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A PRELIMINARY NOTE
ON THE
TREATMENT OF INOPERABLE SARCOMA
BY THE
TOXIC PRODUCTS OF ERYSIPELAS.

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A Preliminary Note on the Treatment of Inoperable Sarcoma by the Toxic Products of Erysipelas.

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In a recent paper published in the *American Journal of Medical Sciences*, May, 1893, I have given the results in a series of cases of malignant tumors treated by repeated inoculations of erysipelas. The paper also contains an abstract of all the cases that I had been able to find in literature, when an attack of erysipelas had occurred in patients suffering from sarcoma or carcinoma. The clinical and experimental data above referred to *conclusively* prove that the germ of erysipelas contains a powerful principle, which has a marked antagonistic effect upon malignant tumors, more especially sarcoma, and which, in a certain proportion of cases, is curative of the same.

The results of my experiments and investigations are in brief as follows:

Of forty-three cases of malignant disease associated with erysipelas, twenty were carcinoma, nineteen sarcoma, and four either sarcoma or carcinoma. In twenty-three cases the erysipelas was accidental, and in fifteen the result of inoculation.

Of the twenty cases of carcinoma, three were permanently cured. In addition one case of probable carcinoma (Hutchinson's) was well five years after the attack of erysipelas. One died from the inoculation. Most of the remaining cases showed more or less improvement, which, though temporary, undoubtedly added to the life of the patient.

Sarcoma.—In the nineteen cases of sarcoma we find eight, or forty-two per cent, well from one to seven years after the attack of erysipelas. Most of these cases have a remarkable history, the details of which may be found in the paper alluded to. Two died as a result of the erysipelas.

These cases have been in no way selected, and every effort has been made to include all cases resting upon competent authority.

When we reflect that in nearly every instance the tumor was not a primary growth amenable to operative treatment, but either a recurrence after operation had been tried and failed, or from its nature and situation inoperable, then we are able to appreciate the importance of erysipelas as a *curative agent*.

During the past two years I have treated twelve cases of inoperable, malignant tumors with repeated inoculations of the living cultures of the streptococcus of erysipelas. Four of these cases were carcinoma and eight were sarcoma.

In but four of the twelve cases did I succeed in producing a true attack of erysipelas, although in nearly all cases the frequently repeated injections of

liquid cultures had more or less effect in diminishing the size of the tumors. The four cases in which erysipelas was produced were all sarcoma. In two, the tumors entirely disappeared. One was very large, 7x5 inches, situated in back, with secondary tumor, size of goose egg, in groin, and the second was a recurrent sarcoma of the neck, with a very large secondary tumor in the tonsil. In the first case both *primary* and *secondary* tumors disappeared, while in the latter the primary tumor disappeared and the tonsil tumor diminished in size, and although nearly two years have passed it has apparently not increased, a fact which seems to prove its malignant nature must have been changed.

Recurrence followed in a few months in the first case. The tumors grew rapidly, but *again disappeared* under a *second* attack of erysipelas. Still another recurrence followed. The focus in the back was removed with the knife, but before the wound healed the disease had reappeared both in the back and the groin. Injections of the *Toxic Products* of erysipelas were then resorted to, and repeated at intervals of forty-eight hours for three weeks. The sarcomatous nodules disappeared, and the patient has entirely regained his normal weight and general health. No recurrence has yet taken place, and it is now fourteen months since the first inoculation, and four months since the injections were discontinued.

Of the remaining two cases where erysipelas was produced, one showed marked decrease in the size of the tumor, but the effect in checking the growth was temporary. The fourth case died on the fifth day as a result of the erysipelas. In these five days the sarcoma had decreased markedly in size.

The uncertainty of being able to produce erysipelas when desired (failure having occurred in two-thirds of my cases) coupled with the fact that frequently repeated injections of the liquid cultures of the erysipelas germs had produced a marked beneficial effect upon the tumors, led me to attempt some plan of isolating and using the active principle of the germ. My first experiments were made with liquid bouillon cultures, prepared by simply subjecting them to a temperature of 100° C.

Injection of cultures thus sterilized produced similar reactions to the living cultures, though the reactions were somewhat less severe. The injections were not continued sufficiently long to ascertain the relative effect upon the tumors, yet it was apparently less marked than the living cultures.

