aged 28, very much emaciated. The patient was suffering from a rapidly growing tumour on the side of the neck. Within a few weeks it had reached the size of a child's head. The whole of the left side of the neck was occupied by a hard, tense, almost hemispherical swelling. The lower border of the jaw could not be felt. The larynx was pushed to one side. The great vessels were buried. The teeth could scarcely be separated, and there was great pain and dyspnœa. In a little while the skin gave way in numerous places, from which blood and serum drained out. The power of deglutition was almost lost.

On February 28, three weeks after admission, erysipelas set in. In a day or two the tumour became softer, so that the patient could open her mouth. By March 6 the mass was reduced to one half its former size, and the glands on the right side of the neck had disappeared. Two days later the size was very much less. The next day the patient was suddenly seized with collapse, and died in the course of a few hours.

At the *post-mortem* examination it was noted that the growth had shrunk to the size of an apple, and was fairly movable. There were no glands enlarged on the right side. The structure of the tumour was reduced to a network of connective tissue, containing a large amount of yellowish fluid in its meshes. The cells had undergone fatty degeneration, and had broken down into a yellowish-white emulsion, containing numberless fat granules. By injecting water into it the growth could be filled out again to its former size. Absorption had probably taken place through the lymphatics.

Portions of the tumour that were still intact showed that it was a soft, round-celled sarcoma.

Busch mentions that in another case in which he removed a tumour from the neck, leaving a mass of glands, owing to the exhausted condition of the patient, this mass completely disappeared. The patient died of pyæmia.

According to the same authority it is not uncommon for lupus to disappear after an attack of erysipelas, provided it is a severe one. The nodules shrink. The cells and nuclei disappear and become absorbed, and ulcers heal over. But the improvement is only of a temporary character.

PLENIO, *Archiv. f. klin. Chirurgie*, B. 34, p. 698.

Melanotic sarcoma of glutæal region, extending to the iliac spine, the fold of the buttock, and on to the abdominal wall. Inguinal glands enormously enlarged.

The patient was a woman, aged 22. An attempt at removal was followed by an attack of erysipelas, with gangrene of the skin, thrombosis, and septicæmia, so that the patient almost died. During convalescence the tumour disappeared completely, and the patient was well two years afterwards.

BIEDERT, *Deutsch. Med. Zeit.*, 1886, No. 4.

Sarcoma of Tonsil.

The patient, a girl aged 11, was suffering from a sarcoma of the left tonsil, which had been growing for upwards of two years. The tumour occupied the whole of the back of the mouth, protruded from between the lips as an ulcerated mass, and had grown into the nose and into both orbits. Tracheotomy became necessary. Three days after it had been performed a severe attack of erysipelas broke out, and lasted for six days, with very high temperature. In this short time the tumour shrank in every direction; the ulcers rapidly healed up, leaving only scars, and the whole growth vanished, with the exception of two little points in the upper eyelid, which were excised. Two years later the girl was well, except for the stenosis due to the cicatrices.

PAMARD, *Bull. de la Soc. de Chirurgie*, 1882, p. 301.

Epithelioma of Tongue.

The patient was operated upon in October, 1880, part of the tongue being removed. In three months the submaxillary glands on the opposite side of the neck had become enlarged. In August the surface gave way, and an ulcer formed. The patient could scarcely open his mouth; he could not eat; deglutition was very difficult, and the tumour had attained an enormous size.

On August 21 patient was seized with a rigor. Erysipelas spread over head and face, lasting ten days. The tumour at the end of that time had almost disappeared. The patient could open his mouth, and eat and swallow without any trouble. A few days later, however, it began to grow

again, and an injection of papain was tried. This was quickly followed by a rigor, intense prostration, gangrene of the lip, and acute septicæmia. In the few days during which he lived the tumour grew rapidly.

In the discussion that followed, a case of Birard's was mentioned (on the authority of Nélaton) in which a submaxillary tumour, having the aspect of carcinoma, disappeared completely during an attack of erysipelas, but in a little while began to grow again ; and Delens mentioned an encephaloid of the breast which disappeared in the same way in fifteen days, but only for a time.

STEIN, *Lond. Med. Record*, May 15, 1883.

Mammary Tumour, Sarcoma, or Carcinoma.

The patient was a woman, aged 48, very much broken down in health. The tumour was fixed, irregular in shape and consistence, hard in places, fluctuating in others, and adherent to the skin.

An injection of pyrophosphate of iron and citrate of soda was made into the dorsal region with the view of treating the anæmia. In twelve hours a severe attack of erysipelas developed, starting from the puncture and spreading over the neck, chest and head. The patient was exceedingly ill for twelve days. At the end of that time the tumour had disappeared, with the exception of two indurated nodules, the size of walnuts, and the patient's health had greatly improved.

MISHTOLT, *Lond. Med. Record*, January 15, 1884.

Sarcoma of Neck.

Patient was admitted with a tumour measuring eight centimetres by four, projecting from the interval between the heads of the left sterno-mastoid. This was treated by parenchymatous injections of a 5 per cent. solution of chloride of zinc. After the second injection an attack of erysipelas developed, starting from the puncture, spreading over the neck, shoulder and chest, and lasting for twelve days. A mucoserous discharge continued to ooze from the puncture

the whole time. The tumour became softer and diminished in size, and at the end of six weeks there was no trace of it to be found.

A year later a recurrent nodule made its appearance near the left nipple.

NEELSEN, *Central. f. Chirurgie*, 1884, p. 729.

Mammary Carcinoma, Double.

The patient was a woman, aged 41. In the left breast was a tumour the size of the fist, quite fixed and adherent to the skin. The axillary glands were enlarged. In the right there was an indurated patch with a process running upwards from it.

The left breast was operated upon on January 17 and the wound allowed to granulate up. On February 16 the patient was seized with a shivering fit; the temperature rose to 40·2° and the skin around the wound became reddened. On the 18th the temperature was 41·6° and the attack had become very severe and extensive. On the 20th pleurisy set in, with dyspnœa so severe that aspiration was necessary. The skin over the right breast became gangrenous and a large abscess formed behind the breast. At length, on March 3, the temperature fell to normal. The tumour in the right breast had diminished somewhat in size.

On March 25 there was a fresh attack, lasting for ten days, and on April 8 the patient died.

At the *post-mortem* the right breast was found to be enlarged and hardened. The muscle behind was inseparable from it and infiltrated with many firm white points of new growth. On microscopic examination the contents of the alveoli had in many places undergone complete fatty degeneration. Many of the alveoli themselves were dilated into cysts, or were filled with *débris;* but in other places the growth had spread and increased, so that the old, empty and degenerate alveoli were crushed together by the development of fresh, rapidly-growing younger ones; and this was especially evident in the skin that had appeared intact. In short, there was atrophy of the older portion of the carcinoma, dating perhaps from the first attack of erysipelas; but this only appears to have encouraged the younger growth by making more room for it.

MOSENGEIL, *Langenbeck's Archiv.*, No. 12, p. 68.

Epithelioma of Nose and Face.

Woman, aged 50. Fifteen years before a tumour had been removed from the nose. On admission there was a large ulcerated swelling occupying the left side of the nose and the left cheek and eyelid. There were numerous pigment spots on the face and arms, and on microscopic examination the tumour contained many melanotic cells. The growth had increased rapidly of late. There were many small ones around, and some of these had fused with it. Recurrence took place within a few days of removal. The actual cautery was applied, and this was followed by a slight attack of erysipelas, lasting only two days. The growth ceased to spread; healthy granulations formed, and the patient went out with the scar sound.

MOSENGEIL, *Langenbeck's Archiv.*, No. 12, p. 107.

A case of epithelioma of the ear in Langenbeck's Clinic, in which spontaneous healing took place after an attack of erysipelas.

RICOCHON, *Gaz. Hebd.*, 1885, No. 26, p. 425.

Multiple Lymphoma with Leukæmia.

