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ACTINOMYCOSIS

by

H. R. MACINTYRE. M.B., Ch.B.

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Actinomycosis is generally looked upon as a rare disease, but, in the experience of many who are constantly on the look out for this condition, this would appear to be by no means the case. It seems probable that many cases are mistaken for another of the infective granulomata, namely - Tuberculosis - which this disease resembles in many respects; or again for malignant disease. Early writers described conditions which were identical with actinomycosis, but classed them as Tuberculous or Cancerous affection. In France in 1826, Leblanc described a disease in cattle characterised by swelling of the jaw. In England in 1833, Professor Dick described a condition of swelling of the jaws in cattle called "clyers"; and, in 1841, stated that the disease was known to affect man in the jaw. In 1845 Langenbeck reported a case of vertebral caries, with yellow grains in the pus. In 1850, Davaine described a case of tumour of the jaw in an ox, in the discharge from which there were yellow granules, which under the microscope had neither the characters of tubercle nor of pus. In 1868, Rivolta discovered rod shaped bodies in pus from tumours of jaws of oxen, which rods he compared to rods of the

retina. He attempted inoculation, but failed.

Bollinger, in 1878, proved that the granules from the tumours of jaws of oxen had a causal relation to the disease: these same granules were examined by Harz, the botanist of Munich, who recognised their parasitic nature, and gave the name "Actinomycosis Bovis". Israel, in 1878, published in "Virchow's Archives" two cases of Mycosis in man, describing and making drawings of the fungus. In 1879, Ponfick suggested the identity of the disease in man and the lower animals. Then Johnne succeeded in producing the disease in the ox by inoculation.

Since that time, a large number of cases of the disease in man have been reported on the Continent - chiefly in Germany and in the South of France.

In America and in the United Kingdom, the number of reported cases is relatively much smaller, either because the disease is more rare, or, as is believed by many observers in both countries, because less attention is paid to the recognition of the disease.

In England the first case in man was described in 1885 by Dr. Harley,⁽¹⁾ who discovered the presence of granules in the lesion, but nevertheless maintained that the condition was tuberculous, and that the granules were

(1) Med.-Surg. Trans. 1886, p. 135.

typical examples of caseous degeneration of tuberculous deposit: which opinion he modified later, on the discovery of Sharkey and Acland of a mycelium in the granules, but still adhered to his opinion that the disease was not due to a fungus, but that the fungus was secondary to the tuberculous disease - an accidental associate - and goes on to say, "If this be so, then much if not all of the so called actinomycotic disease must be relegated to its old, and, as I believe, its proper place, namely "Tubercle" There is no doubt however, that the case was a typical one of actinomycosis of the liver.

I have been able to collect notes on 104 cases* of actinomycosis in man occurring in the United Kingdom since that date, including the case mentioned above, and one is struck by the large number which have not been diagnosed till late in the disease, and then only by the chance discovery of the typical granules; while many again have been recognised only at a post-mortem examination. My attention was called to the disease by such a case, which came under my notice, and which so closely simulated Tuberculous disease of the spine that a correct diagnosis was not made until the lesion was far advanced. This case is also of interest in that it is I believe, only the second case of the disease on record treated by

* See Appendix.

the so called vaccine therapy.

The notes of the case, for permission to use which I am indebted to Mr. Monsarrat, are as follows:-

The patient, J.T., a schoolboy, aged eight years, was admitted to the Northern Hospital, Liverpool, on January 20th, 1907, complaining of pain and swelling in the back of the neck.

History. The history from the parents is rather indefinite. The patient began to complain of pain in the back of the neck about the end of the summer of 1906. The parents state that they do not remember that he complained of his throat at any time, although a doctor, who saw him at this time, informed them that the condition was due to ^{the} tonsils. They did not notice any swelling of the neck at this time, but the boy began to hold his head on one side. The condition improved for a short while, but a month or two later he got worse again, and patient was taken to the Childrens' Infirmary where the parents were told that the boy ought to have a collar. No notice, however, seems to have been taken of this advice. The neck gradually became more painful, and, in December, 1906, a swelling appeared behind the left ear and on the left side of the neck. Another doctor who saw patient at this time informed the parents

that the condition was due to the tonsils. About this time, too, patient's mother noticed that a greenish discharge was coming from the boy's mouth, staining the pillows at night; and about the same time the swelling was noticed to get smaller, but increased again later.

Six weeks before admission (i.e. also in December) the boy began to support his head with his hands when sitting or standing.

Patient was noticed to be getting thinner about the end of the year. At no time do they recollect of his complaining of pain in the throat, nor did he seem to have any difficulty in swallowing.

The pain was never very severe, was worse on movement, and was periodic.

Previous Health. Patient was always thin and wiry, but had good health. No previous illness.

Family History. Patient is the only child. Mother and father well. No history pointing to tuberculosis in the family.

Social Conditions and Habits. There was nothing special to note. The family lived in rather a poor neighbourhood.

I have since ascertained that the patient had never been out of Liverpool: that there was no grain warehouse in the neighbourhood, so far as the parents knew; and

that they had not noticed the child chewing grain or straw.

State on admission. Patient is somewhat emaciated.

He supports his head with his hands when sitting. The head is markedly inclined to the right. No movement of the head or neck are possible.

On examination of the neck, there is a marked swelling commencing behind the left ear and extending down into the posterior triangle of the neck. In the centre of the swelling there is a sinus surrounded by breaking down granulation tissue. A probe could only be passed a short distance down the sinus. On palpation the swelling was tender, and there was a suggestion of deep seated fluctuation.

The condition, then, strongly suggested tuberculous caries of the cervical vertebrae.

The subsequent history of the case was as follows:-

On January 30th, ten days after admission, Mr. Monsarrat made an incision, $1\frac{1}{2}$ inches long, over the swelling: the sinus was opened up, and a small amount of greenish yellow pus escaped. The sinus led down to the lateral mass of the atlas, but no bare bone was found. The cavity was thoroughly scraped out with a spoon, and the wound closed.

The local condition, however, steadily got worse.

I saw the patient first on April 2nd, 1907, and he was under my observation until the end of October of the same year.

His condition on April 2nd was as follows:-

There was considerable general emaciation. On looking at the neck from behind, there was much swelling on both sides of the middle line. The swelling was indurated, more so on the left side than on the right, and only very slightly tender to pressure. Patient at this time complained most of pain and tenderness just below the right mastoid process. The antero-posterior curve of the cervical spine was obliterated, and the head was carried poked forward and inclined somewhat to the right shoulder.

On April 11th, a small superficial collection of yellowish purulent material over the swelling on the left side was incised, but a probe could not be passed down for more than in inch.

His condition got slowly but steadily worse, and, on May 27th, the enormous, hard induration of the soft tissues of the neck was noted.

A fresh superficial collection of pus now occurred on both sides of the neck: these were incised on the 29th, and a small amount of superficial discharge was evacuated: but it was curious, considering the large

amount of induration of the tissues, that no pus was found more deeply, a probe being passed in all directions. It was noticed that the tissues throughout the mass were pale and oedematous, and that there was a certain amount of pale granulation tissue between and involving the muscles.

Ten days later, a small nodule appeared close to the incision on the right side of the back of the neck: this nodule broke down, and in the discharge granules were found on the following day (June 10. 1907), which microscopically were found to contain the typical Mycelium and clubs of Actinomycosis. The granules were very numerous in this discharge, but were not found in the discharge from the other wounds.

Small doses of Potassium Iodide were commenced on June 13th - 12 grains a day being administered - but the drug was discontinued nine days later, as Dr. Leith Murray, Pathologist to the Northern Hospital, in view of the favourable reports of the use of the actinomycotic vaccine in a case of pulmonary actinomycosis, determined to give this method a trial in this case, with the permission of Mr. Monsarrat.

The state of the patient was now as follows:—

The swelling of the neck was now very marked on both sides of the middle line, rather more so on the left than on the right, and measured $10\frac{1}{8}$ inches from the

June 12. '07.



anterior part of the lower end of the tragus on one side to a similar point on the other side, the measurements, of course, being taken round the back of the neck. The swelling had the characters mentioned before, while the position and number of the sinuses are seen in the accompanying photographs. The surfaces of the wounds were covered with pale, unhealthy granulations, and the wounds showed no attempt at healing.

The temperature since admission ranged between 98° in the morning and 99° to 99.6° in the evening as a rule, occasionally rising to 100° or 101° , these rises being more marked for four or five days following the various operations. It rarely fell below 98° , save in the periods immediately following operation. Occasionally the evening temperature would not rise above 99° for a period of a few days, but never for more than a few days at a time, these periods of quiescence not being common.

Patient was markedly emaciated - his weight was 2 stones 11 lbs. - was confined to bed, and could not sit up without supporting his head with his hands.

The conditions of the various systems, were, shortly as follows:-

Respiratory system.

Chest. There was no cough nor pain in the chest.

Marked flattening and hollowing of both infra-

clavicular regions. At the left apex and infraclavicular region the percussion note was dull, and this region moved rather less than on the right side. The breath sounds were hard with prolonged expiration on both sides, but more markedly so on the left side. There were no accompaniments.

Circulatory system. There were no subjective symptoms.

The pulse rate was rather rapid, being usually about 100, but varying from 80 to 120 and the tension was rather low.

Heart. The apex beat was in the fifth interspace, and at the level of the left mid-clavicular line, being distant $2\frac{1}{2}$ inches from the mid-sternal line.

The right border was $\frac{1}{2}$ inch to the right of the mid-sternal line.

The upper border was in the second interspace at the lateral sternal margin.

The left border, at the level of the fourth rib, was 2 inches from the mid-sternal line.

On auscultation, in the aortic and pulmonary areas both sounds were clear and rather abrupt, the second sound being accentuated.

In the tricuspid and mitral areas, the first sound was reduplicated, the second sharp, clear and accentuated. There were no murmurs.

Alimentary system. There was no pain in the abdomen.

The appetite was good. The bowels tended to be rather constipated. There was no impairment of deglutition, no pain or difficulty in swallowing. The tongue was clean. The teeth were fairly good: one tooth, apparently carious, had been removed. It was difficult to get a view of the tonsils and pharynx, since the boy's chin was approximated to his sternum, owing to the flexion of the neck mentioned before, but, so far as could be seen, these parts appeared normal.

Abdomen. There was nothing to note on inspection - no prominence or retraction. On palpation, no tenderness or swelling were discoverable..

Liver. The vertical measurements of the liver were as follows:-

In the right mid-clavicular line, from the fourth interspace above to $\frac{1}{2}$ inch below the lower costal margin, measured $4\frac{3}{4}$ inches.

In the right anterior axillary line, from the sixth interspace to one inch above the lower costal margin measured $3\frac{1}{2}$ inches.

In the mid sternal line the lower border extended down $1\frac{3}{4}$ inches below the lower margin of the sternum.

The lower margin was palpable, the edge was smooth and regular, and of medium consistence. The surface,

felt on deep inspiration, was smooth.

Spleen. The upper border was at the level of the eighth rib in the posterior axillary line. The lower margin extended down to half an inch anterior to the mid-axillary line at the level of the tenth rib. The longest diameter was $3\frac{1}{2}$ inches. The spleen was not palpable.

There was therefore, slight enlargement of the liver and spleen.

There was nothing else to note in the abdomen.

Nervous system. Nothing to note.

The Urine was clear. Specific gravity 1010. There were no abnormal ingredients.

Blood. The leucocyte counts, and differential counts will be referred to later.

There were no evidences then, of involvement of any of the organs of the body, with the possible exception of the apices of the lungs.

This, then, was the condition of the patient at the commencement of the treatment with the actinomycotic vaccine.

As regards the preparation of the vaccine, an attempt was made to cultivate the streptothrix found in the discharge from the neck, but the culture was very impure, and Dr. Leith Murray, (who was responsible for

the vaccine treatment in the case, and to whom I am indebted for the use of the notes relating to it), therefore gave up the attempt, and used a laboratory culture. This culture, which I examined myself, was one of the rapid growing variety, growth being easily visible during the second day, but otherwise - in morphological and staining characteristics, which will be referred to later - did not differ from the more slowly growing varieties. The vaccine was prepared and standardised by Dr. Leith Murray, the process being the same as that described by Dr. Wynn. (2).

The first injection was given subcutaneously, under the skin of the forearm, on June 22nd, 1907, the dose employed being .001 mgr. Subsequent injections with their doses were given as follows:-

July 6.	.002 mgr.
July 14.	.005 mgr.
July 23.	.007 mgr.
Aug. 9.	.007 mgr.
Aug. 20.	.0025 mgr. (a fresh vaccine being
Sept. 3.	.004 mgr. employed)
Sept. 13.	.007 mgr.
Sept. 25.	.008 mgr.
Oct. 10.	.01 mgr.
Oct. 25.	.02 mgr.

The injection on Sept. 13th and those subsequent to it, were given locally, under the skin of the neck.

(2) B.M.J. May 1907. p. 119.

There was no interference surgically, during the vaccine treatment. At first, the only appreciable difference in the case was the behaviour of the temperature, which soon began to assume a somewhat lower range. As I mentioned before, the temperature previous to the vaccine treatment generally ranged between 98° and 99° to 99.6° with occasional short periods of quiescence. Soon after the commencement of the vaccine treatment, from the beginning of July, an elevation to 99° became uncommon - with the exception of the temperature disturbance following on the inoculations, this disturbance being limited to a period of one or two days after the injection. In the month of July, the temperature rose only once to 99° (this rise following two days after an inoculation), after which the temperature ranged between 97° and 98.4° . During the month of August this improvement in the range of temperature was maintained, a rise to 99° occurring only once apart from the period of 48 hours following an inoculation. The boy's condition improved slowly, and by the end of August his general condition was very considerably better than at the commencement of this treatment: he both looked and felt much better. The local condition improved at the same time. While the sinuses still discharged, the granulating surfaces looked healthier and by the commencement of September there was marked

improvement, the surfaces being much smaller. The swelling, too, slowly but definitely diminished in size, the measurement on September 5th, taken from the same points as before, being 9 inches as compared with $10\frac{7}{8}$ inches on June 22nd. Pain was rarely felt, and the patient now sat up in bed without any attempt at supporting the head, and felt no discomfort in doing so. During the months of September and October, the local condition continued to improve. On September 18th the boy was able to get up. On October 25th the granulating surfaces were almost healed, though slight discharge continued, and the measurement across the back of the neck, between the same points, was, now $8\frac{1}{2}$ inches.

The Boy's weight, however, though fluctuating somewhat showed no improvement.

The temperature during the month of September was more unsettled, an elevation to 99.2° taking place on four occasions apart from the periods following immediately on the inoculations; but during October it kept at a fairly constant level at about 98° with the exception of an elevation to 99° and 100° respectively on two consecutive days at the beginning of the month. It must be borne in mind, however, that the patient was not confined to bed during most of this period, so that one could hardly expect the temperature to remain so settled.

The condition of the chest and abdomen showed no change.

This case, then, showed marked improvement in the general state of health, and in the local condition, the improvement coinciding with the treatment by inoculations with a vaccine prepared from a stock laboratory culture of the streptothrix actinomycosis. The only unsatisfactory feature of the case was the fact that there was no improvement in the patient's weight, although the boy was eating well, and both looked and felt very much better. From being unable to sit up without support to his head, he was able to walk about the ward without any such support, and without feeling the slightest discomfort. The treatment was to be continued, but at this stage I lost sight of the case. Whether this improvement was merely a coincidence, or was due to the beneficial effects of the vaccine, one cannot, of course, be positive. If a coincidence, it was certainly a remarkable one, as the boy had been observed for five weeks previous to the commencement of this treatment, and had during that time been steadily getting worse.

As regards the evidence of activity of the vaccine by a consideration of the effects on the opsonic index following individual inoculations, unfortunately I am not able to give many particulars, as this point was not

investigated by any means fully. On one occasion, certainly, when I examined the effects of a dose of the vaccine, the index behaved much in the same way as has been observed in tuberculosis. Thus, on the day of injection (Oct. 25th) the index to actinomycosis stood at 1.06: on the day following the injection it had fallen to .89: three days after the injection, it had fallen still lower to .78: six days after the injection, the index showed a rise, being .98: and nine days after the inoculation, the index stood at 1.28. There was thus a definite negative phase in this instance, followed by a definite rise above the level at the time of inoculation, which is typical of what occurs in tuberculous patients after an injection of tuberculin[&] which is stated never to occur in a patient who is not tuberculous (3). I think one may infer from this that the organism used in the preparation of the vaccine was, at any rate, closely allied to the active organism in the lesion, and therefore active for the disease. It would have been interesting to see how long this rise was maintained, but I was unfortunately unable to continue with this series of counts as I at this time lost sight of the case. I may say that Dr. Leith Murray kindly verified my counts, his results being practically the same.