Considering the complex nature of the Toxic products, there seems good reason to suppose that certain changes were produced by heat in sterilizing the cultures. I therefore determined to obtain, if possible, a preparation of the Toxic principles of the erysipelas germ without the use of heat. This I was finally able to do through the skill of Dr. Alexander Lambert of the Laboratory of the College of Physicians and Surgeons. The streptococcus was grown in bouillon for three weeks and then filtered through a modified Kitasato filter. The fluid thus obtained was found to be *perfectly sterile*. It was then put in glass-stoppered bottles, and kept in a dark, cool place. This preparation I have now used in six cases of Sarcoma. Some of the cases are still under treatment.

CASE I—A boy sixteen years of age, German, with good family and personal history; was referred to me by Dr. L. B. Bangs of this city, in January, 1893, for the treatment of a large, inoperable sarcoma of the abdomen and pelvis. Its transverse diameter was seven inches and its vertical five. It extended nearly to the umbilicus above and was deeply attached to the pelvis below. In consistence it was exceedingly hard. Examination of a section removed proved it to be *sarcoma*. He was sent to me with the view of producing artificial erysipelas, but I decided to try first the effect of the *Toxic products*. Injections of the preparation just described were begun early in February and continued in slightly increasing doses, at intervals of two or three days, for ten weeks. The doses varied from .5 c.c. to 1.5 c.c., and .2 to .3 c.c. of the *Toxic products* of the *Bacillus Prodigiosus* were given to increase the reaction.

The treatment was discontinued May 5, 1893. Careful measurements, made from time to time, showed the tumor to be steadily decreasing in size and the general condition of the patient correspondingly improved.

He had been confined to bed much of the time before the injections were begun. June 1, 1893, the tumor had so far disappeared as to be no longer visible. Examination showed a small, movable mass in the abdominal wall, at site of original tumor, extending but a short distance above the pubes, measuring less than *two inches* in diameter. When the treatment was begun the measurements recorded were *seven inches* by *five*.

The boy gained ten pounds during the last month, and all bladder irritation, which was marked at the beginning, had entirely disappeared. During four weeks the injections were omitted, and as the tumor began to show signs of enlargement the injections were resumed. The case is still under treatment. The reaction following these injections has corresponded almost exactly with the constitutional reaction occurring at the beginning of an attack of true erysipelas. Within one-half hour to twelve hours after the injection a more or less defined chill occurs, usually accompanied by nausea and vomiting. Severe headache and general muscular weakness likewise are present. Within twelve hours the temperature rises from 101° to 104°, depending upon the amount used. Locally the parts about the site of puncture become swollen and reddened. The local and constitutional reaction generally subsides in twenty-four to forty-eight hours. July 17th, the tumor had almost entirely disappeared, and there now remains scarcely more than some enlarged glands in the right groin.

CASE II—Was the sarcoma of the back and groin, given in detail in the paper referred to. The sarcoma had twice disappeared under attack of artificial erysipelas, and had twice recurred. The final disappearance, caused by injections of *Toxic products*, is all the more remarkable in the light of the previous history of the case. Four months have passed and there is absolutely no trace of recurrence.

CASE III—*Recurrent Sarcoma of Thigh*. The primary growth first appeared in the soft part just above the left patella, in July, 1889. It was removed in November, 1891. Local recurrence followed. A second operation was done in July, 1892, and a third in January, 1893. The interval be-

tween the recurrences became shorter and the rapidity of growth more rapid.

On March 12, 1893, examination showed a tumor, two inches in diameter, attached to skin, but movable upon deeper parts, situated just above outer condyle of left femur, in region of old cicatrix. Just above the patella there was an induration two inches in area; a little farther up there was a distinct, separate nodule, $\frac{3}{4}$ of an inch in diameter.

The Toxic products of erysipelas were begun March 12, 1893, and given in the same way as in the two preceding cases. Much larger doses were given, and even then no appreciable rise of temperature followed. The only reaction that followed was severe headache, general muscular pain, and weakness. Locally, the tumors became swollen, even after the injections, and later decreased in size.

While the *filtered cultures* (prepared without heat) were used the tumors not only did not increase in size but decreased considerably. The smallest one could scarcely be detected after six weeks. At the end of eight weeks, having no more of the filtered cultures on hand, cultures sterilized by heat were tried. A severe reaction, both general and local, followed. The temperature rose to 103.4° F., and the patient had a severe chill. The cultures were exactly the same as previously used, except in the method of sterilizing—no heat having been used in the *filtered cultures*.