Woman, aged 55. The cervical glands were enormously enlarged, reaching in one great mass from the spine behind to the chin in front. The tonsils were so big as to interfere seriously with deglutition and respiration. There was also a large mass in the groin. Erysipelas broke out, spreading from an excoriation by the nose, and extended over both sides of the face. By the sixth day the tumours had become very much smaller. The neck could be moved, and the pharynx was free. The diminution continued until the tumours had almost disappeared. Three weeks later they began to grow again. Very soon they had recovered all the ground that they had lost, and in a few months the patient died.

BRUNS, *Beitrage fur Klin. Chirurg.*, 1888, p. 443.

Melanotic Sarcoma of Breast.

Woman, aged 47. Tumour of left breast, eighteen months' duration, the size of a hen's egg, painful and growing

rapidly. In consistence it was soft in some places, firm in others. The surface was uneven. The skin adherent and ulcerated, but the growth was movable upon the muscles beneath. There were two groups of enlarged glands in the axilla, the size of walnuts. The tumours were excised in 1880, and the axilla cleared.

It was shown by microscopic examination to be a typical melanotic sarcoma. The wound healed except for a small fistulous opening, where the drainage tube had been. Recurrence took place rapidly, beginning at the opening, through which a deep black growth soon protruded. Thence it spread along the cicatrix, which gave way and began to gape.

Four weeks after the operation the patient was attacked by erysipelas, which wandered over the greater part of the body, lasting for three weeks, and leaving the patient very much weakened and emaciated.

After the erysipelas had run its course, the growth began to disappear, and in the course of a few weeks vanished entirely. The fistula healed up.

Up to date (1888) the patient has remained perfectly well, and there has been no recurrence.

KLEEBLATT, *Münchener Med. Woch.*, February 18, 1890.

Lymphadenoma.

The patient, a woman, aged 21, came because of a tumour the size of a pigeon's egg, situated upon the face. It was hard, red, growing fairly rapidly, and movable with the skin upon the subjacent structures. At first it was treated with iodide of potash ointment. In three days' time this caused some excoriation, and two days after the raw surface was attacked by erysipelas. The wound suppurated freely. By the time the erysipelas had subsided the tumour, which during the first three days had continued to grow, was reduced to half its former size. The ointment was tried again with the same result. The attack, however, was much more severe, leading to vesication. Desquamation set in on the sixth day, and by that time the tumour had entirely disappeared.

COLEY, *Annals of Surgery*, 1891; and New York Academy of Medicine, April 27, 1891.

Round-celled Sarcoma of Neck, with Five Recurrences in Three Years.

The last operation was performed by Dr. W. T. Bull in September, 1884. The growth was found too extensive for complete removal, and a large open wound, measuring five inches by two, was left. This rapidly filled up with flabby sarcomatous granulations.

Two weeks after the patient was seized with a severe attack of facial erysipelas. Shortly after this had passed off a second attack developed. Meanwhile the granulations quickly disappeared, the wound cicatrised and healed soundly.

Up to date (July, 1891), the patient has remained well, without recurrence.

COLEY, *Amer. Journal of Medical Sciences*, July, 1894.

Cancer en Cuirasse.

Woman, aged 38. Three severe attacks of accidental erysipelas in three months caused slight breaking down of a few nodules and rapid healing of the ulcerated area, but there was no decided check.

COLEY. Same.

Very Large Round-celled Sarcoma of Thigh and Pelvis.

Woman, aged 32. Mild attack of erysipelas followed by slight temporary improvement. Afterwards the tumour increased very rapidly.

DENDRIDGE. Same.

Cancer of Neck.

The tumour decreased until it was scarcely half the size it was before the attack. Then it remained stationary for a while, but it soon began to grow again.

WYETH. Same.

Recurrent Sarcoma of Hip.

The patient was a child aged 7, suffering from a sarcoma of the leg. The thigh was amputated in its lower third. The disease returned rapidly, and disarticulation at the

hip was performed. Recurrence followed, and in a short time there was an enormous fungating and bleeding outgrowth. Erysipelas set in; masses of the growth necrosed and sloughed away, and finally the tumour disappeared. The patient was well seven years later.

WESTBROOK. Same.

Recurrent Carcinoma of Breast.

Mild attack of erysipelas lasting for five days, followed by breaking down of the growth and much discharge. This lasted for three days, but it had no permanent effect upon the growth.

GERSTER, New York Surgical Society, 1892.

Sarcoma of Lower End of Femur.

Amputation was performed through the thigh at the level of the lesser trochanter. Recurrence took place very rapidly. An attack of erysipelas broke out; the tumour entirely disappeared, and the patient was well, without a sign of recurrence, three years afterwards.

CZERNY, *Münch. Med. Woch.*, September 3, 1895, No. 36, p. 833.

Carcinoma of Breast.

Patient had already been operated upon seven times for mammary carcinoma. On admission, the wall of the thorax was extensively infiltrated. At patient's earnest request, Czerny removed an elliptical piece of skin and soft tissue down to the ribs, leaving a wound the size of the hand. The intercostal spaces were full of carcinomatous nodules. Shortly after patient was attacked by erysipelas, which began in the wound and was so severe that she nearly died. When she recovered the wound was covered with healthy granulations, and in eight weeks it had completely cicatrised. Two years after the patient died of subacute pneumonia. There was no trace of carcinoma in the scar or in the axilla, but there were nodules present in the lungs.

In another case of mammary carcinoma, two operations had already been performed, and the scar and tissues around were full of shot-like masses. An elliptical portion of skin was

removed. Erysipelas broke out. The wound healed, and six years later the patient was alive without any recurrence, although the previous period of immunity had been scarcely six months.

Other cases of sarcomata that have disappeared or diminished very greatly in size after an attack of erysipelas have been recorded by Billroth (an inoperable sarcoma of the pharynx which sloughed away leaving a healthy granulating sore) and Tschudnowsky (quoted by Bruns, a lymphoma of the neck, which diminished in size from that of a goose's egg to that of a cherry). Hahn (*Inaug. Diss.*, Bonn, 1870, quoted by Bruns) mentions a rodent ulcer of the lower eyelid which diminished in size during an attack of erysipelas. And Lussana (*Schmidt's Jahrbuch.*, B. 146, p. 345) describes the healing of an ulcerated epithelioma of the temporal region in a woman 52 years of age under similar conditions.

APPENDIX II.

Cases of Sarcoma and Carcinoma in which Erysipelas has been Caused Intentionally.

Busch, *Berl. Klin. Woch.*, 1868, No. 12.

Sarcoma of the Cervical Glands of Five Months' Duration.

The patient was a woman aged 19. The tumour was growing rapidly, and was quite beyond operation. The sterno-mastoid and vessels could not be isolated. The larynx and trachea were pushed to one side. The parotid was infiltrated and the facial nerve paralysed. The mouth could scarcely be opened, but the aperture was sufficiently large to see that the growth involved the pillars of the fauces as well.

The skin was cauterised lightly and the patient placed in a bed notorious for the frequency with which patients in it were attacked by erysipelas. An outbreak occurred in a week, beginning from the cauterised surface. The patient's temperature never rose above 40° C. From the first the tumour diminished rapidly in size. By the end of the second week the masses that lay behind the sterno-mastoid had gone. The skin was loose. The facial nerve became free. The

mouth could be opened and the growth had diminished to the size of a small apple and had become freely movable.

Then, at the end of the second week, the pulse suddenly became small and thready; the temperature fell to below 30° C.; the eyes became glazed and the patient appeared to be dying. The cause suggested was the rapid entrance into the circulation of an enormous amount of the products of the decaying growth. Under stimulation the patient rallied, and as the erysipelas disappeared she regained strength; but simultaneously the tumour began to grow again, and in fourteen days' time it was larger than a child's head.

FEHLEISEN, "Zur Ætiologie der Erysipels."

(1) *Multiple Fibrosarcoma of Skin.*

Woman, aged 58. There was a number of nodules in the left gluteal region, and a dependent tumour so large that the patient could scarcely stand or walk.