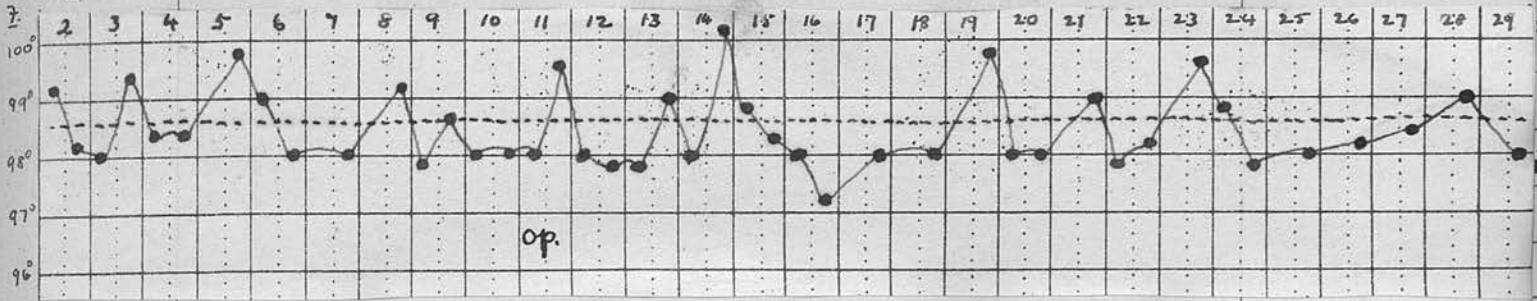
(3) Lawson and Stewart. Lancet. 1905. Vol.II. p. 1680.

Dr. Leith Murray observed the index on six other occasions during a period from August 2nd to September 17th, the lowest being .9 and the highest 1.3, but no observation of the index was made before the commencement of the vaccine treatment. There cannot, of course, be the same degree of accuracy in the counting of mycelial threads as of individual bacteria: but if the same standard of counting is adhered to, and a considerable number of cells are counted (100 to 150 cells were counted in each of the series mentioned above), I think an indication of a rise or fall can certainly be obtained, if such occurs.

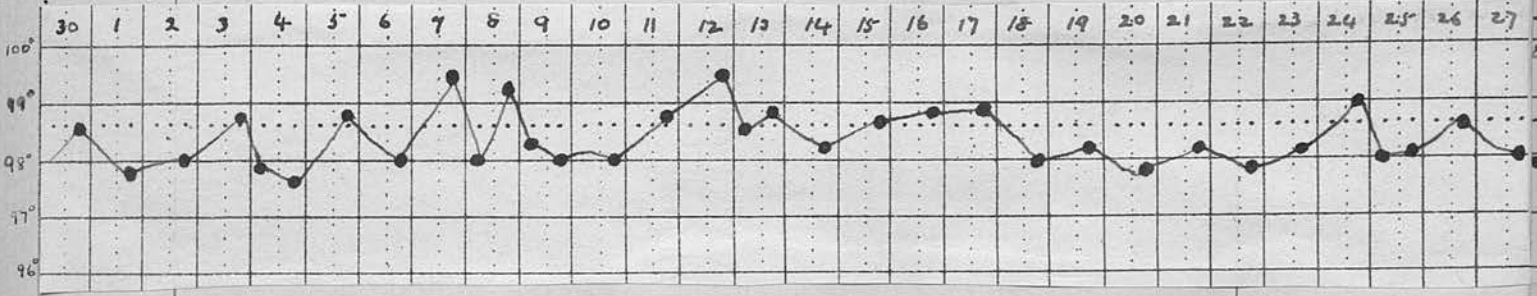
The injection of the vaccine was followed in nearly every case by certain fluctuations in the temperature. This fluctuation took the form of an initial fall, which occurred within 24 hours of the inoculation, followed, usually during the next 24 hours, by a rise above the level at the time of inoculation. This fall and the subsequent rise were never marked, but were quite definite in ~~most~~ cases, and I think one might compare this reaction to that which occurs in a tuberculous patient after injection of tuberculin, and which does not occur in a person who is not tuberculous: from which again, one may infer that the vaccine was active for this disease.

Temperature Charts.

April.

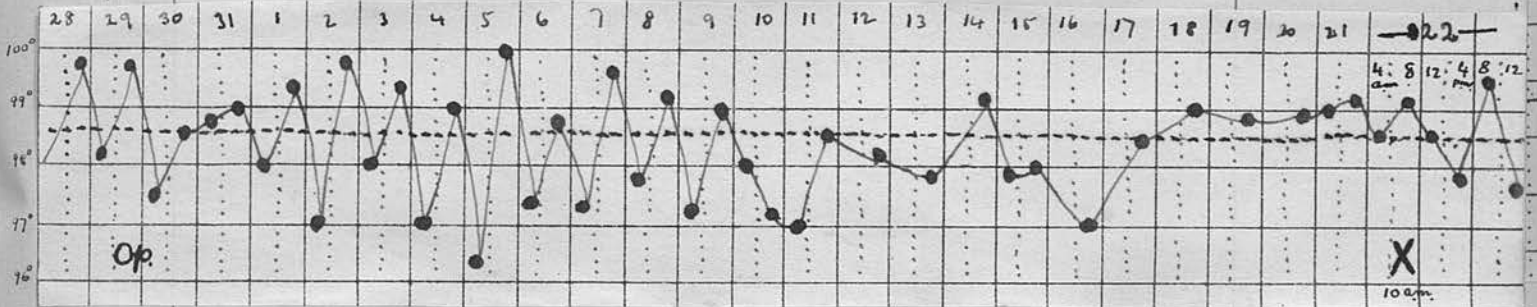


May.



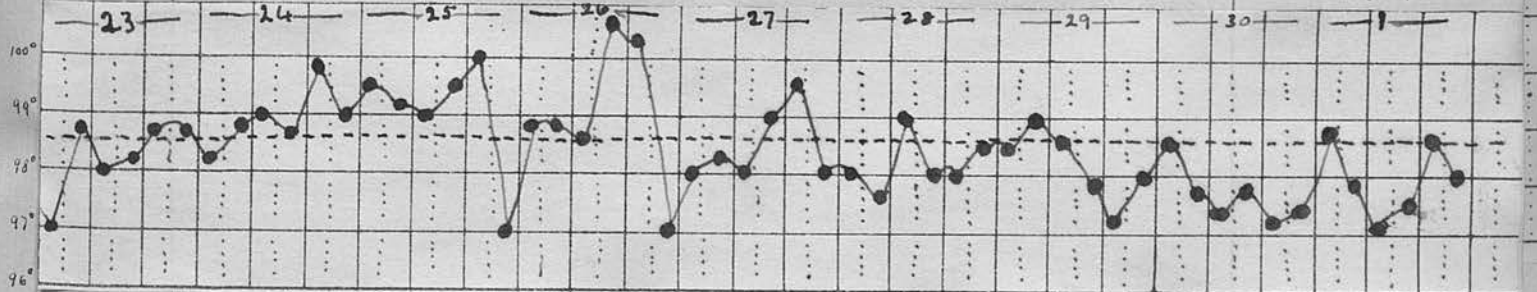
May.

June

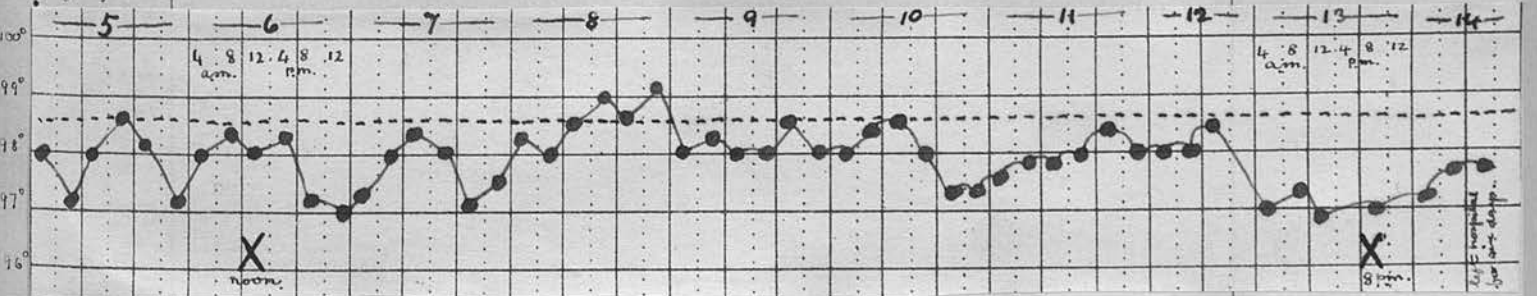


June.

July.



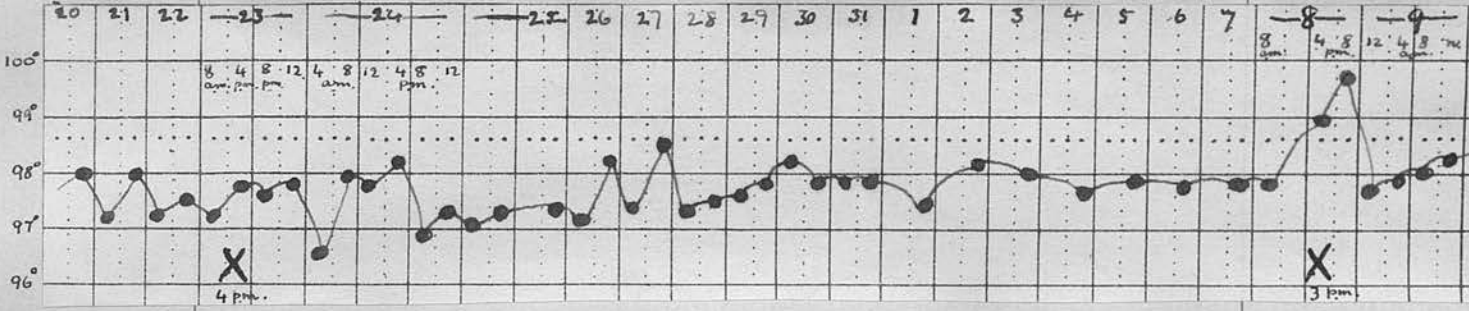
July.



X Inoculation given.

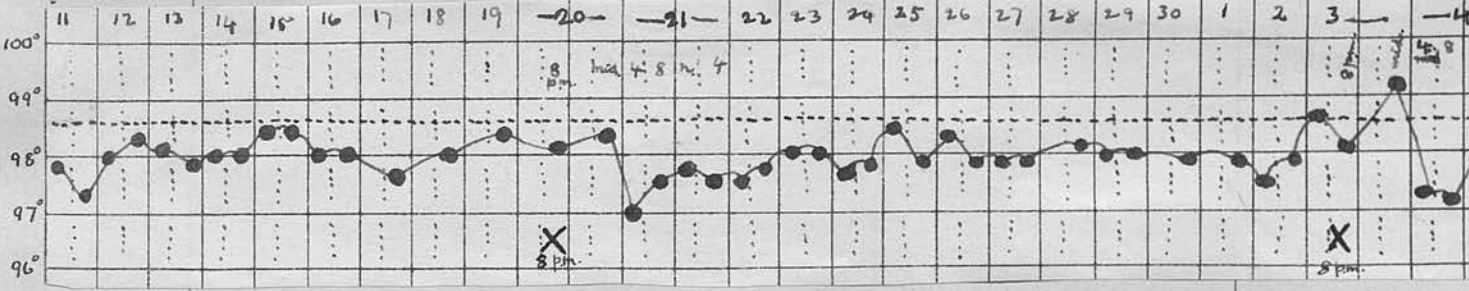
July.

August.

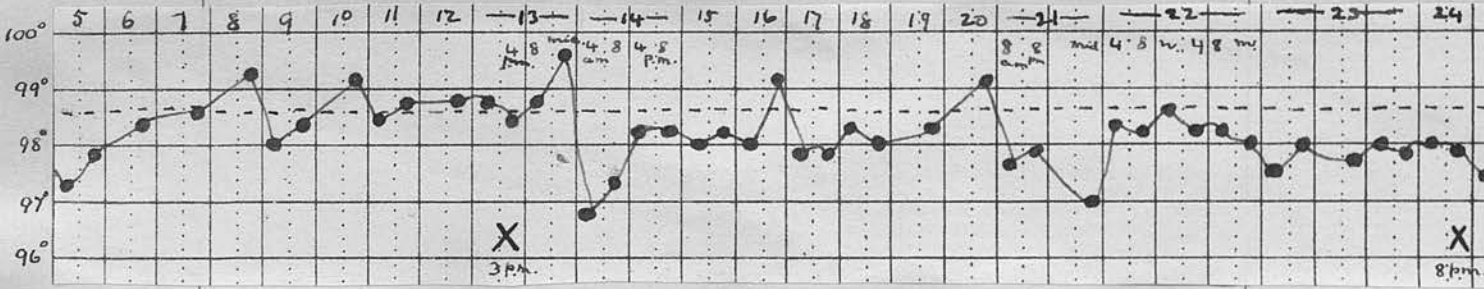


August.

September.

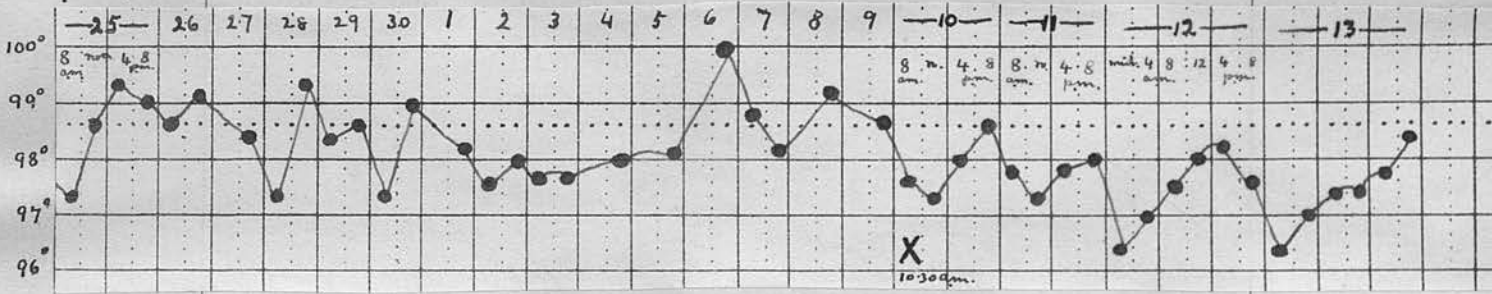


September.

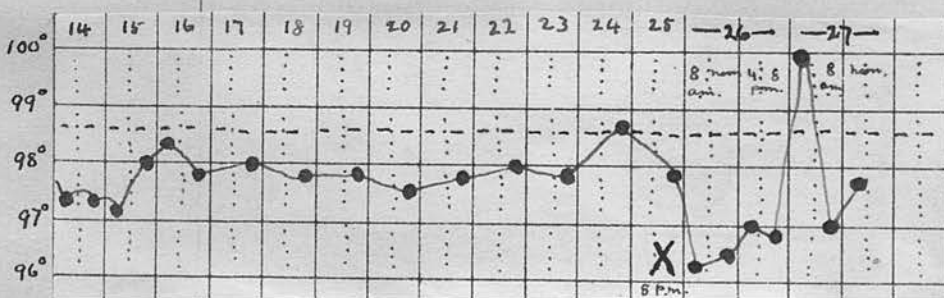


September.

October.



October.



X Inoculation given.

Since the completion of this paper, I have learned that this improvement was unfortunately not maintained. In a Hospital devoted practically entirely to the treatment of acute cases, it was impossible that a bed should be occupied for such a long period as was necessary in this case. The boy was accordingly sent out on October 28th, 1907, to a convalescent home for a short period, but could not, from want of space, be readmitted until December 2nd, part of this time being spent I believe at his own home. During this time, patient received no vaccine treatment. On his readmission, patient's condition was much worse, both generally and locally. There were fresh sinuses in the neck, and there was more discharge. The swelling of the neck had increased again and his temperature was hectic in type, frequently reaching 100°. It seems very likely that the wound became infected with other organisms during his absence from the Hospital. His condition got steadily worse, inoculation with the vaccine now apparently having no effect. The pus burrowed down between the muscles of the back, fresh foci appearing as low as the level of the upper dorsal vertebrae, and his temperature remained hectic until shortly before death, which took place on March 30th.