The injections were continued three weeks, but the tumors began to grow again, and on May 31, had attained the original size of March 12. The tumors were then removed by the knife, with the view of removing the larger part of the disease in the hope of destroying the remainder with erysipelas. The tumors removed were of the soft myxomatous variety, similar to case VIII¹, *loc. cit.*, when erysipelas produced only temporary improvement, therefore the prognosis is not so favorable.

CASE IV—*Recurrent Sarcoma of Hand*. This case, twenty-two years of age, a patient of Dr. Samuel Lloyd, had been operated upon several times for a sarcoma in the soft parts of the palm of the right hand. Local recurrence had followed every operation, and amputation of the arm had been advised by the surgeon and refused by the patient.

The last operation was done in January, 1893. The tumor recurred within a few weeks and grew rapidly. Injections of the *Toxic products* of erysipelas were begun in March and continued up to the present time. The tumor not only ceased to grow but has diminished considerably in size.

CASE V—*Recurrent Sarcoma of Axilla*. The primary tumor was removed two years ago from the back. Recurrence followed in the axilla, and a second operation was performed in January, 1892. Local recurrence was observed in April, 1893, and grew rapidly. June 1, 1893, there was a flat, movable mass, $4\frac{1}{2} \times 3$ inches and 1 inch thick, occupying thoracic side of axilla at site of former cicatrix. Several nodules could also be detected in apex of axilla.

The general condition of patient, who was a man forty-six years of age, was excellent. Injection of *Toxic products* of erysipelas, the same as in

¹American Journal of Medical Science, May, 1893.

previous cases was begun June 1, 1893, and continued at intervals of twenty-four to forty-eight hours. Scarcely any reaction followed, although the doses were increased very much, and the Prodigiosus products were added to the erysipelas; 100.5° F. was the highest temperature reached.

The injections were kept up only three weeks, and as no decided reaction was obtained, the tumors were removed by operation, as far as possible; a nodule was found firmly attached to the axillary vein and almost encircling it. This could not be removed without resecting the vein, which, considering the improbability of being able to remove all the disease, was not thought advisable.

Inoculation with a virulent culture of erysipelas will soon be made. While the Toxic products were being used the growth was apparently checked, although no diminution in the size of the tumor took place. The fact that so little reaction occurred in this case may have been due in part to the non-susceptibility of the patient; but the fact that the cultures from which the products are made had become attenuated by age, probably was the chief cause. The cultures themselves as well as the Toxic products lose their strength rapidly with age.

CASE VI—*Sarcoma of Foot and Groin*. The patient, a woman thirty-two years of age, had observed a small wart-like swelling upon the left instep two years previously. It had twice been removed, but quickly returned. It remained very small, and never became larger than a cherry. In April, 1893, there was a tumor in the left groin the size of two fists, protuberous and ulcerated over a large area. A hard swelling extended above Poupart's ligament to within two inches of the umbilicus and to the median line in front. The ulcerating mass in the groin was removed by Dr. C. A. Powers at the New York Cancer Hospital, in April, 1893, and the following week injections of the Toxic products of erysipelas were begun. Good reaction followed doses of 2 c.c. The effect upon the tumors had not become noticeable when an attack of *accidental* erysipelas occurred. The erysipelas ran the usual course. The attack was not severe. The effect upon the tumor was only a temporary check, and no marked decrease in size was observed. As soon as the attack had subsided the tumor grew very rapidly.

The *Toxic products* were again given in large doses. The reaction gradually became less marked in spite of increasing doses. The largest dose was 3 c.c. of erysipelas products and .75 c.c. of *Bacillus Prodigiosus* products. The growth of the tumor was unmistakably retarded by the injections. They were discontinued for two weeks and then resumed. The short interval seemed to have restored the susceptibility, and good reaction followed. The case is still under treatment, but in view of the great size of the tumors when treatment was begun, nothing more than temporary improvement could be hoped for.

The results from the use of the Toxic principles of erysipelas, in the limited number of cases described, are sufficiently encouraging to make further experiments exceedingly desirable, and there is good reason to believe that most of the value of the erysipelas lies in these Toxic principles.

Similar experiments have very recently been conducted by Dr. C. H. H.