Inoculation with a pure culture after scarification of the skin was tried in August, 1882. Slight reaction followed, but by the third day it had quite disappeared. On the fourth day a genuine attack of erysipelas, with a severe rigor, occurred, the redness beginning a few centimetres from the place where the culture had been inoculated. The temperature continued very high, and on the sixth day the patient's condition was very precarious. On the 7th the thermometer rose to 41·6°, the redness continuing to spread. By the fifteenth day the attack had subsided.

From the first day of the attack the superficial nodules became smaller and softer; some disappeared entirely, but not all. The tumour increased in size and weight during the attack; subsequently it underwent partial degeneration, but the result was not sufficient to justify inoculation a second time.

(2) *Intra-Ocular Sarcoma.*

The patient was a girl, aged 8, whose eye had been removed for sarcoma, and in whose orbit recurrence had taken place. There were also enlarged glands.

An attack of erysipelas was caused by inoculating the skin over the tumour, but it only lasted two days. The tumour

became very red and covered with vesicles, but its size remained the same. The enlarged glands diminished considerably, and subsequent attempts at inoculation failed.

(3) *Carcinoma of Breast. Three recurrences.*

The tumour entirely disappeared in eight days. The skin over the thorax became perfectly flat, where before there had been a hemispherical swelling. One little hard spot the size of a pea persisted for some time, but that too at length disappeared. The patient is described as well. (There was no recurrence at the end of six months.)

(4) *Carcinoma of Breast. Disseminated.*

Eight nodules disappeared. Five remained. This swelling showed a marked diminution by the fourth day, and this continued for a week after the erysipelas had subsided. The skin became wrinkled and was easily movable over the subjacent structure, but no further change took place.

(5) *Carcinoma of Breast, operated upon six years before. Two recurrences.*

Very severe attack of erysipelas, lasting for eleven days. One tumour became soft and fluctuating. On being opened it discharged some 10 cc. of a yellowish-white, pus-like fluid. In three days the incision had closed; no general diminution.

Janicke and Neisser, *Centr. f. Chirurg.*, 1884, p. 401.
Carcinoma of Breast.

Woman, aged 40. First operation in October, 1882, for very rapidly-growing carcinoma. Recurrence in three months, spreading into the soft tissues of the pectoral and axillary regions.

In April, 1883, the arm began to swell and the pain became almost unendurable. On May 20 an erysipelas culture that had been obtained from Fehleisen was rubbed into the skin covering the tumour after it had been well scarified. The same day there was a rigor. On the next day the erysipelas had spread over the whole pectoral region; the temperature was 41°, and the pulse very rapid. The left arm, the chest, abdomen and back were attacked next; in a few hours the

pulse rate became 140 in the minute, and the patient died on the fourth day.

The tumour had changed very considerably both to the eye and the finger. An enlarged gland under the clavicle had disappeared. The size of the main growth had diminished; it was much softer; the skin over it was wrinkled, and when it was cut into, it appeared to consist of connective tissue trabeculæ separated from each other by collections of serum. There was no suppuration.

The microscopic examination showed that the cell nests had been invaded by columns of micrococci, which had penetrated between the cells and surrounded them. Whether the cocci had actually penetrated the cells or not could not be ascertained. The carcinomatous cells themselves did not show any definite change. In places they were paler and less distinct, as if undergoing coagulation necrosis. Nowhere was there any sign of inflammation.

It seems probable that the carcinoma nests corresponding to the invading micrococci are destroyed by the direct action of the organisms, without any inflammatory process; but the destruction is only partial.

KLEEBLATT, *Münchener Med. Woch.*, February 18, 1890.

(1) *Lymphosarcoma of Tonsil.*

The patient was a strongly-built, corpulent man, aged 54. The left tonsil was occupied by a tumour the size of a hen's egg, fairly movable and not involving the surrounding structures. The lymphatic glands behind the angle of the jaw on the same side, and those near the larynx on both sides, were considerably enlarged. The chest was emphysematous; the heart weak and the pulse soft. There was some difficulty in swallowing liquids; solids found their way down more easily.

The patient was operated upon in May, 1887. The lymphatic and submaxillary glands were removed; the lower jaw resected temporarily and the tonsil enucleated. In October some glands made their appearance in the supraclavicular region and were treated with injections of Fowler's solution. Forty-five injections were made in all. The only result was loss of appetite and strength and the formation of six abscesses.

The tonsil enlarged again; dysphagia and dyspnœa made their appearance; and the patient began to fail.

On March 7, 1888, he was attacked with erysipelas. On the 9th the sinuses began to suppurate freely and the tumour became softer. Two days later it was much softer. Desquamation set in on the 18th, by which time the tumour had shrunk to a quarter of its former size, and by the 21st it had almost disappeared. The sinuses left by the abscesses still persisted. In April all that was left were two small growths near the root of the tongue, which were removed successfully.

In May the growth began again, and also made its appearance in the axilla. On the 20th there were enlarged glands in the neck on both sides.

On June 2 the patient was inoculated with an erysipelas culture on both sides of the back. The next day he was seized with shivering. Three days later the tumour was softer, and the sinuses were discharging profusely. Desquamation did not begin until the 15th. All the swelling on the right side had gone, and that on the left was much smaller.

In July recurrence took place again. Inoculation was tried and failed. The patient steadily became weaker and died in November.

KLEEBLATT. *Loc. cit.*

(2) *Lymphosarcoma of Neck.*

The patient, a stout man aged 52, was admitted for a tumour the size of a hazel-nut, situated between the mastoid process and the angle of the jaw on the left side. It was firm and partly fixed. The left nostril was also blocked, as if the growth involved this as well.

Injections of Fowler's solution were tried but without success; the only result was an abscess.

On July 22 a living erysipelas culture was injected. The next day there was a rigor. On the 24th the erysipelas had spread over the body; on the 25th it attacked the head, causing vesicles to form on the scalp. Desquamation began on the 29th.

The tumour began to soften on the second day. The abscess discharged profusely. By August 4 all trace of tumour had disappeared and the nostril was perfectly free.

COLEY, *Amer. Jour. of Med. Sciences*, May, 1893, and September, 1896.

(1) *Inoperable Sarcoma of Neck with secondary Sarcoma of Tonsil. Two recurrences.*

The patient had been operated upon twice by Prof. Durante of Rome, and by Dr. W. T. Bull of New York, in March, 1891. On the last occasion a portion only could be removed. In May, 1891, the tonsillar tumour was so large that only liquid food could be swallowed, and that with difficulty. The patient was only expected to live a short time. Scarification and injection proving useless, bouillon-cultures of the living streptococcus of erysipelas were injected directly into the tumour from May until October. A certain amount of local and constitutional disturbance took place, but no attack of erysipelas. There was, however, some improvement, and whenever the injections were discontinued the growth increased in size. On October 8 a new and especially virulent culture obtained from Prof. Koch was injected, with the result of causing a severe attack. The tumour of the neck began to disappear at once. By the second day it had partially broken down, and had begun to discharge a substance more like the caseous *débris* of a tuberculous gland than pus. The tonsil decreased in size. The outlying nodules disappeared without breaking down, and the patient rapidly improved until he had regained his health and strength.

He had no treatment afterwards. In October, 1895, he was in good health. There was then at the site of the old scars a small mass made up of fibrous and cicatricial tissue which had remained unchanged for four years. The tumour of the tonsil was still present, though it was distinctly smaller. The general condition was excellent.

The portion removed on the last occasion was shown by microscopic examination to be a myxosarcoma.

COLEY, *Amer. Journ. of Med. Sciences*, July, 1894, and September, 1896.

(2) *Recurrent Sarcoma of Back and Groin.*

The patient, a man aged 46, was admitted with a large sarcoma growing in the lower lumbar region and a tumour the size of a goose's egg in the groin. The latter

had been removed and recurred rapidly. The lumbar swelling had been present for five years, was hard and nodular, of a bright red colour, and freely movable with the skin upon the deeper structures.