The notes on the post mortem examination were

shortly as follows:-

On exploring the vertebral column in front the disease was found to extend down as low as the disc between the 6th and 7th dorsal vertebrae, and upwards along and in front of the vertebral column as far as the base of the skull. The bodies of the vertebrae were eroded from the outside, chiefly on the right side. There was similar erosion of the upper ribs.

There were indications that the pharynx was also invaded. Both pleural cavities were invaded by the disease at the apices: the pleura was markedly thickened, and there was some ulceration of the surface of the lung. On section of the lung apices, there was marked fibrosis. At the base of the right upper lobe there was a small calcareous concretion the size of a pea. A microscopical section of the lesion at the apex of the lung showed that the pleura was markedly thickened, and that fibrous bands passed from it into the lung substance, but that there was no actual actinomycotic lesion in the lung substance.

While there was some enlargement of the liver and spleen, there were no metastatic deposits anywhere.

I shall now take up the Etiology of the disease, many particulars of which are of considerable interest.

Etiology. Commencing then, with a description of the organism "streptothrix actinomycosis", we are here met with conflicting opinions, which have an important relation to the mode of infection, and also to treatment of such cases by a vaccine, if this mode of treatment be continued. The specific infective agent exists in the lesions and in the pus in the form of small, irregularly shaped granules, the diameter varying from a fraction of a millimeter to 1 or 2 millimeters. The larger granules are made up of aggregations of smaller ones, and are often mulberry shaped. The colour is usually whitish or yellowish, but they may be of a deeper orange tint, or rarely may be so deeply pigmented as to have a brownish black colour. They may be soft and friable, or hard, resistant and calcareous.

The essential element of the granule is a branching filamentous micro-organism: and over more or less of the periphery are closely set club shaped bodies, while elsewhere the periphery is occupied by radiating filaments. In some cases the clubs are entirely absent. Beneath this peripheral layer is a dense network of branching interlacing filaments, while the central part may be occupied by a homogeneous or granulous matrix, which also

pervades the whole substance of the granule. The filaments are thin, and are composed of a central protoplasm surrounded by a thin sheath.

The club shaped bodies are found at the ends of some of the filaments, and are said to develop out of the peripheral filament by a hyaline swelling of the sheath.

These are the characteristics, shortly, which are generally accepted, but whereas some describe only the two elements, filaments and clubs, as being characteristic of the streptothrix actinomycosis, others, forming the majority, describe other elements, namely coccus-like and bacillus-like bodies. Some of the filaments, especially in the older colonies, are seen to be segmented so as to give the appearance of a chain of cocci, or in some cases of short rod-shaped bodies, enclosed in a fine sheath. In other portions of the same specimen the sheath has disappeared, leaving the chains of cocci or bacillus-like forms: and again the coccal and rod-shaped forms are seen scattered free among the other elements of the granule. These elements are found both in the lesions and in cultures. The question arises, what relation do these elements - coccal and bacillary - bear to the specific infective agent?

Some hold that they are to be regarded as products of degeneration of the filaments: others that they are con-

taminating bodies, and have nothing to do with the causal agent of actinomycosis: while according to another view, they form a stage in the life history of the streptothrix actinomycosis.

In attempting to solve this question, one has, in the first place to trace the stages in the life history and development of the organism by means of cultures - and here descriptions widely differ. In the first place there are differences as regards the rate of growth. The majority of observers, including Wolff and Israel (4) Leith (5), and others, state that the growth is better under anaerobic than aerobic conditions, is slow - no change being observed during the first 5 days at body temperature, while at room temperature the growth was very much slower. At the end of 4 or 5 days at body temperature, small translucent spots appeared, which enlarged slowly, became whitish in colour, and always remained separate. At the end of a fortnight they were about the size of a pin's head. After 3 weeks the colour became yellowish. Bostrom, (quoted by Leith, ib.) in a series of observations on the streptothrix from 11 cases of bovine and 3 cases of human actinomycosis, in which

(4) Virchow's Archives. 1891. Bd. CXXVI.

(5) Edin. Hosp. Reports. Vol. II. p. 166.

the cultures were successful, found a much more rapid growth in cultures, little clear bodies appearing in forty eight hours or even earlier, these bodies rapidly increasing until they form little masses larger than a pin head, becoming at the fourteenth day of a yellowish red colour.

But it is to the microscopical examination of the cultures that I wish particularly to refer. The descriptions of Wolff, Israel and of Leith agree in many particulars. According to Leith (1b) the life history is as follows. An eight day old culture showed a large number of bacillary forms, straight or slightly curved, or in pairs, or placed end to end in short chains. These chains were straight, wavy or sharply bent: but did not show any radiate arrangement. An eleven day old culture showed a profuse development of a radiating colony. The filaments themselves frequently show an interrupted protoplasm. A fifteen day old culture shows similar filaments, and with a much interrupted protoplasm, the segments varying considerably in size, a very few being elongated, but most being rounded. Leith deduces from these observations that (1) The filaments give rise to cocci-like forms. (2). These coccal forms grow into short bacilli. (3). These short bacilli become placed end to end, and fuse to form a filament, or grow out un-

interruptedly into a filament. Leith, however, states that he was not working with pure cultures. Leith's results resembles those of Wolff and Israel (Ib) who found on examining their cultures microscopically, after 24 hours only short bacillary forms. Much the same appearances were presented for the next few days, the bacilli differing more in length, some remaining short, others becoming larger. After about seven days, short threads appeared, later cocci, and long branched threads. They conclude (1). That the cocci do not multiply by division. (2). That there is not yet sufficient evidence for regarding them as spores. (3). That their significance is still undetermined, as there are objections to regarding them as a mere stage of growth, or as broken down pieces of protoplasm. (4) The short bacilli form the filaments.

Bostrom (Ib.) on microscopical examination found the following appearances. His cultures of twenty four hours consisted of abundant filaments, interweaving and branching, and showing a homogeneous protoplasm. On the third day and afterwards they showed numerous short bacillary and coccus forms, both in and outside the filaments. He concluded that the cocci are the spores of the organism, that they grow out into short bacillary forms, and that these bacillary forms grow into filaments.

Other observers describe a similar formation of these coccal and bacillary elements. McFadyean⁽⁶⁾ found that some of the youngest colonies are entirely composed of cocci, that many show a great preponderance of them, and that none, even of the smallest colonies, were entirely free from them. McFadyean also states that the cocci multiply by division, and that some of them elongate into short bacillary forms, and through these to the long filaments. Foulerton and Price Jones⁽⁷⁾ bear similar testimony to the active part played by the coccal and bacillary forms.

These various observers, then, have been agreed as to the active part taken by either the coccal or the bacillary forms, or both, in the development and growth of the streptothrix actinomycosis. Others, however, are of opinion that the cocci and bacilli were the products of contamination. But I wish to refer particularly to the work of a later worker, J.H. Wright, of Harvard, who in a recent contribution⁽⁸⁾ has described his investigations on the organism in 13 cases of human actinomycosis. He states that he found no coccal or bacillary forms in any of his cultures, and that on inoculation into animals he produced, with each strain, a characteristic lesion

(6) Journ. Comp. Path. & Bact. 1889. Vol. II. p.16.

(7) Trans. Path. Soc. Lond. Vol. LII. 1892.

(8) Journ. Med. Research. May. 1905.

containing typical club-bearing colonies. He criticises the work of Bostrom["], firstly, because the inoculation experiments of the latter were unsuccessful, secondly, because there was room for doubt as to the purity of his culture, and thirdly, stating that that observer should have obtained a larger number of successful cultures in view of the fact that so many tubes were inoculated.

(I may state that Bostrom["] made about 700 cultivations in series, but in each series kept only the first tubes in which growth appeared, neglecting the others of the series. Wright raises the objection that, owing to the rapidity of growth of Bostrom["]'s cultures, the latter should have found a growth on many more of his culture media).

Wright raises somewhat similar objections to the culture results of other observers. Wright attributes the presence of coccal and bacillary forms to either a degeneration of the filaments, or to the presence of contaminating organisms. By this term it would appear that Wright refers to other forms of streptothrix, as he states that the various branching micro-organisms claimed to have been cultured may be divided into two groups, in one of which the filaments give rise to spore-like, spherical, reproductive elements, while the members of the other group do not give rise to such elements. He asserts that members of the former group, when inoculated into animals,

have never given rise to lesions like actinomycosis and containing the characteristic granules: while his inoculation experiments with members of the second group were successful. Wright concludes that only one species - namely that in which the filaments do not form coccal or bacillary elements - represent the specific infective agent of true actinomycosis in man.

We are confronted then with the view, that, (1) ^{elements} these _{are} extraneous micro-organisms accidentally infecting the cultures. (2) The coccal and bacillary forms are characteristic of a streptothrix which does not cause actinomycosis, but which is present in the lesion as a secondary invader only. Or (3) the coccal and bacillary elements may occur in the streptothrix which causes actinomycosis, but are due to a process of degeneration of the mycelium, and are not in any way connected with the development or growth of the organism.

(1) That the coccal and bacillary elements are extraneous micro-organisms accidentally infecting the cultures. The fact that these elements are real cocci and bacilli, as has been suggested, is at once refuted by the numerous instances in which they have been observed lying within the mycelial sheath, both in cultures, and in the actual lesion as noted by Leith⁽⁹⁾ and others:

(9) Edin. Hosp. Rep. Vol.II. p. 135.

while McFadyean (loc. cit) has described chains of coccal elements lying alongside the empty sheaths.

(2) That the streptothrix giving rise to these elements is present in the lesion as a secondary invader only. Wright (loc. cit.) bases his opinion chiefly on the belief that no streptothrix characterised by the formation of coccal and bacillary elements from its filaments has been proved to produce by inoculation in animals a lesion like actinomycosis, and containing the characteristic granules. In another part of his paper he states that he believes the organism which he described, and which he maintains is the only species causing true actinomycosis in man, to be identical with that described by Wolff and Israel. Now Wolff and Israel (loc. cit) were successful in their inoculation experiments on animals, as admitted by Wright; and, as we have seen, their cultures were characterised by the presence in the earliest stages of nothing but bacillary forms, filaments not appearing until later. These bacillary forms would probably be considered by Wright as real bacilli contaminating the cultures, but some observations by Lignières and Spitz (quoted by Wright, (loc. cit)) seem to have an important bearing on this point. From cases of a disease in cattle which apparently differs in no respect from actinomycosis except that the granules do not contain

gram-staining filaments, these observers have cultivated a small bacillus growing well but not very characteristically on all the usual culture media. Cattle inoculated with cultures of ^{the} bacillus developed lesions like those of the disease, and in these lesions they found the characteristic club-bearing granules without filaments. Nocard confirmed these observations, but Wright thinks that further confirmation is desirable. I think, however, that these observations are strongly in favour of the view that some of the bacillary forms occurring in actinomycosis are a stage in the life history of the streptothrix actinomycosis.

Again, Wright (loc. cit) himself, in discussing the experiments of Gasperini, mentions that the latter observer with a culture, which Wright describes as belonging to the group of "Nocardia",^{or} streptothrices producing spore-like reproductive elements,) produced by experimental inoculation in an animal a lesion in which the organism grew in the form characteristic of streptothrix actinomycosis.

(3) We have, therefore, instances in which an organism characterised by the formation of coccid and bacillary forms is capable of producing the disease on experimental inoculation. I shall now present some evidences pointing to the fact that these elements are

"spore-like reproductive elements" - that they may take an active part in the propagation of the streptothrix - and are not due to a process of degeneration of the filaments.

In the first place, I may mention again the observations of Lignières and Spitz which clearly demonstrate the activity of certain bacillary forms capable of producing a typical actinomycotic lesion with granules - a very strong argument in favour of the activity of the bacillary forms, and against the theory that they are products of degeneration.

Leith (loc. cit) too, describes two varieties of coecal elements in the actinomycotic lesions, the first and most common in which the elements are prominent and stain well, the second in which the elements are shrunken and have the appearance of small often angular segments of different size and sometimes not staining so well, contained within a slightly withered tube. Leith remarks that this difference in behaviour suggests a different significance, the first form being like a vital process important to the further development of the organism, the latter like some degenerative change ushering in its death.

The description by Moodie⁽¹⁰⁾ of the characters of the streptothrix in a typical case of actinomycosis has also a bearing on this point. In this case, the granules

(10) Journ. Path & Bact. 1903. p. 239.

in the lesion consisted entirely of coccal elements and granular debris, with clubs at the margins of the granules. In cultures prepared from these colonies, a dense tangle of filaments was formed. Now the clubs take no part in the development of the organism. (Boström, (loc. cit.), Delepine⁽¹¹⁾, Wright (loc. cit) and others). Therefore the filaments must have arisen from the coccal elements.

Again, it is certain that in some forms of streptothrix these coccal elements, which are in no way distinguishable from the similar elements in the streptothrix actinomycosis, take an active part in the growth of the organism, as Foulerton and Price Jones (loc. cit) by inoculating the "spores" of one of the more quickly growing species in a hanging drop culture have observed mycelial threads sprouting out from the individual "spores" at the end of eighteen or twenty-four hours: while they quote Doméjean as having observed similar sprouting from spores. Wright would seem to suggest a difference as regards the activity of these elements in the two varieties of streptothrix, but states no reasons for doing so.

Summarising, then, we have (1) the undoubted formation of these coccal bacillary elements by the mycelial

(11) Trans. Path. Soc. May 21. 1889.

threads of the various forms of streptothrix, these elements being identical in morphological and staining characteristics in the various forms, there being no evidence to the contrary. (2) evidence that these elements become free, having been observed lying in chains along the side of the empty sheaths. (3) evidence that these elements are not degenerative products, but are capable of producing filaments in cultures, and in the cases observed by Lignières and Spitz of producing in animals a typical actinomycotic lesion with characteristic granules. (4) and lastly, that organisms characterised by the formation of these elements produce typical lesions on inoculation. From these facts, I think we must conclude that the active infective agent of actinomycosis may be characterised by the presence of spore-like cocal and bacillary bodies.

The importance of this lies in the fact that certain observers have found that these elements have a greater resistance than the filaments themselves. Domec⁽¹²⁾ observed that the filaments of actinomycosis Bovis of Harz, a form which has been found in the actinomycotic lesions in man, were killed at a temperature of 60°C for five minutes while the cocal elements survived this

(12) Archiv. de Med. Exper. et d'Anat. Path. Tome IV. 1892.

temperature, requiring 75°C for the same length of time in order to destroy them. Foulerton and Price Jones (loc. cit) had similar results with some of the species of streptothrix with which they worked, stating that they could not be certain in other species that sporulation had not already commenced.

Vincent⁽¹³⁾ obtained similar results with streptothrix Madurae, and it is interesting to note that Wright (loc. cit) describes this case of Vincent's as presumably a case of actinomycosis complicated by the presence of contaminating organisms.

In conclusion, then, it would seem as has been frequently suggested, that there is more than one variety of streptothrix capable of producing actinomycosis in man. In addition to the sporing and non-sporing form, there are other minor differences in staining reactions and in cultural characteristics, which have led various observers to describe the various forms as belonging to different species.

In connection with this it should be stated that some observers (Foulerton and Price Jones (loc. cit) and others) have found that some sub-cultures would for no accountable reason show great variability from time to time in appearance on the same culture media, and also in staining reactions.

(13) Ann. de l'Inst. Pasteur. 1894. Vol. VIII.

Mode of Infection.

As a result of his investigations, Wright concludes that the widely accepted theories of the mode of infection of the human subject by means of grains of corn or grasses must be rejected, basing his opinion on the fact that the organism he described was anaerobic, did not grow well on all the culture media and practically not at all at room temperature. He states that he does not believe that the active infective agent of actinomycosis has its normal habitat outside the body, but is probably a normal inhabitant of the secretions of the buccal cavity and of the gastro-intestinal tract, both in man and in the lower animals.

There are, however, a large number of cases in the foreign literature, which show a more or less close connection between grains and grasses and the development of an actinomycotic lesion. In many cases the patients are stated to have been in the habit of taking uncooked grains or vegetable material into the mouth. Thus Poncet (14.15) Dubreuilh and Frèche⁽¹⁶⁾, Besse⁽¹⁷⁾, Bevan⁽¹⁸⁾ and others

(14) Gazette Hebdomaire, April 1895.

(15) Mercredi Medical, June 19. 1895.

(16) Annales de Dermatologie, Sept. 1895.

(17) de l'Act. Cervicale. Lyons. 1895.

(18) Annals of Surgery, May, 1905.

quote such cases.

Other cases, again, show a more definite relation between a wound with a portion of grain or straw and the development of the lesion. Thus Guermontez and Angier (19) quote a case in which a man wounded his gum with a corn stalk: eight days later an actinomycotic lesion commenced in the exact situation of the scratch. Erving (20) publishes the notes of a case where the disease followed a wound made by an oat straw, and another case where the disease occurred in the skin of the back of a man who habitually slept on some straw in a stable with his back and shoulders unprotected.