Spronck, Professor at the University of Utrecht, and published in the *Annales d'Institut Pasteur*. October, 1892.

Spronck and his co-workers treated twenty-six cases of malignant tumors with a preparation of the Toxic products of erysipelas.

Spronck, believing that the action of erysipelas upon tumors was for the most part systematic, made all of his injections *remote* from the tumors (usually in the gluteal regions).

He prepared the Toxic products in the same way that Koch did his Tuberculin, viz., by heating liquid bouillon cultures to 100° C, after the addition of 5 per cent glycerine, then evaporating to one-tenth the volume and finally filtering through porcelain.

This preparation was first tried on animals. In certain doses, varying with the virulence of the cultures from which it was derived, when injected into the circulation of a rabbit, caused death in from 24 to 48 hours.

The more virulent the culture the more rapid the death and the smaller the fatal dose.

A dose of 10 to 15 c. c. per kilogramme weight of animal usually caused death within 48 hours. The symptoms preceding death were elevation of temperature, loss of appetite, diarrhœa, albuminuria and paresis of posterior extremities. No changes worthy of note were seen at autopsy.

Spronck then experimented upon tumors in dogs. Some of the tumors were benign, others malignant. Subcutaneous injections of the Toxic products were made in two cases at a distance from the tumors. The doses were repeated several times and increased in quantity yet no effect was observed upon the tumors. They were removed and examination showed the one to be a lipoma and the other a carcinoma (anus).

With five other dogs, however, there was a more or less marked effect upon the tumors. After several injections (remote from tumors) the color of the tumors became of a bluish red and the tumors warmer and more sensitive to touch. Subsequently there occurred a softening and necrosis of the neoplasms.

"In the two cases these latter changes manifested themselves with astonishing rapidity." After the treatment had been continued a short time the remaining portion of the tumors were extirpated and examined. Two were found to be *sarcoma* and three *carcinoma*. In all there were found a condition of fatty degeneration and necrosis with an infiltration of polynuclear leucocytes from the blood.

Spronck very properly admits that such changes frequently occur in malignant tumors, hence it would be difficult to prove the entire effect due to the injections, yet in view of the symptoms following the injections and the change in the tumors dating from the beginning of such injections, a causative relation seems indisputable.

One of his experiments upon dogs is worthy of special note. A large dog had a *very hard* tumor the size of an infant's head, situated in the region of the right shoulder. It was a local recurrence from a small tumor which had been extirpated the previous year. On the fourth day of the treatment the tumor developed a slight swelling, and at the same time it became

of a bluish red color, warmer and more sensitive to touch. Shortly afterwards the consistence of the tumor diminished and on the eighth day fluctuation was present. Three days later the entire tumor was transformed into a soft fluctuating mass, covered only by the skin. Incision was followed by the escape of a voluminous sac filled with a puriform liquid in which were suspended necrosed fragments of tumors which proved on microscopic examination to be composed of detritus of the tumor and a large number of leucocytes. Somewhat later the dog died.

The autopsy showed that of the entire tumor there remained only a small fragment the size of a pullet's egg, where the tumor had been adherent to the skin. Microscopical examination proved it to be *adeno-carcinoma*. There can be scarcely any doubt that these wonderful changes were produced by the Toxic products of erysipelas, and when we reflect that the tumor was *carcinoma* and not *sarcoma*, the significance is far greater.

With the co-operation of Meulen, Renssen, Salzer and seven other physicians, Spronck extended his experiments to twenty-five inoperable malignant tumors in man, eight sarcoma and the remainder carcinoma. The same preparation of Toxic products already described was used and the injections were made without exception *remote* from the tumor. The utmost care was used in these experiments and the doses were very small.

The effect upon the tumors was by no means constant.

In a certain number there was no appreciable change; in a second class they continued to increase in size but the growth appeared retarded; in a third class there was *complete arrest* of growth, and in a fourth *diminution* in size.

In the same patient, with several tumors, the tumors did not diminish with equal rapidity. While some disappeared entirely, a total disappearance of all tumors present was not observed in a single case. In most of them the improvement was only temporary. The effect upon Carcinoma was much less marked than upon Sarcoma.

Still in one case (recurrent cancer of the breast) there was produced an almost complete absorption of the lymphatic enlargements, though they afterwards returned.