Injections of freshly prepared living bouillon-cultures were made into the tumour at intervals of two or three days for three weeks. Each injection was followed by slight local redness with well-marked constitutional reaction. The tumour perceptibly diminished in size, without suppurating or breaking down. The injection of a fresh and more virulent culture then caused a typical attack of erysipelas both in the back and the groin. The temperature rose to 105° and the pulse to 130. The effect was most marked. From the next day the tumour lost its lustre and colour and diminished rapidly in size. The second day it broke down and began to slough. A few days later the tumour in the groin did the same. In three weeks' time both tumours had entirely disappeared. Recovery was retarded by the formation of an empyema, caused by a blow upon the chest.

In two months' time small nodules began to appear again upon the back. Inoculation was tried again. One nodule disappeared; the rest grew and coalesced after a temporary check. Nodules also made their appearance in the groin.

Fresh inoculation was tried from a very virulent case, but although the temperature rose to 101·5°, no attack followed, and as soon as the fever subsided, the tumour, which had shrunk a little, began to grow once more.

After many trials, a genuine attack was caused a second time. This lasted for a week, and at the end of the week the tumour and the nodules had gone.

Two weeks later, in spite of some mild (spontaneous) outbreaks of erysipelas, the growth began again. The tumour in the back was excised, but the granulations began to fungate before the wound had healed. The tumour in the groin also reappeared. Injections of the toxins of the streptococcus and the bacillus prodigiosus, mixed together at the time of using, were then tried with complete success. The tumours rapidly disappeared, the last injection being made in March, 1893.

In April, 1896, the patient was perfectly well, without a sign of recurrence. In September of that year, however, a tumour made its appearance in the abdomen and the patient began to lose flesh and strength.

(3) *Sarcoma of Breast. Seven Recurrences.*

Patient aged 38. The tumour first appeared five years before. On the last occasion it recurred before the wound had healed.

There were three separate masses. The first injection caused an attack of erysipelas that lasted for a week. On the second day the tumours broke down and sloughed, one almost disappearing. Soon, however, they began to grow again.

A second attack was induced by scraping away part of the growth and introducing ten minims of a culture into the wound. This attack lasted for eleven days. All the growths diminished in size, but the check was only temporary. Two were removed subsequently, leaving large open wounds which healed up very easily. The patient gained weight and strength. Since then she has been treated with mixed toxins.

COLEY, *Annals of Surgery*, 1891.

(4) *Sarcoma, Round-celled, of lower end of Femur.*

The patient was aged 16. Six months before the knee had been injured. On admission the lower end of the femur was enlarged, especially on the outer side, by an enormous round-celled sarcoma that had started in connection with the periosteum and made its way into the medulla. The general health was very bad.

Scarification of the skin, injection of fresh cultures, and placing the virus on the fungating surface were all tried successively, without inducing an attack. There was some reaction, the temperature rising to 103° and the pulse to 120; but there was no chill or vomiting and the symptoms soon subsided. Three days later another injection was made into the tumour. This was followed by a temperature of 104·5° and vomiting; but everything disappeared in the course of four or five days. The only change so far as the tumour was concerned was that the sloughing granulations on which the virus had been placed were beginning to clear.

A third injection into the tumour was followed by a very severe reaction. A rigor set in within half an hour; the pulse became so rapid and weak that brandy had to be

administered, and the temperature rose to 105°. The granulations continued to improve in appearance, but there was no change in the general health. The tumour formed an enormous fungating mass. Enlarged glands made their appearance in the groin, and though two more injections were made, there was no further change.

COLEY, *Annals of Surgery*, 1891.

(5) *Sarcoma of Dorsal Spine.*

The patient was admitted with a swelling over the dorsal region of the spine that had developed one year and a-half after an injury. The tumour was removed in April, 1891, and found to be a round-celled sarcoma attached to the spines of two of the vertebræ. The spines were removed with it.

Recurrence took place almost immediately, and a second operation was performed in June of the same year. This also was followed by recurrence, and in July inoculation was tried.

The two first injections, made in the subcutaneous tissue, were followed by a certain amount of redness, but by no constitutional symptoms; a third, made into the tumour itself, was followed in two hours' time by a severe chill (temperature 103°), vomiting and headache. This subsided in two days, leaving the tumour more movable and smaller in size. Two more inoculations were tried without any apparent effect; and as the tumour began to increase again a third operation was performed.

COLEY, *Amer. Jour. of Med. Sciences*, July, 1894.

(6) *Recurrent Sarcoma of Neck.*

Man, aged 65. Considerable decrease in size, but patient died on the fourth day.

COLEY. Same.

(7) *Recurrent Sarcoma of Breast.*

Female, aged 55. Acute pleurisy and death on the sixth day.

COLEY. Same.

(8) *Enormous Sarcoma of Femur and Pelvis.*

Man, aged 48. Slight but temporary decrease in size. Death two months later. Abdomen found to be full of pus.

In the following cases, reported by Coley (*Journal of American Med. Sciences*, May, 1893), the attempt at exciting an attack of erysipelas was not successful. Injections of living cultures of the streptococcus of erysipelas in bouillon were made at frequent intervals, but they were not followed by more than a temporary and transient reaction. The temperature rose; nausea, vomiting, malaise, headache, &c., followed; sometimes there was an erythematous rash; but the symptoms subsided within thirty-six hours. They were, in other words, the same as those induced by sterilised or filtered cultures of weak intensity.

One of these was an inoperable sarcoma of the face involving the entire left side, and adherent to the bones, in a man aged 75. Three injections of bouillon cultures were made without exciting an attack, although the temperature rose to 102·5°. The only effect was a slight softening. A second was that of a man, aged 45, suffering from a recurrent sarcoma of the back. The tumour, which occupied the entire midscapular region, had been removed a year and a-half before, and recurred at the end of four months. No result followed, the cultures being too attenuated.

In three other cases the tumours were carcinomatous. One was that of a woman, 40 years of age, who had had four operations in less than a year for recurrent carcinoma of the breast. The tumour was the size of a goose's egg, protuberant and ulcerated, and there was a hard nodule in the opposite breast also. In a second there was recurrent carcinoma of the cervical glands; and in a third, an old man 75 years of age, enlargement of the inguinal ones, after amputation of the penis. In none of these was there any real improvement, although in the two first there was partial degeneration and temporary diminution in size.

APPENDIX III.

Cases of Sarcoma and Carcinoma which have been Treated by the Injection of the Toxins of the Streptococcus of Erysipelas alone, or in conjunction with those produced by the Bacillus Prodigiosus.

Lassar, *Deutsch. Med. Woch.*, No. 29, July, 1891.

Lassar was the first to utilise Brieger and Frankel's discovery that toxins could be separated from the organisms that produced them, and to inject the toxins by themselves.

The streptococcus of erysipelas was grown in bouillon for several weeks at a temperature of from 32° to 35° C. The products thus obtained were separated off by filtration, sterilised with steam and injected into the ear of a rabbit. This was followed by swelling, redness and desquamation, the local signs of erysipelas, but not by any general symptoms or rise of temperature. Dr. Friedlander then experimented upon himself with the solution of toxins diluted to one tenth. In five hours the injection was followed by pain, redness and œdema, but not by fever. The swelling increased until there was a thickened patch the size of a crown piece, and the next day the hand was stiff, and there was loss of appetite with headache and sleeplessness, but in five days' time all the symptoms had disappeared.

The next step was to inject the solution into the nodules of a case of epithelioma of the face supervening upon lupus, in which Koch's tuberculin had been tried and failed. Less than half the amount that Friedlander injected into himself was used. The local effect was similar but less in degree. Subsequently larger doses were employed. After some time these failed to give rise to any reaction, and at the end of some weeks, as the tumour did not show any signs of disappearing, the treatment was abandoned.