Again, Jöhne (21) and Boström (22) and others have found the remains of grain or a sheath of straw in the lesions - the latter in 11 cases, and this observer showed the intimate relation of the organism with the fragments of grain or straw.

In the United Kingdom, out of 105 cases, the notes of which I was able to collect, there was a history of the patient being in the habit of chewing stalks of grass

(19) Gazette des Hopitaux, Feb. 11. 1902.

(20) Bull. Johns Hopkins Hosp. Nov. 1902.

(21) Rurah, Annals of Surgery. Vol. 30. 1889.

(22) quoted by Leith, Loc. cit. p. 180.

or grains, in 6 cases^(x), the lesion occurring in the mouth, cheek, angle of jaw, tongue, abdomen, and lung respectively: while in 5 other cases there is a more definite relation between the time of onset and the history of chewing grain or of being wounded by some such foreign body. In one case⁽²³⁾ a piece of chaff became fixed into the floor of the mouth, ^{and within a month} a swelling commenced which proved to be a typical actinomycotic lesion, the swelling occurring in the floor of the mouth.

In another case⁽²⁴⁾ occurring in the same locality a fine "spear" of wheat lodged in the throat, while patient was preparing some thatch from straw: a fortnight later a swelling appeared under the left side of the jaw, this swelling proving to be due to a typical actinomycosis. In the left anterior pillar of the fauces a small ulcer was present.

In a third case⁽²⁵⁾, while patient was eating some grains of oats one became stuck in the right tonsil: efforts were made to dislodge it, but a few days later the tonsil swelled: the inflammation subsided, but about a

(x) Notes of the cases will be found in (1) Lancet, 1906. Vol.II. p.1307: (2) & (3), Lancet, 1901. Vol.I.p.3. (4), Lancet.1898. Vol.II. p.1061: (5), Edin.Hosp. Reports, Vol.II. p. 123: (6) Lancet. 1897.Vol.II. p. 311.

(23) Lancet, 1897. Vol.I. p. 311

(24) Lancet, ib.

(25) B.M.J. 1896. Vol.I. p. 1555.

month after the date of the lesion he noticed a swelling just under the jaw on the right side. This proved to be a case of typical actinomycosis.

These three cases then show a very definite relation between an abrasion by a piece of straw or a grain and the development of an actinomycotic lesion, at, or in close relation to, the site of the lesion.

In two other cases the lesion followed closely on the chewing of grain or straw. In one⁽²⁶⁾ the patient developed a typical actinomycotic lesion beneath the jaw, the symptoms commencing a fortnight after he had been chewing some straw while watching a threshing machine.

In the other⁽²⁷⁾ abdominal symptoms commenced two months after patient had been eating fresh ears of barley and wheat at harvest time, a typical actinomycotic lesion being found later in the rectum.

In two other cases⁽²⁸⁾, again, the lesion occurred in farm servants soon after assisting at harvest, one lesion being situated behind the angle of the jaw, and the other having ~~first~~ involved the gum.

In the notes of the cases occurring in Great Britain,

(26) Pract. 1898. Vol. 60. p. 398.

(27) Lancet, 1891. Vol. II. p. 1101

(28) Lancet, 1897, Vol. I. p. 734, and B.M.J. 1896, Vol. I. p. 1553.

I have been able to discover only two in which a fragment of grain was found as the nucleus of the actinomycotic lesion. In one case⁽²⁹⁾ a seed, very like a small oat seed, was found in the scrapings from the lesion. In the other case⁽³⁰⁾ a spear-head body like a piece of straw was found in the section of the actinomycotic lesion. This patient was hardly ever without a piece of straw in his mouth when at work.

It will be seen, then, that the view that the organism often gains entrance to the system by means of grains and grasses is supported by a considerable number of apparent instances occurring in this country.

The seasonal incidence of the disease bears a certain amount of corroborative testimony in favour of such a mode of infection. Bostrom⁽³¹⁾ states that out of 84 cases in man, the disease commenced in 77 per cent during the months August to January inclusive - in fact, during the months when there was greater opportunity for the chewing of corn and barley grains. Wright⁽³²⁾ has also stated that most cases occur from August to January. I examined the notes of the British cases to discover if

(29) Glas. Med. Journ. 1895. Vol.64. p. 277.

(30) B.M.J. 1906. Vol. II. p. 137.

(31) quoted in Treve's System of Surgery, "Actinomycosis". Vol. I. p. 315.

(32) Osler & McCrae's Text Book of Medicine. 1907. "Actinomycosis."

there was any such seasonal incidence, but found that taking the disease as a whole there was no such great preponderance of cases occurring in the periods following the harvest. Out of 50 cases in which the month of commencement of the symptoms was stated, in 29 the disease began in the period from August to January inclusive, and 21 from February to July.

But I think it is undoubted that a considerable interval may elapse between the time of infection and the date of the first symptoms referable to the disease in, for example, the abdomen and lung, where the onset is often very insidious. On the other hand, one would expect a much closer relationship between the time of infection and the date of the first symptoms in more superficial regions, namely the common site about the face and mouth, and in the skin: and on looking at the seasonal incidence of the disease in these regions we find that a large proportion of the cases occur in the months during and after harvest. In the head and neck the month of commencement was noted in 19 cases. Of these, 13 or 68.4 per cent, commenced during the months from August to December inclusive, while in the other 7 months of the year there were only 6 cases or 31.6 per cent. In the two skin cases, the disease commenced in the months of October and November respectively.

The seasonal incidence, however, has not been sufficiently observed to allow of one drawing conclusions, but so far as it goes it is in favour of the view of infection by grains or grasses.

Jensen (33) made some interesting observations which seemed to strongly favour the infection of cattle by barley. He observed that the disease was each year more or less prevalent in cattle which had been fed on grain grown on certain land reclaimed from the sea, and that in the late autumn of 1879 and the winter following, the outbreak was so great that nearly the whole herd was affected.

Though many forms of streptothrix have been isolated from grasses, it has not been conclusively proved that they are capable of causing in man or cattle a typical actinomycosis. " Rurah(loc. cit.) however, quotes Liebman who inoculated the seeds of beans, lentils and barley with the streptothrix actinomycosis: the plants and parasites developed simultaneously. The plants were invaded with short rod-like bodies and the streptothrix was also found in the form common in animals. The organism obtained from the plants could infect animals, and also grew on inoculation into other media. Liebman

(33) quoted by Leith, Loc. cit. p. 180.

states that the organism is attenuated by passing through animals, but regains its virulence after being grown on plants. Rurah states that he attempted many times to grow the streptothrix actinomycosis on plants, but never succeeded. If Liebman's work be accepted, there can be no doubt that grains and grasses or other vegetable material are the common means of introducing the organism into the system, but, as far as I can see, his work has not been confirmed by others; while Wright⁽³⁴⁾ failed to get any growth on oat infusions with his organism, and one doubtful growth out of five in potato infusion.

To recapitulate, then, we have in favour of infection by grains or grasses -

- (1) The large number of cases in which there is a history of a habit of chewing grains or grasses, in some cases showing a definite relation in time to the infection.
- (2) A considerable number of cases where actinomycosis followed closely on a wound or abrasion by grains or grasses.
- (3) A considerable number of cases in which portions of grains or grass were found in the actinomycotic lesion, Bostrom finding them in intimate relation with one another.

(34). Journ. Med. Res. May. 1905.

- (4) The seasonal incidence - so far as has yet been observed - a considerable preponderance of the cases commencing within the few months following harvest.
- (5) The observations of Jensen in cattle, an outbreak having occurred in those fed with grain from a certain seed.
- (6) The fact that some part of the alimentary system is by far the commonest site may also be added.

Wright explains the first three by stating that the grain or straw merely acts by causing an abrasion and allowing the entrance of the organism which is normally present in the buccal and intestinal secretions, and that the portions of grain or straw in the lesions merely act by lowering the resistance of the surrounding tissues. But the large number of cases in which the foreign body present in the lesion or causing the abrasion is straw or grain is certainly highly suggestive. Other foreign bodies have caused wounds resulting in actinomycosis, but the number of cases is very few in comparison with lesions caused by straw or grain. As regards the presence of the grain or grass acting solely by its irritative or traumatic effect, Wright himself (loc. cit.) found no such benefit to the micro-organism in his inocu-

lation experiment, those cases in which he introduced setons not showing any more marked lesion than those in which no foreign body was introduced.

Wright further objects to the theory of this mode of infection, in that he found that very little growth occurs at room temperature, that growth is anaerobic, and that growth on vegetable infusions was unsatisfactory. Both Leith (loc. cit.) and Wolff and Israel (loc. cit.) however, state that growth does take place aerobically, though not so well as under anaerobic conditions. The slight growth at room temperature is certainly against the theory of a normal habitat outside the body, but does not, I think, preclude such a habitat. As regards the cultural experiments on vegetable matter, I think they also cannot be regarded as conclusive evidence.

The balance of evidence is, I think, in favour of grains and grasses being a common means of introducing the organism into the system.

The view that the streptothrix actinomycosis has an existence outside the body is favoured by the high degree of resistance which these organisms possess. Liebman⁽³⁵⁾ states as its maximum vitality that it will resist boiling for 14 minutes: that 5 per cent carbolic acid had little

(35) quoted by Ruräh(loc. cit.).

effect on it, and that 1 in 1000 perchloride of mercury solution took 5 minutes to kill the organism. Other observers, however, do not place the maximum vitality so high. Bérard and Nicholas⁽³⁶⁾ found that an exposure at 75°C to 80°C was necessary to destroy cultures. J.H. Wright (loc. cit.) found that 62°C to 64°C for ten minutes was required to destroy the cultures, and the same observer concluded that the organism was quite resistant to drying, being active when tested after fifty to eighty days. It is quite evident from these facts that the organism can exist indefinitely outside the body and still be capable of infecting man.

I fail to see, then, what reasons Wright has for stating his belief that the organism is normally present in the secretions of the alimentary tract, and there are strong reasons against this view. One is the occurrence of primary actinomycotic lesions in the skin. While uncommon in man, they undoubtedly do occur; and in cattle this is a common site.⁽³⁷⁾

Again it would be impossible to account for the outbreaks in cattle on this assumption. One such outbreak has been observed by Jensen, as mentioned before:

(36) Comptes Rendus de la Soc. de Biol. 1900. Vol. 52. p. 837.

(37) Professor Crookshank, "Actinomycosis and Madura Disease". Lancet, Jan. 1897.

and Crookshank (ib) mentions a similar one occurring in this country, eight per cent of the cattle on one farm becoming affected; and another large outbreak on an Australian farm.

As regards infection from other foodstuffs, Besse (loc. cit.) has stated that there is some evidence that infection may occur from meat, potatoes, and even milk. Leith (loc. cit.) has come to the conclusion, after a search of the literature, that there is no evidence to show any danger in consuming the flesh of animals suffering from the disease. Foulerton and Price Jones (loc. cit) state that the ordinary temperature reached in the interior of meat during cooking is not usually much above 65°C, which is below the temperature necessary to kill the organism according to most observers, and they state that meat must therefore be considered as a probable means of infection. Although no one has yet succeeded in producing the disease experimentally by mixing the parasite with the food, it must nevertheless be considered a possibility, given favourable conditions of susceptibility, and perhaps an abrasion in the mucous membrane of the alimentary canal.

As regards milk, Leith (loc. cit.) states that the parasite has never been found here, and moreover the fact that the disease is very uncommon in young children is

against such a mode of infection. Crookshank (loc. cit.) mentions that in cattle a few cases have occurred in the udder: and Leith describes the pathological changes in a specimen which he procured. In this there was no direct invasion of the gland tubes, but there was some alteration in them, and Leith remarks that it is difficult to believe that the parasite does not in some form or other invade the tubes. Milk cannot therefore be altogether excluded as a possible means of infection.

As regards the question of the direct passage of infection from animal to man, the evidence in favour of this means of infection is not by any means strong. Cases are certainly on record where the patients have had to do with cattle suffering from the disease, but such examples are not numerous. In 6 of the 100 American cases collected by Rurah (loc. cit.) and Erving (loc. cit.) there was a definite history of the patient having cared for an animal suffering from the disease during a considerable period preceding the manifestation in the patient: and Malcolm Morris (37a) states that cases have been reported by Poncet, Mayde, Bulhoes, Hartman and others. I have not been able to find any instance in this country. That the disease is not a markedly contagious one is

(37a) Lancet, 1896. Vol. I. p. 1553.

evident, and in connection with this an experiment was made in America^(37b), 21 healthy cattle being kept in close quarters with diseased cattle for three months without showing any sign of infection. There is no evidence of direct infection from man to man.

Age. In the notes of the 105 cases occurring in this country, the ages were stated in 79 cases, and were as follows:-

<u>Years.</u>								
1-5.	5-10.	10-15.	15-20.	20-30.	30-40.	40-50.	50-60.	60-70.
<u>No. of Cases.</u>								
1	4	8	14	20	14	9	4	5

The youngest was 5 years: the oldest 65 years.

The age incidence of these cases corresponds pretty much with that of cases collected in other countries. Leith (loc. cit) in 392 cases, collected in this and other countries up to 1894, found that the disease had been observed as early as 1, 4, and 5 years of age respectively, and as late as 77, but was not common before 10 or after 60: and that the period of young adult life is apparently most favourable to the disease, especially the third decade. The statistics of the American cases collected by Ruräh["](loc. cit.) and by Erving(loc.cit.) also correspond with the above.

(37b) B.M.J. March, 1893.

Sex. In the British cases, out of 94 cases in which the sex was recorded I found that 65, (or 69.1 per cent) were males, and 29 (or 30.8 per cent) were females. The disease has therefore, in this country, been more than twice as common among males than among females. Leith (Ib.) out of 405 cases found the proportion of males to females as nearly $2\frac{2}{3}$ to 1. Erving (loc. cit.) in America, and Poncet and Bérard (quoted by Rurah loc. cit) show a similar preponderance of the affection in males.

Occupation. The occupation was mentioned in 50 of the British cases, and was very varied. Nine had to do with horse or cattle: nine were country men or farmers: three were domestic servants: there were two each of labourers, clerks, merchants, gentlemen and surgeons: while of the others nine followed out-door and ten indoor occupations. It cannot be said that any occupation had any preponderance.

Cases in foreign literature do not show any more definite occupational incidence. Leith found that almost every occupation or calling in life supplied instances, and out of 100 cases at random ten were coachmen or grooms. 32 peasants or workers in the field (5 of whom were specially mentioned as being much engaged

about cattle), 25 were farmers, grieves, or landowners:
8 bakers or millers: 17 merchants or commercial tra-
vellers: 5 students: and 3 physicians.

Rurāh's observations (loc. cit.) in the American
cases tally with the above. It would seem that a larger
proportion of the cases are engaged in out-door occupation.

PATHOLOGY .

The pathology of this condition is in many ways an interesting one.

The general pathological features are granulation tissue formation, with suppuration and tissue destruction. A purely formative type - the form common in cattle - is rare in man. Before the advent of suppuration the foci are characterised by areas of caseation and necrosis, surrounded by rows of small mononuclear cells, and epithelioid cells, while giant cells are found about the periphery, so that the minute changes resemble those in tuberculosis. The giant cells differ, however, in having more numerous nuclei, which are arranged in the centre or at one end and not disposed round the periphery as in tubercle. They may contain fragments of filaments and clubs. Later there is the formation of new connective tissue about the focus of infection, which later may form dense bands, in the interstices of which the colonies of the organism are found. In addition to this tissue formation, there is in man in most cases a formation of pus, which surrounds the colonies within the meshwork of connective tissue.

The new formed connective tissue is vascular (38) thus differing from that found round tuberculous foci: and Leith states that the new formed vessels are

(38) Leith (loc.cit.) Delépine. Trans. Path. Soc. 1889. May 21.

always rudimentary, shewing little beyond a layer of endothelial cells lying on a fine thread-like fibrous layer. Clinically, proof is supplied of this fact, it being often stated in the notes of the cases occurring in the British Isles that haemorrhage on incision into the mass was free and difficult to control. (39)

The disease is characterised by a marked tendency to extension, and a peculiar feature of this extension is that it is not limited to the organ in which the disease is manifest, but spreads to the surrounding tissues, - the lesion does not respect anatomical boundaries, - thus differing from tubercle.