The most favorable effect was observed in a case of inoperable *sarcoma* treated by *Renssen*. After several weeks' treatment the primary tumor, of very considerable size, *completely disappeared*, and the secondary tumors were much diminished in size. They were no larger than a pea, with one exception, and that the size of a pigeon's egg. Failing to decrease further they were extirpated. Sufficient time had not elapsed to determine whether or not a radical cure had been obtained. The symptoms following the injections were very similar to those observed in my own cases and already noted. Elevation of temperature varying with the doses used, and with different subjects, was the most constant symptom.

In most cases the rise in temperature began 4 or 5 hours after the injections, never went beyond 103.1° and usually returned to normal at the end of 12 hours. In my cases the temperature has a few times risen beyond 104° , but usually it has ranged between 101° and 103.5° .

I have frequently observed a much more rapid onset, a chill occurring within a quarter of an hour after the injection, quickly followed by a sharp rise of temperature, nausea, vomiting, severe headache, general muscular pain, and malaise were more or less constantly seen. Spronck found that the relative susceptibility of the different patients varied greatly, some being entirely satisfactory. I have noted the same thing in my cases. Yet in one case that had failed to show any rise of temperature after frequent injections of my preparation of Toxic products (sterilized without heat) showed a marked rise, 103.4° , when cultures from the *same* source and of the same virulence, sterilized by heat, were used. The important difference, however, in the effect of the two preparations, was that the first although producing less constitutional reaction than the heated cul-

tures, caused a *diminution* in the size of the tumors (sarcoma) while the second failed to even check their growth. My experiments in this case together with others carried on in 1892, with cultures sterilized by heat, have convinced me that a portion at least of the value of the Toxic principles is destroyed by a temperature of 100 C.

Although I had practically arrived at this conclusion almost a year ago (before the publication of Spronck's cases), I was unable to obtain a good preparation of Toxic products of erysipelas sterilized without heat until February, 1893. My results although they cover a smaller number of cases than Spronck's are yet more remarkable.

In one case the sarcomata have entirely disappeared under injections of Toxic products, and the patient is still free from recurrence.

In a second case, a very large inoperable sarcoma of the abdominal wall, the tumor has so far diminished in size that only a small nodule remains. In two others there was decrease in the size, and they are still under treatment. The remaining cases are too recent to more than mention. In one, however, the improvement has been very doubtful.

The elaborate investigations of Roger with the Toxic products of erysipelas, upon animals, recently published in Rev. de Med., December, 1891, show that instead of a single Toxic principle the erysipelas germ grown in bouillon forms a considerable number of soluble products, some of which differ so widely from others that they are directly antagonistic.

He further found that these Toxic products were capable of killing animals in doses of 13 to 20 c. c. per kilogramme weight and that they were precipitated by alcohol and destroyed by heat.

He also found that *filtered* cultures *not heated* in doses of 5 to 12 c. c., injected into the circulation of rabbits exercised a predisposing action, making the animal more susceptible to inoculation. On the other hand, *heated* cultures (104-110° C.) rendered the animals immune.

In extremely large doses these products produced a more or less chronic form of Septicæmia, which caused death in a few hours to several weeks. Space will not permit a more detailed description of these experiments. They are cited to prove that in the soluble products of erysipelas we have a very powerful and complex combination of active principles; that some are directly antagonistic to others; and finally that heat has a very decided effect upon them.

Aside from the difference in the method of preparation of the soluble products of erysipelas, my experiments differ from Spronck's in the fact that he sought for a systemic action alone, whereas I have endeavored to obtain both systemic and local action by making the injections into the tumor or its immediate vicinity, and I believe my results show this to be the best plan.

Spronck in conclusion says: "If in man the results have been less satisfactory (than in dogs) one should not lose sight of the numerous difficulties that lie in the way of their first attempts towards a clinical application, or of the unfavorable conditions in which we have been placed, or finally of the fact that in nearly all of the patients the tumors were in a very advanced stage." He further states: "I believe that I am authorized to conclude that the products of erysipelas, in certain cases at least, can act in a *curative* manner upon malignant tumors."

While the treatment of malignant tumors by erysipelas inoculations or by injections of the *Toxic principles* of erysipelas is still in the experimental stage, we cannot but recognize that a long step in advance has been made and there is good ground for confidence that further investigation along these lines will be followed by ever more brilliant results than those already obtained.