Coley, *Amer. Journ. of Med. Sciences*, 1896.

(1) *Sarcoma of Abdominal Wall and Pelvis.*

The patient was a boy aged 16. The growth measured six inches by five; involved apparently the entire thickness of the abdominal wall; was attached to the pelvis; and from

the symptoms and position involved the wall of the bladder as well. A section that was removed proved that it was a spindle-celled sarcoma.

The patient was treated for nearly four months with the mixed filtered toxins of the erysipelas streptococcus, and the bacillus prodigiosus. At the end of that time the tumour had nearly disappeared, and after the injections were left off the little that remained was gradually absorbed.

The treatment was commenced in January, 1893. In May, 1896, the patient was well and there was no sign of recurrence.

(2) *Sarcoma of Abdominal Wall.*

The patient was a woman aged 28. An exploratory operation had been performed, but it was found impossible to remove the tumour. A portion taken for examination showed that it was a fibrosarcoma.

Local injections of the mixed filtered toxins were given for six weeks; then, after an interval of a month, for four weeks more. At the end of that time all that remained was a slight induration, and this disappeared a few weeks later.

Two years and a-half afterwards the patient was in perfect health, without a trace of hardness.

(3) *Recurrent (three times) Sarcoma of Leg and Popliteal Region.*

The patient, a girl aged 15, had been operated upon three times by Dr. W. T. Bull, of New York. The tumour was a spindle-celled sarcoma, originally starting in one of the metatarsal bones. Syme's amputation was performed in 1890. Six months later recurrence took place in the stump and in the popliteal region. In January, 1894, the tumour in the popliteal region was the size of a child's head, and the one in the stump the size of a hen's egg. The former was partly excised.

Toxins were injected for two months. The tumour of the stump entirely disappeared, and the patient gained seventeen pounds in weight. The indurated mass in the calf also disappeared, and the patient remained in good health until October, 1895. Then a tumour was discovered in the right gluteal region. The injections were begun again, and the mass slowly diminished in size, and became more movable.

In February, 1896, it was sufficiently free to be removed. The pathologist reported that it was a spindle-celled sarcoma.

(4) *Sarcoma of Scapula, involving Wall of Thorax.*

The patient, a girl aged 16, was admitted into the incurable ward of the New York Cancer Hospital, in June, 1894. The tumour had begun in the region of the left scapula four months before, and at the time treatment was commenced the growth extended to the vertebral line behind, measured thirteen inches vertically, and reached beneath the axilla to the sternum in front. It was firmly fixed, but the skin over it was free. Movement of the arm was much impaired, and the general condition very unsatisfactory.

Mixed unfiltered toxins were injected locally, and continued at short intervals for three months. After three weeks the arm could be raised to a vertical position, and in three months the mass had entirely disappeared.

A microscopic examination of a portion that was removed for the purpose, showed that it was a spindle-celled sarcoma.

(5) *Round-celled Sarcoma of Abdomen, probably springing from Omentum.*

The patient, a woman aged 23, began to suffer from pain in the right hypochondriac region in May, 1894. A tumour was found in August, 1894, and an exploratory operation performed by Dr. Willy Meyer. On opening the abdominal cavity a hard irregular infiltration was found, involving the omentum, ascending colon, a loop of small intestine and the border of the liver, matting them all together. A wedge-shaped piece removed for microscopic examination, proved it to be a round-celled sarcoma.

In September the wound had closed to a sinus, and treatment with mixed toxins was begun, injections being made sometimes into the abdominal wall, sometimes into the buttocks. This was kept up with intervals until February, 1895. By that time only an indistinct resistance remained, and the general health was perfect. An attempt was made to close the sinus in September, 1895, and again in March, 1896. On the latter occasion it was found to communicate with the gall-bladder. Several calculi were removed; the peritoneal

cavity was opened and explored, but there was not the slightest evidence of the original tumour.

(6) *Sarcoma of Spine.*

Woman aged 28. History of a small growth having been removed from between the breast and axilla a year and a-half before. A year ago a small swelling made its appearance over the dorsal spine. At present the patient is very much emaciated and bedridden. The lower limbs are paralysed; there are bed-sores, and albumin and casts are present in the urine. Over the lower dorsal region there is a fusiform swelling about six inches in length, absolutely fixed to the bones beneath. Injections of very small doses were made for a month, with a wonderful degree of improvement. The tumour diminished very markedly in size; the patient was able to move both legs; the bed-sores partly healed, and the general condition greatly improved. In April, 1895, the patient could stand and even walk a few steps; and had regained control over rectum and bladder. But after this there was no further improvement, and the patient died in August, several other growths having developed meanwhile.

The injections were given in the back, but two small recurrent nodules in the breast disappeared.

There was no microscopic examination, but the diagnosis does not admit of doubt.

(7) *Sarcoma of Iliac Fossa.*

Patient aged 55. Pulsating tumour of six months' duration in right iliac fossa, the size of two fists. Microscopic examination.

Injections of the mixed toxins were made for the greater part of the year. The tumour slowly decreased in size, and the patient remained in good health. At the end of that time he disappeared.

(8) *Spindle-celled Sarcoma of Hand, recurring six times.*

The patient was operated upon for the first time in 1888, for a rapidly growing sarcoma of the palm of the hand. The first recurrence was in 1891; the fifth in January, 1893. The tumour very soon made its appearance again, and the axillary

glands became enlarged. Injections of the mixed toxins were kept up more or less regularly throughout the spring of 1893, with the result that the tumour decreased in size and ceased growing, even when the injections were stopped. In October, 1893, the axillary glands were removed. In June, 1894, the condition was very unsatisfactory, and the patient was admitted into hospital in order that the treatment might be pushed. At the end of three weeks the patient's health began to give way, and as the tumour had softened and necrosed, ether was administered and the whole mass scraped out. No further injections were made and the patient soon regained health and put on twenty pounds in weight. She remained well until August, 1895, when there was a local recurrence, and the forearm was amputated. The patient now shows signs of recurrence in the brain (September, 1896).

(9) *Osteochondroma of Ilium.*

Patient was a man aged 23. The tumour, which was of one year's duration, extended from the sacrum behind to the rectus in front, and filled up the greater part of the right iliac fossa. The patient was much emaciated.

Mixed filtered toxins were injected for five weeks. The tumour softened and broke down and large masses sloughed out. High temperatures continued for a month after the injections had been stopped, due to the absorption of dead tissue. Then the patient rapidly regained health and strength. In seven months from the beginning of the treatment the tumour had entirely disappeared and the patient had put on forty pounds in weight. Two months later recurrence took place and continued in spite of further treatment.

(10) *Spindle-celled Sarcoma of Hand.*

Patient aged 18. In July, 1895, a small swelling was noticed in the palm of the hand. This was excised in October, and shown by microscopic examination to be a spindle-celled sarcoma. Recurrence took place and a second operation was performed in January. In February it had returned again, and a mass had made its appearance above the wrist as well. Injections of the filtered toxins and later of unfiltered ones were given, the latter producing a severe reaction. By the

end of March the mass had almost disappeared, and in May there was no trace of it. All the injections were made in the arm.

(11) *Probable Sarcoma of Sacrum.*

Patient aged 38. In February, 1895, he began to lose flesh and strength; this was followed by great pain in the sacral region and down the legs, and by loss of power over the legs. *Per rectum* a mass could be felt fixed to the anterior surface of the sacrum, of firm consistence. The patient was much emaciated.

Mixed unfiltered toxins were injected into the buttocks in May, daily. In one week there was improvement; in six weeks the patient returned home, and by the end of June he had gained twenty-eight pounds in weight and was as well as ever. One year later he was in perfect physical health.

In addition to these cases Dr. Coley (*Amer. Journ. of Med. Sciences*, September, 1896) quotes the following, under the care of other surgeons.