Now this local spread does not occur by a simple outgrowth of foci, as the organism is only found in the centre of abscesses, and not towards the margins of the foci: and again the typical mode of extension is seen to be by the formation of smaller abscesses quite definitely isolated from the margin of the main mass. (40) That this mode of extension does not take place by the lymphatics is evident from the generally recognised fact that lymphatic glands are never, or very rarely involved, and that in the lesion the lymphatic vessels are never or very rarely involved; (41); while, on the other hand, there are local appearances as well as the occurrence of metastases, which point to the blood-vessels being the channels

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- 9) (Godlee a series of cases. Lancet. 1901 Vol.I. p.3
and others.
0) Leith, Delépine (loc.cit.) Wright (loc.cit.) & others.
1) Leith Loc.cit.

through which this curious form of local extension is brought about. In the liver, where the pathology has been most closely observed, both Leith and Delépine found that the process of formation of new connective tissue was continued beyond the margin of the actinomycotic focus into the liver substance as an intercellular cirrhosis, and Leith observed that the bloodvessels of the reticular tissue were continuous in places with the intercellular capillaries. Again the branches of the hepatic artery and portal vein, especially the former, showed a proliferation of their endothelium, the adventitia was also thickened and blended with the markedly increased connective tissue in the portal spaces. Both Leith and Delépine attribute these changes at the margins of the foci to the passage of bacterial excretions through the vessels, Delépine because he found only a very few actual streptothrices in the vessels in this region, and Leith because he found no actual streptothrices. Leith, however, states that he found micrococci here, in some cases forming plugs filling the sublobular veins: that these cocci were of much the same size and character as the coccal forms in actinomycotic cultures, and that there was a possibility of their being of actinomycotic nature. Samter, (quoted by Leith), however, believed that this cirrhotic change was due to some early form of the streptothrix or other accompanying organism, which after setting up an inflammatory

process, again disappeared without further development. Now Delépine (loc.cit.) has described a condition in his case which favours, I think, the opinion that these changes are partially, at any rate, due to the passage of some form of the organism. He found, at a distance from the main mass and separated from it by comparatively healthy tissue, small patches of small round-celled infiltration or of necrosis, but in these he was unable to find any organism: he attributed these patches to the action of the toxin, however, though it seems to me more likely, from their isolation and their circumscribed nature that they were due to the action of some early form of the organism. Again, if these changes be entirely toxic, it appears to me that one would expect a considerable degree of general toxæmia: but it is remarkable that a fairly marked actinomycotic lesion may be present for a considerable time without any marked change as to the system as a whole, which point is illustrated by many of the British cases, and which has been observed by others, including Foulerton and Price Jones (loc,cit.) who add that it is only in long standing cases or when lesions are unusually extensive that any marked wasting of tissues is seen, and that where wasting is prominent it is usually the effect of secondary infection by actively pyrogenic organisms. Leith's case itself illustrates this very well, the patient being "well nourished" although the lesion in

the liver was of large size.

Again, Harris (42) has described a lesion in the liver in which there was an almost complete mapping out of the liver lobules by mycelial threads beyond the main mass, these threads having insinuated themselves between the columns of liver cells, and in places it was noted that the capillaries were blocked by means of threads of mycelium.

It would seem likely, then, that these changes are brought about to some extent by the passage of some form of the organism through the vessels.

In conclusion, I would suggest that owing to the large amount of vessels of embryonic type in the new formed tissue, the streptothrix passes in some form readily into the vessels: that some are arrested after passing a short distance and there grow into new actinomycotic foci, or are destroyed by the tissue cells - the close neighbourhood to the main mass being a favourable site owing to the lowered "bacteriotropic pressure", and to some toxic action of the neighbouring organisms: that others again pass on into the general circulation, where, owing to their slight degree of virulence they may be destroyed, or may set up metastatic foci elsewhere.

The curious and very marked tendency on the part of this organism to overstep anatomical boundaries, and its frequent extension through muscles and fascia

(42) (Journ. Path. & Bact. 1898. p.182.)

instead of following the lines of least resistance, may I think be explained on this view of its mode of local extension. For example, in lesions of the lung or liver, when the lesion reaches the pleura or peritoneum adhesions would occur between the adjacent serous surfaces: these adhesions forming the limit of an actinomycotic focus would become vascularised, and the organism gaining a ready entrance into the rudimentary vessels in the active focus would pass easily into and beyond the adherent pleura and peritoneum, and there would set up new foci: and this process would be continued through the various muscular and fascicular layers separating the main growth from the surface of the body, leading eventually to the characteristic appearance of a number of sinuses discharging externally.

With regard to metastasis, Martin (43) states that its occurrence is comparatively rare. This was by no means the case in those cases occurring in this country. One would certainly expect a comparative frequency, from the local pathological conditions - the vascularity of the new formed tissue and the rudimentary nature of the new formed vessels - and this is borne out by the British cases, at any rate. On examining the notes of the cases occurring in this country, I find that metastasis was present in 29 out of the 105 cases, or 27.6 per cent. I have of course

(43) (Journ.Path.& Bacter. 1896. p.78.)

been careful to distinguish between a real metastasis and a possible extension of the disease by continuity. Those cases of the disease occurring primarily in the abdomen most frequently give rise to metastasis, out of 39 primary cases metastasis occurring in 18, or 46 per cent. Thus almost half of the primary abdominal cases were followed by metastasis. Those cases of the disease primary in the lungs came next in order of frequency of the occurrence of metastasis, out of 19 primary cases, 7, or 37 per cent, showing metastatic growths elsewhere. In primary head and neck cases, the relative frequency of metastasis was much less, out of 41 primary cases only 3, or 7.3 per cent. showing metastasis, out of the 3 cases apparently primary in the skin, one showed metastatic foci: about this case (44) however, I think there must be considerable doubt as to the primary origin in the skin the probability being that the primary origin was in the abdomen.

One case apparently occurring in the testicle did not give rise to metastasis: and another case was represented merely by a pathological specimen.

(44) (Reported by Delépine - *Trans. Path. Soc.* 1889.
May 21.)

Turning now to the various sites in which metastatic growths occurred, I have prepared a table showing the organs and tissues which were the seat of metastatic growths.

<u>Primary in</u>	Head & Neck.	Abdomen.	Lungs.	Skin.	
With metastatic growths in :-					
Lungs	3	7	3	1	Total 14
Liver	0	10	2	1	Total 13
Spleen	0	2	1	0	Total 3
Kidney	1	2	2	0	Total 5
Ovary & Tube	0	1	0	0	Total 1
Retroperitoneal	0	2	1	0	Total 3
Brain	0	2	1	1	Total 4
Joints	0	1	0	0	Total 1
Subcutaneous	0	2	1	0	Total 3
Intermuscular	0	1	1	0	Total 2
In abdomen - site not stated	1	0	2	0	Total 3

The liver and lungs were the organs most frequently affected by metastatic growths, as one would expect, infection being probably carried to the liver through the portal system, as no less than 10 of the 13 cases in which the liver was involved by metastasis had their primary origin in the abdomen.

The kidney, brain, and spleen come next in frequency as regards the occurrence of metastatic growths. In some cases there was wide diffusion of the organism through the body, notably in a case ^{reported} by Mr. Godlee. (45) Where the lesion was apparently primary in the liver, and secondary foci were found in the kidney, retro-peritoneal tissue, cerebrum, subcutaneous tissue, and in various joints - hip, knee, and metatarso-phalangeal joint of the great toe.

As regards the form in which the organism circulates in the blood it is difficult to make any positive statement.

If we accept the opinion that the coccal and bacillary forms are capable of propagating the organism it would seem likely that they are the common means of producing metastatic growths, as they would easily find their way into the bloodvessels. A specimen described by Moodie (46) certainly favours this view. Close to a lesion in the liver secondary to the disease in the jaw, he found in some places a very striking appearance - what appeared to be membranous capsules partially filled with coccus-like bodies similar to those found in the main lesion and also staining by Gram's method. These bodies were grouped in a dense band just inside the capsule, or arranged in clumps throughout, or scattered irregularly. "In some cases

(45) (Lancet. 1901, vol.I. p.3. case 6.)

(46) (Journ.Path.& Bact. 1903. p.239.)

apparently from the thickest part of ~~what~~ we shall call their "wall", delicate processes with dilated extremities could be seen, which presented the appearance of early club formation. In others it looked as if the wall had ruptured and allowed the coccus-like bodies to escape, while the wall at the point of rupture took on the appearance of homogeneous bands bearing clubs". Moodie explains this interesting feature on the belief that the capsule like aspect was produced by the coccal elements entering the lumen of the capillary in the form of an embolus, and by their growth distending the walls to an abnormal degree.

This case I have mentioned before as being interesting in that no filaments were found in the lesion, coccal elements and clubs being alone present: while filaments were found abundantly on making cultures.

Moodie mentions another case very similar to this one, described by Chiari, and in this case the cell nuclei of the distended wall could be demonstrated.

I shall now refer to the frequency and to the actual site in the various regions.

Head and Neck. In Erving's (loc.cit.) collection of American cases the head and neck formed the primary site in 53 per cent of all cases. Leith out of 383 collected cases found the head and neck primary in 54 per cent: Illich (quoted by Ruräh) in 55 per cent.

The figures of other observers are much the same, pointing to the primary head and neck cases forming more than half of the total cases. In the British cases the proportion was not so great - 41 out of a total of 105 cases being primary in this region, forming 39 per cent. Their distribution was as follows:- in the temporo-maxillary region 26 - 2 in the upper jaw, 10 in the cheek, 8 in the lower jaw, while 6 were stated to be in the "jaw": in the submaxillary region 6: in the tongue, 2: peripharyngeal, 6, including 4 in which the primary affection was evidently from the tonsil. In one case the primary site was ⁱⁿ definite. The temporo-maxillary is, of course, considered the classical form of the disease owing to its frequency here and its generally well known characteristics. The disease in this region is generally stated to commence in connection with a carious tooth, but ~~V. Baracz~~ Baracz (47) found that many of his cases showed infection through the buccal mucous membrane, just as in cattle whose teeth are always sound, and he is inclined to disbelieve the alleged important part played by carious teeth. Of the **26** cases occurring in this region among the British cases, I found that 10 were primary in the cheek. In those cases commencing in the upper and lower jaws - 16 in all - 4 were stated to have started in connection with a carious tooth:

(47) Arch. f. Klin. Chir. LXVIII. 4.)

in 3 other cases it was mentioned that there were carious teeth in the vicinity. There does not seem to be a close connection, then, with carious teeth: and the rarity of bone involvement in this region,^{as} it is elsewhere, is against the theory of the entrance of the organism into the tooth socket through a carious tooth. While in a few of the British cases the abscesses were stated to be periosteal, in only one case was bare bone felt with a probe, pointing to the probability of the abscesses being external to the periosteum. The disease may attack the bone of the jaw peripherally, but there are very few cases on record where a central actinomycosis of the jaw has been found. Von Bruns (48) mentions one such case, and he states that he could find only one other case on record.

But the presence of carious teeth in the mouth must predispose to a lesion in the mouth by the possibility of abrasions of the mucous membrane of the cheek, and also by the presence of an unhealthy condition of the gum, and perhaps some slight ulceration here.

In the cheek the condition has a tendency to spread outwards, in a large proportion of cases involving the skin and discharging externally.

In the submaxillary form the infection has spread down from the gum of the lower jaw, or from the floor

(48) (Munch. Med. Woch. 1903. Vol.6.)

of the mouth, by direct extension.

Those cases occurring behind the angle of the jaw are probably due to infection from the fauces. Two of the British cases illustrate this mode of extension well, one (49) where the primary lesion was on the anterior pillar of the fauces: and the other (50) where the tonsil was the seat of the lesion.

The tongue - a common site in cattle - is comparatively rare in man. Leith (loc. cit.) found 13 out of 220 cases primary in the head and neck. The much greater frequency in cattle is no doubt due to greater liability of abrasion, the tongue being almost a prehensile organ in grazing.

Pharyngeal. I have included under this heading cases occurring primarily in the pillars of the fauces (1 case) and in the tonsil (3 cases) Three of these cases were principally manifest in the submaxillary region and behind the angle of the jaw, while one of the cases apparently primary in the tonsil was manifest chiefly in the prevertebral tissues and the cervical vertebrae.

The point of entrance in the fifth case was not evident, nor was it in the case which came under my notice: but the tonsil and fauces appear to be a favourable site for infection. Cases have been reported of primary brain actinomycosis, (51)but the

- (49) (Lancet. 1897. Vol.I. p.311. Case 2.)
(50) (B.M.J. 1896. Vol.I. p.1555.)
(51) (Höllinger. Münch. Med. Woch. 1887.)

condition is very rare - if it ever does occur, the possibility presenting itself of the lesion being a metastatic one from a primary lesion which has escaped notice. By extension and metastasis, the condition is not very uncommon. Among the British cases I have found 5. Of these one was by extension from the upper jaw through the orbit (52), while the other four cases were metastatic.

Lungs.

Frequency. Out of the total of 105 British cases the primary lesion was in the lung in 19, that is in 18 per cent.

Wright (53) states that 15 per cent of all cases are primary in the lung: Leith (loc.cit.) 14 per cent. Poncet and Bérard (loc.cit.) 15 per cent.

As regards the side affected, West (54) out of 27 collected cases found that the primary condition was more common in the left lung, in the proportion of two to one. This was not so in the British cases, there being 9 in the right lung and 8 in the left, the side not being stated in two cases.

The lower lobe is more commonly affected than the upper. West (loc.cit.) found in 20 cases that the lower lobe was affected in 13, the upper in 3, and the middle in 4. Erving (loc.cit.) in 10 cases

(52) (B.M.J. 1896. Vol. I. p. 1553.)

(53) (Osler & Mc Crae's Text Book of Medicine "Actinomycosis"-

(54) (Trans. Path. Soc. 1897. p. 17.)

found the lower lobe affected in 7, and the upper in 3. Out of 16 primary British cases in which the site was stated, the lower lobe was affected in 10, the upper in 5 (of which 2 were situated at the apex), and both upper and lower in 1.

The pathology of the lung cases is interesting from the point of view of infection, as it has been stated that infection occurs by breathing the dust of grains and chaff. The common site in the lower lobe is quite in accord with this theory, but on examining the notes of those cases occurring in the lung as a result of metastasis we find that there was even a greater preponderance in favour of the base - 7 in the lower lobe, and 1 in the upper lobe, while 1 was in both upper and lower lobes. (I do not refer to infection of the base of the lung by direct extension, of which there were seven examples.)

As regards the type of lung involvement, the disease may in the first place be limited to the bronchi, evincing itself in a catarrhal inflammation. This form is undoubtedly rare. Among the British cases there is one described by Leith (*loc.cit.*) in which changes of an acute character were limited to the bronchi, the patient having suffered for a considerable time from actinomycosis in the abdomen. Ruräh (*loc.cit.*) mentions such a case, the evidences being obtained from a clinical examination of the patient.

A second is broncho-pneumonic in type, the appearances suggesting that the disease has started in the smaller bronchi or bronchioles, and ^{has} spreading rapidly to adjacent alveoli. This type is mentioned by Ruräh (loc.cit.) and others.

A third form is pleuro-pneumonic in type. In these cases the pleura is thickened and contains actinomycotic foci: while the lung tissue in the immediate neighbourhood as a rule takes part in the change, the alteration being often of a fibroid character, numerous bands running in different directions and often being of a honeycomb character, with areas of suppuration in the meshes. (Ruräh and others.)

A fourth form has been described where there are numerous small miliary deposits in the lung. West (loc.cit.) found in the collected cases three of this type, and states that in the early stages it is like miliary tuberculosis in the lung: two of his cases were secondary to the disease in some other part of the body. I can only find two of this type in the British cases, both being secondary to the disease elsewhere. One (55) where the condition was secondary to the disease in the abdomen, and the other (56) where the condition was secondary to a lesion in the other lung.

As regards the relative frequency of the broncho-pneumonic and pleuro-pneumonic types, West (loc.cit.)

(55) (Guy's Hosp. Rep. 1891. Vol. 48. p.311.)

(56) (Trans. Path. Soc. 1894. p.233.)

states that in most cases the lung is primary and the pleura secondary, but adds that in nearly every one of the cases the chest wall was involved. I can find no other reference in the literature at my disposal bearing on this point except the observations of Erving (*loc.cit.*) who states that in nine of the 20 American cases the disease seemed to confine itself chiefly to the pleural cavity and thoracic wall.

The cases occurring in this country showed a marked affection of the pleura. Out of 15 cases in which the site was mentioned, 13 involved the pleura with more or less involvement of the subjacent lung substance, while only two were situated entirely within the substance of the lung. In 4 cases the disease was very largely confined to the pleura, the subjacent lung substance being only slightly involved. In most of these 13 cases there was marked thickening of the pleura, and in many cases there was involvement of the chest wall. A definite collection of pus in the pleural cavity occurred in 5 of the primary cases, and in 3 of the secondary.