(1) *Sarcoma of Tibia, under the care of Dr. John E. Owens.*

Myeloid sarcoma (central) of tibia in a boy aged 7, five months' duration. Injections from April 10, 1895, to July 10, at intervals of one or two days. The leg became almost normal in size, the difference in circumference being only half an inch.

In November, 1895, the scar appeared somewhat elevated, but further treatment was refused.

(2) *Spindle-celled Sarcoma of Calf, under the care of Dr. L. L. McArthur.*

The original growth was removed by operation. Recurrence took place in seven months. Treatment was continued for twelve weeks with the result that the tumour slowly and steadily disappeared. The patient, a woman aged 40, was three and a-half months pregnant.

Seven months later there was no recurrence. In April, 1896, there was a slight suspicion.

(3) *Osteosarcoma of the lower end of Radius, under the care of Dr. McArthur.*

The tumour had already been removed three times. Amputation was advised. After twelve weeks' treatment the growth had entirely disappeared. Three months later there was no recurrence.

(4) *Round-celled Sarcoma of Orbit, under care of Dr. McArthur.*

The patient, a child aged $5\frac{1}{2}$ years, was almost moribund. There was a sarcoma growing from the antrum, protruding into the nose, causing exophthalmos, and attended by enlargement of the cervical glands. The toxins were injected every other day, and at the end of two weeks the patient was eating heartily and running about. The enlarged glands were removed, and later the contents of the nasal cavity and antrum. The wounds healed up and the child's weight increased from thirty-seven pounds to sixty-nine. Treatment was discontinued; recurrence followed; the toxins were tried again, and although there was some improvement, it did not continue.

(5) *Round-celled Sarcoma of Orbit, under the care of Dr. Tilly and Dr. McArthur.*

The tumour entirely disappeared. A short time afterwards the patient, apparently cured, died quite suddenly.

(6) *Round-celled Sarcoma of Breast, eight times recurrent, under the care of Dr. T. F. Rumgold.*

The tumour entirely disappeared. The patient died a few weeks later with numerous internal metastases.

(7) *Spindle-celled Sarcoma of Uterus, under the care of Drs. R. M. R. Stone and C. C. Allison.*

The cervix had been removed, but now the disease was too far advanced for hysterectomy. The patient was exhausted by repeated hæmorrhages.

Injections were made into the scapular region and later into the tumour. In six weeks the tumour had apparently disappeared and the patient was up and about.

(8) *Spindle-celled Sarcoma of the Axilla, under the care of Dr. M. Storrs.*

Portions of the growth were removed on three occasions. In four months it entirely disappeared.

(9) *Myxosarcoma of Hand, under the care of Dr. S. W. Wilcox.*

The tumour nearly disappeared.

(10) *Recurrent Sarcoma of Arm, under the care of Dr. J. Flippen.*

The patient was aged 74. During one year he had undergone twenty operations. Under treatment by the toxins the growth diminished in size from that of a fist to that of a filbert, and the patient improved to such an extent that he was able to get up and attend to his work. The injections were left off. In three weeks the tumour began to increase. Amputation was performed and in three weeks it returned in the stump.

(11) *Carcinoma of Breast, under the care of Dr. Howland.*

The tumour diminished so much in size and became so free that it could have been removed. Patient declined operation. The injections were left off for two months; the tumour began to increase again; and when the injections were resumed they did not appear to have any effect.

Dr. W. B. Johnson, *New York Med. Rec.*, November 17, 1894.

Spindle-celled Sarcoma of Palate.

The patient was a boy aged 16, who had always been delicate and had frequently suffered from attacks of sore throat and tonsillitis. Six weeks before he had complained of soreness of the throat, difficulty of deglutition and slight dyspnœa. On examination, the entire soft palate, the greater part of the hard, the pillars of the fauces, tonsils, base of tongue, epiglottis, upper part of larynx and back of pharynx, were covered with cauliflower-like granulations, some of which were already ulcerated. The tissues everywhere were enormously thickened, and in places dusky from distended and tortuous vessels.

A portion removed for microscopic examination was proved to be spindle-celled sarcoma.

Injections were commenced on October 31, 1893. At first filtered cultures of the erysipelas coccus only were used. As the dose increased the toxins formed by the bacillus prodigiosus were added. The injections were given in various parts of the body, and generally caused pain, redness and swelling. There was usually a rise of temperature with a feeling of chilliness, and sometimes a very violent rigor, without its being possible to offer a reason for the difference. One chill was so violent and followed by such serious symptoms, that the patient was confined to bed for a fortnight and all treatment stopped.

A peculiar attack of keratitis developed at the end of five months. This also caused an interruption in the treatment for three weeks.

The result was a steady but slow improvement. In two weeks the soreness left the throat and he was able to swallow solids as well as fluids. The granular masses disappeared, some by necrobiosis, others by absorption, and the patient's weight increased from eighty-six pounds to one hundred and seven. No injections were made after June.

In October, 1894, there were only one or two spots of ulceration; cicatrisation and contraction had taken place and white bands of adhesion extended from the hard palate to all parts of the fauces.

In September, 1896, the patient was perfectly well, and there was no sign of any recurrence.

Czerny (*Münch. Med. Woch.*, September 3, 1895, No. 36, p. 833) made use of toxins prepared by Werner and Petersen. The streptococcus from a case of erysipelas was cultivated in bouillon for three weeks, mixed with the bacillus prodigiosus and sterilised at 58° C. The dead bodies were not separated by filtration.

The patient was a woman aged 35. During pregnancy a swelling had made its appearance in the right parotid region. This had grown rapidly and had made its way into the meatus, fungating through the skin and causing facial paralysis. Behind the ear there was a mass the size of a large fist, and the soft structures around were infiltrated for

quite two inches. Along the sterno-mastoid were a number of painful glands. The tumour was diagnosed as a diffuse infiltrating carcinoma of the parotid, but under the microscope it appeared to have the structure of a small round-celled sarcoma with scattered epithelial nests and cells.

Eighteen injections in all were made into the tumour. The reaction bore no proportion to the amount injected. On many occasions there were rigors, with severe pain in the head and back. The tumour swelled up and became œdematous. The portion in the meatus disappeared so that the membrane became visible. The facial paralysis almost went, and the growth contracted to a small thickening behind the ear. The pain disappeared. The skin became movable again, and the parotid was quite soft. At this stage the patient left the hospital.

Czerny mentions three other cases of sarcoma of the pharynx in which he was trying injections, but the time was too short to say whether any good would result or not.

The following are the conclusions to which Czerny came:—

The sterilised, unfiltered, mixed cultures of the bacillus prodigiosus and the streptococcus of erysipelas cause fever, with rigors and other constitutional symptoms, but very little local inflammation. The intensity depends upon the dose, the individual, and the rapidity of absorption. It is greater when the injection is made directly into the tumour. After a time loss of appetite, &c., may follow.

Injections have a definite effect upon sarcomata and under favourable conditions may lead to healing. The tumours fill with serum and are absorbed; or they may soften more rapidly and slough.

In carcinoma the injections may delay growth but they do not lead to cure.

Spronck (*Ann. de l'Institut Pasteur*, 1892, p. 883) experimented upon twenty five cases (eight sarcomata, two of which were melanotic and seventeen carcinomata) with very little success. The cultures employed were of various ages and were grown under different conditions. The culture fluid consisted of beef bouillon mixed with peptones, white of egg and serum. Half the product was sterilised by steam and concentrated, after having 5 per cent. glycerin added to it.

The other half was sterilised by filtration and then the two were mixed together. The object apparently was to secure the maximum effect, it being thought that some of the toxins might be destroyed or weakened either by one process or the other.

The injections were tried first of all upon dogs. Two (one with an epithelioma of the anus, the other with a fatty tumour) were not affected in any way. In five others (three epitheliomata and two sarcomata) the tumours became dusky, hot and painful, and in two softening and necrosis set in. The growths were removed before they had altogether disappeared, and sufficient evidence was found to show that they were undergoing rapid fatty degeneration.

Of the twenty-five cases none were cured. The injections were usually followed by a rise of temperature, with a certain amount of pain in the tumour and in the large secondary growths. In three there was a good deal of swelling and redness.

The best result was obtained with the sarcomata. In one a large growth disappeared and some secondary ones became smaller. In the others the improvement was very slight, and only of a temporary character. In some of the tumours that were removed there was evidence of degeneration, the fibrous tissue stroma enclosing spaces filled with pigment, *débris* and leucocytes. The carcinomata showed very little change at all.

Friedrich (*Langenbeck's Archiv*, No. 50, p. 709, and the *Proceedings of the 24th Congress of German Surgeons*, 1895) met with little or no success.

The material for injection was prepared in various ways. The streptococcus was taken from different cases, none of which, however, had proved fatal. (1) Cultures of the s. longus of various ages were sterilised by heating for an hour to between 56° and 60°. (2) A culture of the same was inoculated with the bacillus prodigiosus, kept for seven days at 37°, and then sterilised by raising the temperature to 100° for an hour. (3) Another culture of the s. longus was filtered through Kitasato's filter under a pressure of 60 cm., and (4) a similar culture was inoculated with the bacillus prodigiosus and filtered in the same way at the end of

seven days. Friedrich throws some doubt upon the question whether the bacillus prodigiosus is killed by exposure to a temperature of 58° for an hour.

So far as the cultures of the pure streptococcus were concerned, Friedrich found that injections were borne equally well, whether sterilisation by heat or filtration had been employed. Exceptionally there was a rise of temperature with shivering.

In the case of mixed cultures, even small doses caused rigors and high fever. Those a little larger were followed by collapse, cyanosis, dyspnœa, coldness of the extremities, and even more alarming symptoms.

Subcutaneous injections never suppurated and caused only a certain amount of local inconvenience with redness on the surface.

Parenchymatous ones into the tumour itself were followed by pain, tension, œdema, and in six cases sloughing. In two the whole growth sloughed.

In tumours that were not injected there was no microscopic change perceptible. Those that were injected directly showed an infiltration of leucocytes with a certain amount of evidence of degeneration. The nuclei and the cells did not stain so well as they usually do; but there was no new formation of vessels or of connective tissue. Friedrich remarks that infiltration such as this would speedily cause local changes, and where there were other injurious influences at work, such as vascular obstruction, would naturally lead to necrosis.

In one case there was some hyaline degeneration of the connective tissue with fatty metamorphosis of the carcinomatous cells; but no weight can be attached to this, as similar appearances are by no means uncommon in carcinoma.

Friedrich tried injections in thirteen cases of carcinoma, four of sarcoma, and two of lymphosarcoma.

In two cases of carcinoma the growth seemed to spread the more rapidly.

One case of carcinoma of the breast apparently shrank and diminished in size, so did some carcinomatous inguinal glands in another case; a parotid sarcoma in a third; and some recurrent lymphosarcomatous nodules in a fourth. But this was the utmost of the improvement locally.

In six some sloughing took place. In two (an epithelioma and an endothelioma) the whole tumour sloughed out.

One patient with carcinoma of the breast, who was in such a state of marasmus that her death was expected daily, improved considerably for a time, and put on weight. In another (carcinoma of the ovary) the œdema of the legs disappeared, and one or two others were apparently benefited, but only for a time.

Freidrich concludes that the toxins have no specific effect whatever, and that the changes the tumours sometimes undergo are merely the expression of the cumulative action of a number of injurious influences working together.

CAMPANINI, *Il Policlinico*, July 1, 1895.

Sarcoma of Nasopharynx.

An injection of ½ ccm. into the tumour was followed by a rigor, very high temperature, drowsiness, headache and tinnitus. This continued for ten hours. At the same time there was suppression of urine with intense thirst.

The next day a second smaller injection was followed by even more alarming symptoms. After this experience an attempt was made to attenuate the toxins by dilution and exposure to high temperature. This attenuated toxin was injected on thirty occasions in the course of a month, the dose being progressively increased.

The tumour continued to grow, and a part that was removed for microscopic examination showed no sign of any retrogressive change.

A negative result was also obtained in a case of sarcoma of the breast.

GOTHAM BACON, *Trans. Amer. Otological Society*, 1895.

Sarcoma of Neck.

The growth made its first appearance below the left ear, and extended in a very little while from the mastoid to the angle of the jaw and the middle of the sternomastoid. The left tonsil was also involved. Mixed toxins were injected into the tumour, apparently checking its growth and setting up local suppuration. The patient gradually sank, death being caused immediately by arterial hæmorrhage from the tonsil.

The immediate effect of the injections was a rise of temperature of from 2° to 3°, with some failing of the pulse. There was a distinct retardation of the growth and a gradual softening and formation of abscess over the places where the fluid was injected.

RÉPIN, *Revue de Chirurgie*, 1895, p. 465.

Répin experimented with the streptococcus from a fatal case of erysipelas and with a culture which had been intensified by passing through rabbits. The toxins were sterilised either by heat or by filtration. The former were of little strength, the latter, when injected, gave rise to a good deal of redness with œdema that persisted for twenty-four hours or more, and pain. The lymphatic glands never became affected.

In order to diminish the pain, dilution was tried first, and then intravenous injection. The latter plan succeeded, but the effect was much more intense than when the injection was made subcutaneously, rigors and severe headache being not uncommon.

Répin did not make use of the toxins of the bacillus prodigiosus. He admits that they are toxic in the case of men, but denies that they have any effect upon the growth of tumours, and he suggests that Coley has been misled in making use of them for this purpose. The bacillus prodigiosus undoubtedly renders guinea-pigs much more susceptible to tetanus than they otherwise are, but this is because the toxins formed by the bacillus prodigiosus supply the place of those which the tetanus bacillus has not yet had time to form. The help, in other words, that is given by the bacillus prodigiosus is given to the organism and not to the toxin that it produces.

Répin tried the injections in four cases altogether, but in only one was there any conspicuous effect. This was a case of cystic sarcoma of the shoulder in a man aged 43. He was operated upon in July, 1894; the tumour recurred, was removed, and recurred again, forming a fungating bleeding mass the size of the palm of the hand. The general state was good and there were no lymphatic glands involved.

Injections were begun on October 30, 1894, and were given twice a day. The reaction was very violent, and in

a few days was followed by prostration, and pain in the growth.

On November 4 the tumour was flatter, less vascular, and darker in colour. On the 7th it began to slough, and on the 9th the sloughing was becoming extensive. The patient had, however, lost six kilos. in weight and the injections were consequently stopped for a day. On the 13th fresh growth was noticed on the margins from whence the slough had separated, and these growths seemed to be unaffected by the injections. Owing to the pain, two intravenous injections were then given causing violent reaction, but without further result, and then the treatment was stopped.

SENN, *Journal of Amer. Med. Ass.*, July 27, 1895.

Senn tried injections of toxins in nine cases altogether. In none was there any improvement, even of a temporary character. In some the local and general conditions appeared to have been aggravated.

Age.	Nature of growth.	Number of injections.
35	Multiple melanosarcoma of breast and glands	25
32	Sarcoma of testicle and glands	25
47	Sarcoma of thigh	50
50	Recurrent sarcoma of shoulder after amputation	110
48	Fascia sarcoma of back	40
36	Carcinoma of penis and glands	30
55	Sarcoma of mouth	65
52	Secondary sarcoma of lymphatic glands of ureter	25
45	Carcinoma of uterus	75

At the same meeting Coley replied to the effect that of the nine six were unfortunately chosen (three were carcinomata, one was a melanosarcoma, which is singularly malignant in character, and two were periosteal sarcomata, a kind of tumour which Coley himself had found to be exceptionally refractory); and that in consequence Senn came to a negative result on the result of three cases only.

MYNTER, *New York Med. Rec.*, February 9, 1895.

Sarcoma of Abdomen.