The feature of the disease, then, as evidenced in the cases occurring in this country, was a marked affection of the pleura and more or less of the subjacent lung, rather than an affection of the lung substance, and this is scarcely what one would expect if the pulmonary condition were produced by inspiration

of the infective organism. How, then, is the infection carried to this region? If primary in the pleura or subjacent lung, we must presume that the organism obtains entrance into the blood stream from the alimentary tract or elsewhere, which in itself is unlikely, and shows a marked preference for the pleura, or lung substance immediately beneath it. The morbid anatomy is certainly against the theory of air-borne infection. I think, then, that it is probable that most of these cases are involved secondarily. Secondary extension might take place from the chest wall, but this must be exceedingly rare if it ever does occur, since primary skin lesions are distinctly rare.

Extension from the abdomen is another possibility. The pleura is frequently involved secondarily to the liver (10 cases): but many of the cases could not have such an origin as the basal portions of the lung and pleura were free of disease

Lastly extension from the mediastinum is a possibility, the pharynx and oesophagus being the primary seat, or at any rate the site of entrance of the organism. This seems to me to be the most probable mode of infection of the lungs in the pleuro-pneumonic type - that is in the type occurring commonly in this country. I would suggest then that many of these cases occurring apparently primarily in the lung are caused by the organism gaining an entrance through the wall

of the oesophagus, perhaps through an abrasion, and passing thence into the cellular tissue of the mediastinum without causing any appreciable damage to the oesophageal wall - a very similar condition to that which undoubtedly frequently occurs in the abdomen as I shall point out later: and that in the cellular tissue of the mediastinum growth takes place, as frequently occurs in the retroperitoneal tissue. Infection of the pleura from the mediastinum may then readily take place. West's case (loc.cit.) illustrates the possibility of this mode of infection in the pleura, the actinomycotic tissue spreading into the mediastinum and being firmly adherent to the aorta.

In the lung tissue there was sometimes cavity formation, but the cavities were not as a rule large. Abscess formation is common as elsewhere, generally in the form of small abscesses enclosed in a meshwork of connective tissue.

Abdomen.

Frequency. Among the cases occurring in this country 39 (or 37.1 per cent) were primary in the abdomen. Wright (loc.cit.) places the number at 20 per cent: Leith (loc.cit.) at 24 per cent: Erving (loc.cit.) in America, at 23 per cent. The British figures are therefore larger than elsewhere.

As regards the location of the primary site in the abdomen in the British cases, 19 (or 48.7 per cent) originated in the neighbourhood of the right iliac fossa, 7 (or 18 per cent.) in the colon, 1 in the stomach, 1 in the rectum and sigmoid, 1 in the rectum and prostate, and 7 (or 18 per cent.) apparently in the liver: while in 3 cases the primary site was indefinite or not stated. (In many cases there was considerable difficulty in deciding on what was really the primary site. My figures differ very widely from those given by Hitchens (57) who stated the primary site in 39 abdominal cases ^{occurring in this country} up to 1905, and observed that 20 of these occurred primarily in the liver. In the notes of the cases many are stated to be primary in the liver because the lesion was largest. It seemed to me more likely, for reasons that will appear later, that the liver condition should be secondary to the intestinal even though the lesion in the former were larger, and I have classified the lesions accordingly. I should state that in one or two instances I have placed the primary lesion in the intestine even though no trace of active disease was discoverable in the latter at the time of examination, evidence of old disease, however, being present.)

Grill (58) out of 40 cases found the primary site in the appendix and caecum in 45 per cent. Hinglais (59) in 100 cases found 60 per cent. in the region

(57) (B.M.J. 1905. Vol.II. p.1168.)

(58) (Beit. f. Klin. Chir. 1895.)

(59) (Thèse. de Lyons. 1897.)

of the caecum and appendix.

As regards the lesions, an interesting fact about those cases, at any rate, occurring in this country, was that the disease in by far the majority of the cases did not seem to attack chiefly the intestinal wall itself, but rather to pass through the wall of the intestine resulting in a lesion outside the gut, the actual lesion of the gut wall being slight, and in some cases hardly discernible.

In the region of the caecum and appendix, out of 13 cases in which a description of the lesion was given, the appendix was attacked in two cases, the caecum in 3, and both caecum and appendix in 2: while the lesion was practically entirely outside the wall of the gut in 6 cases (1 being round the appendix, and 5 rebro-caecal.) In nearly all the cases the lesion was more marked outside the wall of the gut than actually in the gut walls.

The cases occurring in the colon were disposed as follows - ascending colon, 2: hepatic flexure, 2: splenic flexure, 2: descending colon, 1. In only one of these was there any marked lesion of the gut wall itself. (case described by Leith, loc.cit.) In one other there was an ulcer which had perforated, by far the most marked lesion being outside the gut wall: while in another there was a sinus communicating with a large abscess behind the colon. In the other 4 cases

there was practically no involvement of the wall of the gut, the mucous membrane in each case being intact and showing no signs of disease though in two of the cases a lesion of considerable extent lay just outside the wall of the gut. One (60) of these cases was rather curious. The growth involved the transversalis muscle and peritoneum, and was closely attached everywhere to the ascending colon but could be separated from the bowel without cutting its coats except at one point where the peritoneum was nicked. In a section of the tumour a husk of a grain of wheat was found, demonstrating positively its origin from the interior of the gut. The stomach case showed a perforating ulcer leading into a large actinomycotic abscess outside the stomach wall: and one of the rectal cases showed a sinus with a similar large mass outside the wall of the gut, and practically no involvement of the rectal wall.

These cases, then, show that the organism has a preference for the tissues outside the gut rather than for the gut wall itself, the retro-peritoneal tissues and the muscles of the abdominal wall being frequently affected.

In the intestinal wall itself the mucous membrane may first be involved (61), ulceration following, and the process may then spread to the submucous and deeper

(60) (B.M.J. 1906. Vol. II. p. 137.)

(61) (V. Baracz. Arch. f. Klin. Chir. LXVIII. 4.)

coats. As stated, there was ulceration in some of the British cases, but the condition was rare. No description of the ulcers was given. In other cases, and I think the majority, there is no apparent involvement of the mucous membrane, the actinomycotic abscesses occurring in the submucous coat as in Leith's case (loc.cit.) in which neither the mucous membrane nor the peritoneal surface showed any evidence of the lesion in this situation. It would seem that the organism can gain entrance into the submucous coat and there develop or pass through the wall without any ulceration of the mucous membrane, and that this is the commonest form in this country at any rate. Some of the small abscesses in Leith's case appeared to be approaching the lumen of the canal, and Leith suggests that the organism may be spontaneously discharged in this way.

The liver is a common site for an actinomycotic lesion, being affected in 23 out of the 105 British cases, that is in 21.9 per cent. Of these, I have stated that 7 were apparently primary, but it is probable that most, if not all, cases apparently primary in the liver are really secondary to some slight actinomycotic lesion in the gut wall or outside it, which has passed unrecognised, or has healed by spontaneous extension of the organism. That such lesions might be easily missed we have already seen.

The liver is also involved by extension and by metastasis. The right lobe was most commonly affected. The lesion may be single or multiple. The size varies from a small nodule, to the size of a foetal head in one case. The typical abscess in this situation presents the appearance of a honeycomb structure of fibrous tissues, in the meshes of which are found pus and debris and actinomycotic colonies: but another form of lesion is also found in the liver in the form of caseous nodules without the formation of abscesses, as observed by Eve (62) and as described in other cases, in one of which (63) both caseous areas and abscesses were present, while in the other the caseous masses alone occurred (64). The minute changes in the neighbourhood of the actinomycotic mass have already been described.

As regards the other abdominal organs, the kidney was affected in 5 cases (4 by metastasis and 1 by extension): the spleen in 4 cases (3 by metastasis and 1 by extension). There was nothing particular to note in the lesions in these organs

(62) (Trans.Path.Soc. 1889. XL. p.405.)

(63) (Lancet. 1901. Vol.I. p.3. Case.7.)

(64) (Reported in Lancet 1901. Vol.I. p.3. case 8.)

Reproductive System.

Though a few cases have been reported as occurring primarily in the reproductive organs, it seems probable that the condition is secondary to the disease elsewhere. In this country Grainger, Stewart and Muir (65) report a primary case occurring in the ovary and they suggest the probability of vaginal infection. But the probability of extension from the rectum suggests itself in this case, as the uterus was bound down by firm adhesions to that viscus, and the ovary was also drawn down into the pelvis by adhesions.

Another case (66) which was stated to be primary in the ovary and to have resulted from vaginal infection, was later found to have a retrocaecal abscess and a liver abscess, so that the evidence of the condition being primary in the ovary is not sufficient. One of the British cases (67) however, is a more debatable one, as the lesion occurred in the spermatic cord outside the external abdominal ring: but the question of metastasis or extension down the cord must be strongly considered before accepting such a case as being primary.

Skin.

Some cases seem to be undoubtedly primary in the skin, though it would appear that many so stated are

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- (65) (Edin. Hosp. Rep. Vol. I.)
(66) (B.M.J. 1907. Vol.I. p.984.)
(67) (B.M.J. 1899. Vol.II. p.1704.)

extensions from within, or possibly the result of metastasis into the subcutaneous tissue. Two of the British cases seemed to me to be undoubtedly primary in the skin. One (68) occurred in the skin of the flank as the result of a bruise, the history pointing definitely to a superficial condition from the first. Another case (69) is reported where the lesion occurred in the scalp as the result of a wound. About the third case (70) there is a considerable amount of doubt, as it seems quite possible that the skin condition was secondary. Several cases are mentioned in foreign literature.

But by far the majority of the skin cases are secondarily affected by extension from deeper parts, this being exceedingly common. Three cases in this country have occurred as the result of metastasis (71) ^{& in these} the lesions were situated in the subcutaneous tissue in the form of multiple abscesses.

The appearances will be referred to later: they were suggestive of the condition being chiefly situated in the subcutaneous tissue rather than in the true skin.

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- (68) (Lancet 1905. Vol.II. p.157.)
(69) (B.M.J. 1906. Vol.II. p. 1128.)
(70) (Delepine. Trans. Path. Soc. May 21. 1889.)
(71) (1) Journ. Path. Bact. 1898. p.182. (2) Trans. Path. Soc. 1894. p.233. (3) Lancet 1901. Vol.1. p.3. case.6.)

Clinical Features.

The disease is usually chronic in character, but may be subacute and even somewhat acute. Fever may or may not be present, and when present is not usually higher than between 99° and 100°. The temperature usually rises a little at night in these cases, being intermittent or remittent in type. In the presence of secondary infections by other organisms, however, fever is a more marked symptom, and may be markedly hectic in type.

Pain may or may not be present. Some observers have stated that severe pain is a characteristic feature of the disease in many regions, while others again state that the disease is insidious in its onset and progress, giving rise to very few symptoms until it may have produced very grave pathological lesions. Most of the British cases would appear to conform to this latter type rather than to the former. A feature of the disease in the British cases has often been the periodicity of the symptoms, longer or shorter intervals of more or less perfect health intervening. A characteristic feature of the disease in the internal organs is the frequency with which the lesion spreads to the surface and involves the skin. In these cases a swelling appears, which is usually inflammatory in character, is hard and board-like, infiltrating and not usually tender. The skin over it gradually

becomes oedematous, and assumes a purple or as some describe it a violet colour, these appearances gradually shading off into sound skin. In time one or more nodules make their appearance on the swelling, and these break down, so that there may be several sinuses discharging as a rule a clear, viscid or semipurulent fluid, or thick pus, the discharge containing in many cases the characteristic granules. (It is often, however, ~~over~~, stated in the notes of the British cases that granules have not been found for long periods although a careful search has been made for them.) Further, on incising such a swelling, it is found to consist of an indefinite spongy structure, which in the British cases is often noted to bleed very freely: and the amount of pus found is usually much less than one would have expected from the nature of the physical signs.

In cases uncomplicated by secondary invasion with other organisms, the absence of involvement of the lymphatic glands is a marked feature, and is an important point in diagnosis from tuberculous or malignant affections.

Regarding the blood changes in actinomycosis, I have not been able to find many accounts. Ruräh (loc. cit.) states that in all cases where the blood examination was made, there has been slight leucocytosis mentioning one case where the leucocyte count stood

at 12,000 per c.mm. and another case where there was a slight relative leucocytosis. Erving (loc.cit.) reports a case in which the leucocytes were 12,000 per c.mm., another in which they were 24,000 to 36,000 per c.mm. and a third in which they were 10,000 per c.mm. when first examined but rose later to 21,000, the swelling having in the meantime increased.

Bevan (72) notes one case at 22,000. In only one of the British cases are the leucocytes mentioned (73) and in this they are stated to be "in excess". In the case which came under my notice the leucocytes were counted on several occasions, the count varying from 22,000 to 33,000 per c.mm. as a rule, but on one occasion was as low as 17,000. There is, therefore, in all these cases a leucocytosis. In Erving's case where the leucocytes were between 24,000 and 36,000 the lesion was in the liver, in which necrotic tissue was found at the time of operation but no pus definitely discovered. In his other two cases pus was present. In Bevan's case pus was present: while in the case which I have reported there were granulating wounds in the neck, with semi-purulent discharge from them and from the sinuses. In this case the differential leucocyte count was also observed on several occasions, and while varying slightly the relative proportions

(72) Annals of Surgery. May, 1905.

(73) Guy's Hosp. Rep. 1897. Vol.LIV.

were much as follows - Polymorphnuclear cells 68.7 per cent, Lymphocytes 18.6 per cent, Large mononucleated cells 12.2 per cent., eosiophiles .5 per cent. I can find only one other reference to a differential leucocyte count, made by Ruräh (loc.cit.) in which there were $2\frac{1}{2}$ per cent small mononuclears, 12 per cent large mononuclears, and 85 per cent polymorphnuclears: and in which a different classification has evidently been adopted.

The leucocytosis which has been generally found would aid in diagnosing the condition from a tuberculous one; but one cannot call in the aid of a differential count as observations on it do not seem to have been largely made. In the case which I have reported there was certainly ~~no~~^{no} relative increase of Polymorph cells, which fact would enable one to distinguish the condition from purely inflammatory affections.

Turning now to the ^{Special} Clinical Features in the various regions of the body.

In the Head and Neck the common situation is in an area bounded above by the zygoma, behind by the ascending ramus of the lower jaw, and below by the body of the lower jaw. The majority of the British cases in this region were subacute in type, while many were chronic, and a few were distinctly acute. The most important features according to Ruräh (loc. cit.) are almost constant sharp pain, the early

appearance of trismus of varying intensity and the swelling, which has the characteristics mentioned before; while the absence of involvement of the lymphatics is an important feature. In the British cases pain was more pronounced in this region than in any other, it being severe in several cases. Most observers also comment on the severity of the pain in this region as being an important symptom. Early trismus is stated by many observers to be an important feature and was considered by Foucet and Bérard (loc,cit.) to be pathognomic of the disease: but this symptom was not marked in the British cases, difficulty in opening the jaws being observed in only 3 out of the 26 cases occurring in the temporo-maxillary region. The swelling in most of the British cases tended to point outwards, discharging by one or more sinuses. On introducing a probe it is a common feature to find that these sinuses do not lead to bare bone.

Diagnosis .

The condition for which the disease in this region is most liable to be mistaken is that of alveolar abscess. In the early stages and in the more acute cases, it must be very difficult or impossible to distinguish between the two conditions unless granules be found in the discharge. But in the subacute or ~~chr~~ chronic forms the characteristic appearance and feel of the swelling, the absence or slight degree of

tenderness, the early involvement of the skin, the frequently numerous sinuses which do not lead down to bare bone, and the clear syrupy discharge (in which granules may be found) all point strongly to such a swelling being of an actinomycotic nature. Trismus may also be mentioned, though it was by no means a common feature in the cases occurring in this country. Tuberculosis and malignant disease in this region may also have to be considered as a diagnosis, the absence of lymphatic involvement and the absence of involvement of bone being important guides towards the probability of the lesion being actinomycotic.

In the submaxillary region I would suggest that a frequent connection would be found with the floor of the mouth thus distinguishing the condition from the enlargement of the lymphatic glands in this region, for which the disease might be mistaken. The commonly inflammatory nature of the swelling would distinguish it from tumours or cysts in this region.

In the tongue, Illich (loc.cit.) states that the distinguishing characteristics are slowness of growth, and the fact the the nodules are isolated and well defined. Von Baracz (loc.cit.) states that the disease may give rise to a tumour sharply differentiated from the tongue substance, or to a diffuse suppurative condition. In the two British cases the swelling was nodular, and was situated on the dorsum and side of

the tongue in one case, and on the dorsum in the other case. These cases were not reported very fully however.