The patient, a girl aged 12, had sustained a blow in the left inguinal region a few weeks before. A swelling formed soon afterwards and continued to increase until it formed

an indistinct mass that filled the abdomen below the umbilicus. The temperature was 102°; the pulse 130. The patient had been losing flesh and strength, and was suffering from dyspnœa, loss of appetite, œdema of the extremities and extreme weakness. Micturition was involuntary.

On exploration two quarts of chocolate-coloured fluid escaped, and a soft vascular growth was found involving the parietal peritoneum, the mesentery, pelvic organs and the cæcum. Hæmorrhage was so profuse that the cavity had to be packed with gauze, and the patient became livid and pulseless.

Four days later the gauze was removed and much more of the same fluid escaped. Injections with the filtered toxins of the erysipelas coccus were then commenced.

In the course of the next week large masses of the growth began to slough out. By August 7 the tumour had become smaller and the abdomen had diminished in size; the character of the fluid that escaped had also changed, so that it resembled pus. On the 13th the cavity was irrigated with hydrogen peroxide, with the result that many more fragments came away. On the 23rd it was noted that there was still some swelling deep down in the pelvis and that a fistula persisted.

On September 17 the patient was stated to be a "picture of health." All the swelling had gone, there was still a small fistula which, however, was closing; and the only trace of the growth left was some infiltration of the anterior abdominal wall, around the place in which the drainage tube had been.

BUTLIN, *Clinical Journal*, January 29, 1896.

(1) *Lymphosarcoma or Lymphadenoma.*

The patient, a man aged 68, was admitted with an enormous mass of enlarged glands. These had subsided once under arsenic, but had enlarged again, and now the arsenic had no further effect. Injections (two minims) of erysipelas toxins were tried first without effect; then some of Coley's fluid. The reaction was characteristic, but the injections, though repeated almost every day for some time, had no effect upon the growth, which continued to enlarge. At last the patient died from exhaustion.

(2) *Sarcoma of the side of Pelvis and Abdomen, connected with the Iliac Bone. Round- and Spindle- celled.*

The patient was a man, aged 45, very much wasted. The tumour had been growing for five months. Injections were carried on for eighteen days, the dose being raised gradually to eight minims. Then some fluid prepared in the hospital was used. This injection was followed by similar symptoms, but the patient remained ill; the temperature did not fall; vomiting set in, and death ensued from asthenia in the course of a week.

(3) *Sarcoma of Inner Side of Thigh.*

The tumour had been growing for six years and the inguinal glands were enlarged. Toxins prepared by Dr. Rüffer were injected. Each injection was followed by the characteristic symptoms, but not always by a rigor. The patient continued very ill, without improving in any way. At length the main part of the tumour became livid in colour, soft, and semi-fluctuating. The surface sloughed, but this had no effect upon the rest, which appeared to grow all the faster.

Sheild, *Brit. Med. Journ.*, January 23, 1897.

Recurrent Sarcoma of Mammary Gland.

The patient was a woman, aged 44, who had had the left breast removed for myeloid sarcoma in January, 1896. The axilla then appeared to be free.

Within six weeks the disease returned in the scar, in the axilla and beneath the clavicle. On admission there were two masses in the centre of the scar; one was the size of a large walnut, the other smaller, on the point of fungating.

Injections were begun on April 3, one minim of Coley's fluid being thrown into the larger nodule. In a little more than an hour there was a slight rigor. Redness made its appearance and extended up to the clavicle. The pulse quickened and the temperature rose 1°. April 4, two minims were injected, and the temperature rose to 102·6°. The blush made its appearance again. The patient volunteered that the pain in the tumour was less, but complained of numbness in the hands and feet. After this injections were

continued at intervals, gradually increasing the amount, with the result that the larger growth discharged freely and became considerably smaller. By April 20 it had entirely disappeared; the smaller one was semi-necrotic, and the mass beneath the clavicle less prominent. Two days afterwards the patient was seized with a shivering fit, and the temperature did not fall again. Pulse and respiration became very rapid; pustules appeared in the legs with petechial spots on the abdomen, and the patient became unconscious and died on April 24.

The fluid proved to be sterile, and just after the last injection an injection of equal magnitude was made in a case of carcinoma with but slight effect. The syringe was always sterilised.

It is noted that smart reaction followed the first two injections. After that three injections in gradually increasing quantities failed to have any effect. After a week's interval severe reaction was again established.

The effect on the growth was certainly very marked. It caused its undoubted shrinkage and apparent disappearance. This seemed due purely to inflammatory action in a soft neoplasm, rather than to any specific action of the fluid itself.

At the *post-mortem* there was general pyæmia. The growth beneath the clavicle was necrotic and there was some purulent infiltration of the thoracic muscles. The organism present was the staphylococcus aureus, not a streptococcus.

Mr. Sheild suggests that the flaw in this case was possibly due to imperfect disinfection of the skin. "The more virulent the fluid, the more marked the effect upon the neoplasm, and curative action and danger to life are in direct proportion."

APPENDIX IV.

Cases of Disease other than Sarcoma and Carcinoma, in which either Erysipelas has broken out or the Mixed Toxins have been Injected.

Volkmann, Billroth and Pitha, Bd. 1, Abth. 2, p. 175.

Keloid on the dorsum of a foot disappeared completely after a severe attack of erysipelas lasting for eight days.

Schwimmer, *Pest. Med. Chi. Presse*, 1887, No. 37.

Keloid on the back and arm of a girl, aged 15.

Erysipelas lasting for ten days, severe, with great loss of strength. As the fever subsided and desquamation began, the tumour became flatter and skin more smooth. Where the inflammation was less severe the change was less marked.

Second attack three weeks later. The rest of the keloid disappeared entirely, and the cure is described as permanent.

In another case, a girl, aged 20, some tuberculous glands in the neck diminished very much in size after an attack of erysipelas.

Minelli, *Lond. Med. Rec.*, November 15, 1880.

Tubercular Syphilide.

The patient, a woman aged 50, was suffering from a very severe tubercular syphilide of the face. While under treatment she was attacked by erysipelas, with the result that the syphilitic eruption rapidly underwent resolution and was cured.

Fehleisen, "Zur Ætiologie der Erysipels."

Lupus.

(1) Woman, aged 29, with very extensive lupus of face. Inoculation with pure culture. Attack of erysipelas lasting four days, with a temperature of 40·1°. Lupus healed, with the exception of a few nodules.

(2) Patient a man, aged 20, had had lupus for twelve years. During these twelve years he had had many attacks of erysipelas. Inoculated without result.

COLEY, *Amer. Journ. of Med. Sciences*, September, 1896.

(1) *Fibroangioma of Lip.*

Patient was aged 32. Since birth his upper lip had been thick. When he was 21 it began to grow slowly. In the last four years it has grown very rapidly. At present it is the size of a very large orange, being nine inches from one corner of the mouth to the other. Tumour pulsates distinctly.

The greater part of the growth was excised in November, 1895. Two weeks afterwards it was growing rapidly. In the same month injections of toxins were commenced. Improvement was immediate, and in three weeks the swelling had almost disappeared.

(2) *Tuberculous Tumour of Sternum.* (*New York Med. Record*, January, 1895, and *loc. cit.*)

The patient was a woman aged 39. There was a firm swelling, three inches in diameter, over the upper end of the sternum. It was of four months' duration, and was quite fixed. The patient had two sisters suffering from cancer, and had lost weight. There were a few enlarged glands along the border of the left pectoralis major.

Injections were commenced in August, 1894, and given every other day. Reaction was very severe. At the end of a week the tumour had become soft and fluctuating. An incision was made under cocaine, and a lot of broken-down tissue allowed to escape. In four weeks the tumour had disappeared, with the exception of two sinuses, and the patient's health had much improved. Tubercle bacilli were found in the discharge in January, 1895.

A second tumour, of apparently similar nature, in the left lumbar region, extending over upper part of ilium, underwent rapid degeneration during the injections of the toxins into the sternal tumour, but this was followed by a sinus that failed to close.