Peripharyngeal. The disease in this region is apt to be very insidious in its onset, the symptoms being vague until the lesion is far advanced, when bony involvement may occur, so closely simulating Tuberculous caries of the spine that diagnosis is rendered very difficult. The disease spreads widely in this region, involving the muscles of the neck and in the absence of evidences of bony involvement might be mistaken for malignant disease, from which it may be distinguished by the insidious onset, the probability of absence of involvement of the functions of the larynx or oesophagus, the marked involvement of the muscles in this region, and the slight rises of temperature, while the absence of involvement of lymphatic glands would be an important guide in distinguishing the condition from a carcinomatous affection. The reported cases in this country are, however, too few to permit of a definite classification of the symptoms, and I cannot find many references to the symptomatology of the disease in this region in the foreign literature at my disposal.

From tuberculous caries of the cervical vertebrae, the earlier and more marked involvement of the soft structures than of the bone would be important in distinguishing the two conditions..

In the Brain, there would appear to be no symptoms differentiating the condition from tumour formation, or from other forms of abscess formation.

Thoracic. The affection of the lung is usually of a chronic type. The symptoms are very vague. Rurāh states that one of the most constant symptoms is pain: this is of course what one would expect from the marked tendency to pleural involvement. This pain may be very severe: in one of the British cases the patient screamed out with it.

Cough, with or without expectoration, occurs. The ^{sputum}~~symptom~~ is in most cases foetid (Rurāh and others) and in some cases may be rusty or streaked with blood, but severe haemorrhage is extremely rare - a fact which has been explained by the greater formation of connective tissue, and I would suggest also from the fact that cavities of large size are rarely found - though of course the evidence of haemorrhage is not always proportionate to the size of the cavity. Sabrazès and Cabanès (73) state that the sputum is sometimes milky white, the appearance being due according to Israël to the large amount of fatty cells present, and that it does not seem to contain elastic tissue. In the British cases the sputum is generally stated to be foetid and was in many cases copious: was mucopurulent or purulent: generally yellowish, sometimes greenish in colour, and in one case a peculiar colour

(73) Rev. de Med. Jan. 1899.

like pale anchovy sauce. Slight haemoptysis was noted in five cases: the sputum was stated to be rusty in one case: and in another case there was a more marked haemorrhage, half a cupful of blood being brought up in this case on one occasion while the sputum was frequently streaked with blood. The history in some cases of expectorating large quantities of purulent material mentioned by Godlee (74) was present in two of the British cases. The granules may be found in the sputum: in 21 cases observed by Illich (quoted by Ruräh) they were found in 18. Out of the 36 lung cases (primary and secondary) occurring in this country, granules were found in the sputum only in 9: but in many cases no mention at all is made of the sputum.

The fever is stated to be variable in type, but in the main like that of Tuberculosis, except that the range of temperature is somewhat lower in actinomycosis. (Ruräh) Fever is usually one of the early symptoms, but it may come on late, and in some cases it has been absent entirely, leading to the suggestion that its presence or degree is mainly due to secondary infection. In the British cases the temperature rose to from 101° to 103° at night in those cases where mention was made of it. Night sweats are stated to be sometimes present: only two of the British cases presented this feature. Foucet and Bérard (75) mention the relative integrity

(74) "Diseases of the Lungs" 1898. p.403. (Fowler & Godlee)

(75) Traite Clin. de l'Actinomycons Humaine.
Paris. 1898.

of the other functions and of the general state of health in the disease in this region as being an important point.

As regards the physical signs, Erving (loc.cit.) states that they are mainly those of bronchitis and pleurisy. The great majority of the British cases showed physical signs pointing to involvement of the pleura. Frequently the signs led to the diagnosis of pleural effusion, but on exploring the chest no fluid was found - evidences, therefore, of a markedly thickened pleura. In other cases there were evidences of consolidation in addition to thickening of the pleura. In the later stages involvement of the chest wall is a frequent and very important feature.

Diagnosis. The clinical picture of many of the cases is very similar to that of pulmonary tuberculosis. There are several points, however, on which the two diseases differ. The common situation in the lower lobe, the very common and marked involvement of the pleura, with later the characteristic involvement of the chest wall: the absence of enlargement of lymphatic glands: the less degree of wasting: and possibly the somewhat lower range of temperature are all in favour of actinomycosis. The sputum also differs from that in Tuberculosis in that it is not nummulated, is foetid, and that severe haemorrhage is rare: in the absence of Tubercle bacilli, and the presence in some cases of

actinomycotic granules: and in the absence of elastic fibres.

Chronic interstitial fibrous of the lung, and new growths of the lung and pleura are also conditions which resemble somewhat actinomycosis, while gangrene of the lung and other forms of pulmonary abscess may have to be differentiated from it.

Abdominal. The clinical features of the disease in the abdomen are more vague and indefinite than in the pulmonary cases, no definite diagnosis being possible until the disease is far advanced, with the exception perhaps of those rare cases in which granules are found in the stools.

The course may be acute, with much fever and pain: or may be subacute and chronic with little or no fever or pain. Of 35 British cases in which the symptoms were described 4 were acute in the onset of the symptoms and somewhat acute in the progress of the lesion, all four cases occurring in the region of the caecum or vermiform appendix. It seems to me likely that the acute onset of the symptoms in these cases would be attributed to some cause such as constipation leading to a congestion of the parts, in which the disease was already far advanced, rather than to the actual advance of the disease itself. This congestion, on the other hand, would naturally lead to a more rapid extension of the lesion, if the mode of extension takes

place by the bloodvessels as suggested.

The symptoms and signs in these acute cases resembled, in the British cases, very much the ordinary signs of ~~the~~ acute appendicitis. The great majority of the cases were chronic in type. Of these we may first take those cases affecting the gastro-intestinal tract. Hinglais (76) in describing the appendiculo-caecal form in which site as we have seen the disease is most common, states that at first there are viscerals symptoms pointing to some intestinal disturbance - diarrhoea, with in some cases blood and mucus in the stools, the diarrhoea being accompanied by tenesmus and pain: Later localised pain more or less continued, and tumour formation, the tumour being of unequal resistance and having later the characteristic appearances of skin involvement. He adds that there may in such cases be several remittances with periods of more or less perfect health.

Out of 26 British cases affecting the gastro-intestinal tract in which the symptoms were described, in 2 there was an entire absence of pain throughout the course of the disease, the patient complaining simply of a sense of fulness, or of the swelling: in 2 cases pain was entirely absent until late in the disease, when it became marked in one case and in the other colicky: while in 2 other cases pain was not mentioned as a symptom. In only one case was pain stated to be severe.

(76) These de Lyons. 1897.)

In the great majority of the cases the onset and progress of the disease was very insidious. In no less than 13 of the 26 cases the pain was intermittent, intervals of months frequently elapsing between the periods of pain: while in two of these cases the intervals lasted for a year or more, the patient apparently being in perfect health in the meantime. Those cases of this type occurring in the right iliac fossa bore frequently a marked resemblance to ordinary relapsing appendicitis.

The function of the bowel was not interfered with markedly in many of the cases, apart from the periods of the acute exacerbations which were often accompanied by constipation. Late in the disease attacks of diarrhoea occurred in 5 of the cases, while in one case there was constipation alternating with diarrhoea: but there was never any marked evidence of chronic obstruction in any of the cases. Blood was found in the stools in three cases, mucus was present in one case, while in another case there were frequent discharges of purulent gelatinous material in the motions. In only two cases were the granules found in the stools. One (77) in which blood had been found at one time, and in which at a post-mortem examination curiously enough no ulceration or other change was found in the mucous membrane of the intestine although

(77) Lancet 1902. Vol .II. p.671. case 1.

granules were found free in the lumen of the gut: the other (78) in which the disease affected the rectum and prostate, granules being found also in the urine.

The absence of evidence of chronic obstruction is quite in accordance with the pathological changes found in the British cases, the gut wall itself being little or not at all involved in the lesion.

The temperature had much the same range as mentioned under general characteristics: but during the acute exacerbations it frequently rose to 101° or 102° and during the later stages was often hectic in type. As regards the physical signs, the swelling was generally stated to be hard, and in some cases was of unequal consistence. In most cases tenderness was not marked. Later again in a large number of cases the abdominal wall was involved early, leading to the characteristic appearance of the skin when the tumour approached the surface.

Diagnosis. The clinical features in some cases point to a lesion of the nature of a new growth, though this was not so common. Most of the cases were inflammatory in nature and the majority of them were chronic. The acute cases would seem to present no special features enabling a diagnosis. The chronic inflammatory cases might resemble tuberculous lesions: but those cases where the symptoms are intermittent, with fairly long periods of more or less perfect health are very

(78) Lancet 1891. Vol.II. p.1100.

suggestive. I should suggest, too, that the absence of involvement of the functions of the bowel - the absence of evidences of chronic obstruction - is suggestive of actinomycosis. The disease also differs in this feature from malignant disease of the bowel (which it resembles in some cases), and again in the slight degree of **wasting** shown in the former as a rule. The diagnosis must be very difficult at this stage - before the involvement of the abdominal wall - unless actinomycotic granules be found in the stools.

If an operation be undertaken, however, certain points mentioned before would guide us - namely the spongy and highly vascular growth, evidently chiefly outside the gut, and often infiltrating the deeper strata of the abdominal wall; and the small amount of pus present in those cases of an inflammatory type. Granules, too, may be found in the pus.

In the later stages when the disease has infiltrated the abdominal wall and is approaching the surface a diagnosis may be more readily made.

The hepatic cases are stated by Ariband (quoted by Ruräh, loc.cit.) to show enlargement of the liver with only little pain, and usually but little temperature: a heavy pain over the lower ribs was noted in several cases. He states that these patients are apt to have constipation and considerable disturbance in the general health. In one case there was slight

jaundice. In the notes of the cases occurring in this country the symptoms and signs of the disease in the liver have not been very fully described. Out of 18 cases of liver involvement where the symptoms as a whole were described, in 8 the liver was not referred to at all, two of these cases having lung symptoms solely. In 3 other cases the lung symptoms were the most notable feature. I do not include those cases of liver involvement secondary to lung disease. In 4 cases pain was stated to have been absent, or only occurring at a ^{late} period and then slight. In only 2 cases was pain a marked feature: while in one case the swelling alone called attention to the condition of the liver.

Enlargement of the liver was as a rule not noticed until there were evidences of involvement of the abdominal wall: in one case the liver surface was noted to be nodular.

It is evident, then, that the condition in the liver is insidious in its course: and that pain was not a marked feature, when present being generally of a dull aching character. Ascites was mentioned in only one case, and Wright (79) states that it rarely occurs. Jaundice was mentioned in one case only, and in this case lasted only a short time.

Involvement of the thoracic and abdominal wall was common, and in the ^{later} ~~early~~ stages would aid one in

(79) Osler & McCrae's Text Book of Medicine.
"Actinomyces"

diagnosing the condition. Apart from this feature, the marked tendency to involvement of the pleura and base of the right lung - this occurring in 10 out of the 18 cases - would be an important guide in differentiating the condition from other abscess formation or from malignant or hydatid disease, and would appear to me to be the most important diagnostic feature of the disease in the liver.

The symptoms in those cases where the spleen and kidney were affected did not apparently call attention particularly to those organs.

Skin. Reference has already been made to the appearance of the disease involving the skin by extension.

As regards the cases occurring primarily in the skin, Leser (80) states that there are two forms, (1) an ulcerating form, where there is a partially necrotic part, and a partially hard firm granular part. This form is an actively productive process. (2) a discrete, nodular skin inflammation with central cicatrisation and peripheral extension as in lupus. He adds that the two forms may occur together. Leser also suggests that cases stated to be lupus in which Tubercle Bacilli are not found may be actinomycosis, remarking that in his cases it was sometimes extremely difficult to find granules. The same observer remarks that the absence of involvement of lymphatics, and the grossly nodular character are not usual in

(80) Archiv. f. Chirurgie. 1889)

other conditions.

Norman Walker (81) says that actinomycosis of the face may be mistaken for rodent ulcer, the differential diagnosis being made on the fact that in the former there are small ~~blue~~-like granulations.

In the British cases, one (82) followed a bruise to the flank, two small papules appearing a fortnight later, ~~these~~ being associated with the appearances of a cellulitis. The condition remained stationary for three months, when it began to spread rapidly and became very extensive, though remaining superficial. The appearances differed in no way from the description given previously of those cases in which the skin was involved secondarily.

The other definite case (83) occurred in a wound of the scalp which refused to heal, and which showed two months later an irregular ulcer of the scalp, with an indefinite hard infiltration of the side of the head and neck in which there were a few more localised swellings. Actinomycotic granules were found in the pus..

Those lesions occurring as the result of metastases were situated in the subcutaneous tissue, at first appearing as rounded swellings, which later involved the skin and gave rise to the characteristic appearances of the disease.

(81) International Clinico 1897. Vol. 3. p. 252

(82) Lancet 1905. Vol. II. p. 157.

(83) B.M.J. 1906. Vol. II. 1128.

Prognosis.

In by far the most of the cases the condition as we have seen is a chronic one. The average duration, (as ascertained by the occurrence of symptoms) in the various regions in the British cases were as follows -

In the Head and Neck, out of 16 cases in which the duration of the symptoms could be ascertained, the average was 10 months. The shortest duration was a few weeks - the case occurring in the tongue and being cured by excision: the longest 4 years, this case ending fatally.

In the lungs, out of 10 cases in which the duration could be ascertained, the average was 15 months, the shortest being 5 months and the longest 27 months.

In the abdomen, out of 31 cases the average duration was 12 months: the shortest being 2 months and the longest 28 months.

It will be seen then that the average duration for all the areas is about 12 months.

Wright (loc.cit.) state that spontaneous recovery though rare, sometimes occurs.

The prognosis will depend on the virulence of the organism, on the powers of resistance of the patient, on the site and extent of the lesion, and on the presence or absence of secondary infection with pyogenic organisms.

The virulence of the organism, or perhaps the powers of resistance of the patient, seems to vary considerably in different cases, as the disease is much more actively progressive in some cases than in others. The site of the lesion, as we shall see, is an important factor in the prognosis.

As regards the extent of the lesion it is notable that several extensive lesions have recovered. Secondary infection with other organisms is generally stated to have as unfavourable an influence on the prognosis as in the case of Tuberculosis. Ruráh (loc.cit.) states that these cases are more liable to be extensive; and that metastases are more liable to occur, on account of the fact that the additional organisms often cause ulcerations through the walls of the bloodvessels, and so make a way for the actinomycotic organism.

Out of 91 of the British cases in which the result was stated, 42 died the cases ~~of~~ mortality being therefore 46.1 per cent: but as this includes 14 cases which were stated to have improved, or to be improving, and 2 cases in which there was no improvement, the case mortality would probably be considerably larger. Again, recurrence not infrequently occurs after apparent cure, and Wright (loc.cit.) states that no case should be considered as cured until a period of two years has elapsed without recurrence.

The prognosis varies markedly with the primary

site. Those cases in which the primary site is in the Head and Neck are far the more favourable, while the pulmonary cases are stated by all to be the most fatal, the abdominal cases holding an intermediate position. I have not been able to find any figures for those cases primary in the skin, but they would certainly appear to be more favourable than any other form. Of those cases apparently primary in the skin in this country two were cured, and one (which was very possibly primary in the abdomen) died.

Of those cases occurring in the head and neck, Poncet and Bérard (loc.cit.) state that 75 per cent recover, V. Baracz (84) found that out of 56 cases 89 per cent recovered and 7 per cent died.

Lieblein (85) out of 49 cases, 73 per cent recovered and 6 per cent died.

Erving (loc.cit.) out of 53 cases, 68 per cent recovered and 9 per cent died: while Jiron (quoted by Rurah, loc.cit.) states that the mortality is 11 per cent.

Of the 39 British cases, 23 (or 59 per cent) recovered; 5 (or 12.8 per cent.) were improved; 6 (or 15.4 per cent) died: while in 5 the result was not stated.

Those cases occurring in the upper jaw, and the peripharyngeal cases are generally stated to be less favourable than cases occurring elsewhere in the head

(84) Arch. f. Klin. Chir. 1902. LXVIII. p.1050.
(85) Beitr. z. Klin. Chir. XXVIII. 1898.

and neck: (Rurah and others) while all cases in which an intracranial lesion has occurred have ended fatally - this being true for the British cases also.

The pulmonary cases are universally stated to be much more serious. Wright (loc.cit.) states that apparently only about half a dozen cases of pulmonary actinomycosis in which recovery is claimed are recorded in the literature, and that in most of these the permanency is doubtful.

Jirou (loc.cit.) places the mortality at 83 per cent. Hodenpuy1 (86) found that out of 34 cases collected all died but two. Out of 58 cases collected by Illich (87) there were no recoveries. Erving (loc cit.) in 20 American cases, found that two were stated to be cured, two improved, one showed no improvement and 15 died.

In the British cases the result was as follows - 1 case recovered; 7 stated to be improving; death occurred in 8; while in 3 cases the result was not stated. One must conclude, as regards the British cases, that a considerable number of those cases stated to be improving would have been found to end fatally if followed up.

The abdominal cases have not a good prognosis, but the prospect is not so unfavourable as in the Pulmonary cases. Harz (quoted by Rurah. loc.cit.) analysed 64 cases out of which number 34.4 per cent recovered

(86) N.Y.Med.Rec. 1890. XXXVIII, p.658..

(87) Beit. z. Klin. der Actinomycose. Wttn. 1892.

and the same number died. Grill (88) found that out of 67 cases 32.8 per cent recovered and 67.2 per cent died. Erving (loc.cit.) found that out of 23 cases 21.7 per cent were cured, and 43.4 per cent died.

Firon (loc.cit.) states that the mortality is 71 per cent..

Of the cases occurring in this country, 8 (or 21 per cent) were cured: one was stated to have improved: 27 (or 71 per cent) died: and in 2 cases there was no improvement.

Treatment.

The treatment of this disease has therefore from the consideration of the above figures, given very unsatisfactory results. Hitherto the treatment has been mainly by the use of surgical measures, and by the internal administration of certain drugs - pre-eminently Potassium Iodide, and there can be no doubt, on reading the reports of the British and other cases that active and radical surgical measures have produced the more favourable results. Total excision of the actinomycotic growth, when practicable, is undoubtedly the most certain method of cure, but unfortunately, the great majority of the cases, from their situation and extent, cannot possibly be dealt with in this way. In a suitable case it would be important to cut rather wide of the disease, as cases have be

(88) Beitr. z. Klin. Chir. 1895. XIII. p.551.

been reported where recurrence has taken place in the original site after the removal of apparently all the growth, the recurrence in such cases being no doubt due to a small focus at some distance away from the main growth - a condition, which, as we have seen, frequently occurs. Lesions occurring in the tongue, in the skin, and situated superficially, and some of those situated in the face, are those suitable for this mode of treatment. In lesions which cannot be totally excised, but which are surgically approachable, active measures, such as incision and scraping, frequently repeated, if necessary, with free drainage undoubtedly should be adopted. The risk of free bleeding must be provided for. Such a mode of procedure ought to be adopted in the more extensive lesions in the head and neck, in those cases involving largely the pleura, and in those abdominal cases which are approaching the surface.

The injection into the actinomycotic mass of various antiseptics in solution has been recommended. Illich recommended solution of Perchloride of Mercury. Volkmann used Boracic acid; Geissler and Jaenecke used chloride of zinc. Boström used carbolic acid and salicylic acid. Beyond the possibility of lowering the vitality of a very minute portion of the active organism present in the lesion, I do not see what good purpose these injections could subserve, while the

damage to the tissues actively engaged ⁱⁿ resisting the growth of the organism would seriously prejudice their chances of success.

Cauterisation - By the actual cautery, by different acids, and caustic preparations such as silver Nitrate, and Zinc Chloride has been recommended by various observers, but I fail to see how this treatment could injure any but the most superficial and least important foci of the active organism, while by coagulating the superficial layers of the lesion a barrier would be formed to the free escape of the discharges and of the granules themselves.

Treatment by subjecting the lesion to the action of X-rays has been tried in some cases, and is highly recommended by Wright (loc.cit.), while others speak well of this mode of treatment.

In addition to these various local measures, medicinal treatment has been adopted in a considerable number of cases. Mention may briefly be made of Thyroid extract, used by Pringle (89) in two cases with good results in one; of arsenic and sulphate of copper; and of Eucalyptus oil in the pulmonary cases, which ^{means} have all been recommended.

The drug which has been most largely used and which has gained the reputation of being almost a specific remedy for the disease, is Potassium Iodide.

(89) Brit. Journ. Dermat. January 1896.)

This drug was first used by Thomassen (90) in cases of the disease in cattle, who reported that 63 per cent of the cases treated in this way recovered, surgical measures being at the same time adopted.. Nocard (quoted by Rurah (loc.cit.) also commented on its beneficial action in cattle, stating that the drug promptly cured cases of actinomycotic growths in cases formerly deemed hopeless: he used large doses, pushing the drug until evidences of Iodism appeared, and adds that marked improvement was often noticed in about 8 days . In man, Potassium Iodide was first used by Van Itersen, who reported favourably on its action, since when the drug has been used in a large number of cases in man. Poucet, Jirou, and Besse in France have borne strong testimony to its value: Nocard and Netter remark on it favourably: while Wright states that it is generally admitted to have favourable effects. But others, again, who have met with a large number of cases of the disease, do not bear by any means such favourable testimony. Bérard(91) states that in two-thirds of the cases of chronic actinomycosis affecting the face and neck, the results of Iodide treatment are nil.

In three-quarters of the recent cases, ^{he continues,} recovery followed its use, combined with surgical treatment: while in one quarter recovery followed the use of

(90) Report of the Bureau of Animal Industry, New York, 1893.

(91) France Méd. Paris. 1897.

Iodide alone. Bérard remarks that these results are not superior to those which are obtained by surgical methods alone, and that Potassium Iodide cannot, therefore, be regarded as a specific in actinomycesis in man: and that it can only be prescribed in limited and recent cases with much hope of success. He adds that in case of visceral actinomycesis which are inaccessible to the surgeon, Potassium Iodide can only arrest the condition at its commencement and when a diagnosis is practically impossible. Again, in later years when a more thorough trial of the drug has been made, V. Baracz (92) who had then seen 60 cases of the disease in man, states that the internal administration of Potassium Iodide is of little or no advantage. Erving (*loc.cit.*) in 1902 deals with the American cases treated with Potassium Iodide. The data, he states, regarding the 43 cases in which Potassium Iodide was used, were very incomplete. In 4 cases it was certainly discontinued without a fair trial, while in the remainder the duration of treatment is only seldom given. The amount varied from 16 to 600 grains daily. He tabulates the results as follows :-

(92) Arch. f. Klin. Chir. Berlin. 1903. XLVIII. 4.

Result	Potassium Iodide used. No surgical measures.	Surgical measures only.	use of Combined Potassium Iodide and surgical methods.
	21 cases treated .	32 cases treated.	53 cases treated.
Cured	12 (or 57%)	24 (or 75%)	36 (or 67.9%)
Improved	5 (or 24%)	2 (or 6%)	7 (or 13.2%)
No improvement	1 (or 5%)	4 (or 13%)	5 (or 9.4%)
Died	3 (or 14%)	2 (or 6%)	5 (or 9.4%)

These figures, so far as they go, show that those cases treated by surgical methods alone had a considerably greater per centage of recoveries, and a much smaller per centage of deaths while those cases treated by Potassium Iodide combined with surgical measures held an intermediate position. But, obviously, much stress cannot be laid on these figures, no account being taken of the extent of the lesion at the time of commencement of treatment, and, as Erving states, the data regarding the dosage and duration of treatment by the drug being very incomplete. It seems to me that the site is mainly of importance in discussing the opinion of the value of the respective modes of treatment in that it is an indication of the extent and duration of the disease, treatment being presumably commenced at an earlier period in those cases occurring in the Head and Neck.

I have attempted in the British cases to draw up a table on similar lines to that of Erving, but found

the same difficulties as regards the incomplete data regarding the duration of treatment by Potassium Iodide. I have prepared a separate table for each region, and in the Head and Neck I have attempted to draw a distinction between slight cases, or those cases in which treatment was commenced at an early stage, and cases which were marked at the time of commencement of treatment. In the abdomen and lungs the lesion in all the cases was advanced before treatment was commenced. Figures alone cannot give one a very good idea of the actual value of Potassium Iodide, and I ^{have} therefore in each region added a few notes illustrating the action of Potassium Iodide on the course of the disease when mentioned.

Head and Neck. Potassium Iodide in doses of 15 to 330 grains ^{per diem}; average per diem in 17 cases in which the dose was given - 98 grains.

(1) Slight cases, or those in which treatment was commenced early.

	Potassium Iodide used: no surgical treatment.	Surgical measures alone: no Potassium Iodide used.	Combined Treatment with Potassium Iodide & surgical measures.
Cure	1	7	6
Improved	2	0	1
No improvement	0	0	0
Death	0	0	0

As regards the surgical treatment employed in these cases, excision of the mass was performed in two cases, both resulting in cure: simple incisions or incisions and scraping in the other cases. These figures point to the fact that when seen at an early stage and actively treated by surgical methods, the disease in the head and neck seems to be fairly amenable to treatment, but one cannot come to any conclusion from them regarding the value of Potassium Iodide.

(2) In those cases in which the disease was already fairly advanced before treatment was commenced .

	Potassium Iodide alone.	Surgical methods alone.	Combined use of Potassium Iodide & surgical measures.
Cure	0	3	6
Im proved	1	0	0
No im prove-ment	0	0	0
Death	2	1	2

The case ending fatally, in which surgical methods alone were adopted, was complicated by Pulmonary Tuberculosis.

In 4 cases in which death took place, Potassium Iodide was given in large doses and for considerable periods without any effect. In one case resulting in recovery (93) it was stated that the good result was evidently due to the surgical methods rather than to

(93) B.M.J.1903. Vol.II. p.1460.

Potassium Iodide. In another case (94) resulting in cure, 100 grains of Potassium Iodide were given daily for a fortnight without any improvement: surgical measures were then adopted, and the patient at once began to improve, the Iodide being continued in smaller doses.

On the other hand, in one case (95) the disease rapidly progressed while small doses of Iodide were being given, but when large doses - 330 grains per diem - were used, the disease began to improve, the improvement being attributed to the Potassium Iodide rather than to the X-rays which were employed at the same time: and in another case (96) there seemed to be benefit by the use of the drug, the condition getting worse when the administration of the drug was stopped.

Pulmonary . Potassium Iodide ^{in the 6 cases in which the dose was mentioned} 24 to 100 grains per diem: average in ^{the} 6 cases 81 grains.

	Potassium Iodide alone.	Surgical treatment alone.	Combined use of Potassium Iodide & surgical treatment.
Cure	0	1	0
Improving	2	1	3
Death	0	7	0

- (94) B.M.J. 1896. Vol.I. p.1555.
 (95) Lancet. 1904. I. 1126.
 (96) Lancet. 1901. I. 3. Case 15.

One case (97) stated to be practically cured received no treatment by Potassium Iodide or by surgical measures; the patient, however, returned later with an actinomycotic lesion in the abdomen. With regard to the apparent action of the Iodide in some of the cases, one (98) which did not seem to improve much when surgical measures alone were used, responded at once to Potassium Iodide (the patient subsequently dying under chloroform administered for the purpose of abstracting a tooth).

On the other hand, in one case (99) the Potassium Iodide (90 grains a day) was found unsatisfactory, while surgical measures at once improved her condition: while in another case (100) the lesion continued to progress, while 150 grains of Potassium Iodide per diem were being administered: some time later the condition improved somewhat, however.

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- (97) Lancet. 1906. II. 158.
(98) Lancet. 1897. I. 1025.
(99) Lancet. 1904. II. 1216.
(100) Lancet. 1897. I. 311.

Abdominal. Potassium Iodide, dose mentioned in 16 cases, from 30 to 210 grains per diem: average 90 grains.

	Treatment by Potassium Iodide alone.	Treatment by surgical measures alone.	Combined treatment by surgical measures & Potassium Iodide.	No mention of Potassium Iodide or of surgical measures.
Cure	0	3	3	0
Improved	0	0	1	0
No improvement	0	0	1	0
Death	3	5	13	7

As regards the clinical course, some cases seemed to derive benefit from the Iodide: one (101) in which the growths increased when the Potassium Iodide was stopped, and diminished as often as the drug was administered, the administration being stopped several times during attacks of diarrhoea.

Another (102) showed no improvement with smaller doses, but as the amount was increased the induration began to disappear. While in 3 other cases (103) there was temporary improvement after the commencement of the administration of Potassium Iodide, this improvement being followed later by an advance of the disease, the drug being continued.

Other cases again, six in number, did not appear

- (101) Lancet. 1904. II. 1216.
 (102) St. Barth. Hosp. Rep. 1905. p.197.
 (103) (1) Lancet. 1901. I. 3. Case 12.
 (2) Lancet. 1897. I. 1025.
 (3) Ib.

to be at all influenced by the drug (104). One of these cases (case 3) showed no improvement, although the amount of Iodide reached 120 grains a day: patient left hospital, the treatment apparently not being continued outside, and on being seen four months later had improved greatly. In two of the cases the treatment was commenced when the disease was far advanced.

Skin. One case was cured by excision; the other by surgical measures, and the administration of Potassium Iodide, and in this case it was stated that with the administration of the drug ^(gr. 60 per diem) the wound at once began to heal.

It will thus be seen that in the British cases referring first to the figures, in the Head and Neck the results attained by surgical measures alone were superior to those attained by Potassium Iodide alone, being equal to those in which surgical treatment was combined with the administration of Potassium Iodide.

Too few of the Pulmonary cases have been followed to the ultimate result to allow of any conclusions being based on them, but it may be observed that the only case which was apparently cured - a case which will be referred to later - received no treatment by

(104) Reported as follows -

- (1) Lancet. 1902. II. 671.
- (2) Ib. p.672.
- (3) B.M.J. 1902. II. 1588.
- (4) Journ. Path. & Bact. 1898. p.182.
- (5) St. Barth. Hosp. Rep. 1905. p.197. case 6.
- (6) Ib. case 7.

Potassium Iodide, beyond a few small doses for about a week.

In the abdominal region, the results obtained by surgical measures alone show a larger per centage of cures and a smaller percentage of deaths than those cases treated by Potassium Iodide alone, while those cases receiving both surgical treatment and treatment by Potassium Iodide hold an intermediate position as regards the percentage of cures and of deaths.

Both the cases occurring in the skin were cured, one by surgical measures alone, and the other by the combined use of Potassium Iodide and of surgical measures.

In all there were 84 of the British cases in the notes of which an account of the treatment and result was given, and these may be tabulated as follows -

	With the use of Potassium Iodide alone: no surgical measures.	With surgical measures alone, no Potassium Iodide being used.	With the combined use of Potassium Iodide & of surgical measures.	No surgical measures & no Potassium Iodide used.
	Total 11 cases	Total 29 cases	Total 37 cases	Total 7 cases.
Cure	1 (9.2%)	15 (51.7%)	16 (43.2%)	0
Improved	5 (45.4%)	1	5 (13.5%)	0
No improvement	0	0	1	0
Death	5 (45.4%)	13 (44.8%)	15 (40.5%)	7

Thus the death rate in all cases was much the same whether Potassium Iodide was used alone, or surgical measures alone, or ^{with} combined surgical and Iodide treatment: while the percentage of cures was considerably lower in those cases treated by the administration of Potassium Iodide than in either of the other modes of treatment.

These figures, then, taken in conjunction with those of Erving and of Bérard, would seem to indicate that Potassium Iodide has little beneficial action - if any - on the course of the disease.

Clinically, this conclusion is supported by many of the British cases, in which it was noted that the drug produced absolutely no improvement in the lesion or in the general condition, while some of these cases improved after operation - a fair trial of the drug having been given. But in a certain number of cases occurring in this country Potassium Iodide has certainly appeared to have some beneficial action on the course of the disease, improvement synchronous with the administration of the drug being observed in several cases, while in one case it was noted that the lesion advanced on the cessation of the drug and diminished again during the periods of administration of the Iodide.

I think it must be conceded, then, that Potassium Iodide has some ~~action~~ ^{action} beneficial ~~on~~ the disease,

though this action may not be sufficient to show any marked effect on the percentages of cures and of deaths. This action, however, would certainly seem to be far from a specific one. What, then, is the action of the Iodide? Some believe that the drug has a specific action on the active organism of actinomycosis, either in the form of the Iodide or in virtue of the free Iodine liberated in the tissues. Attempts have therefore been made to get a greater local action by the injection of Potassium Iodide in one per cent solution into the substance of the actinomycotic lesion. This method has been used by Rydygier (105) who reported two cases which showed good results, Potassium Iodide being administered by the mouth at the same time in one of the cases: and by Sawyers (106) who reported three cases treated in this way along with the administration of the drug by the mouth, two of the cases being followed by recovery.

Poncet, again, has used solution of Potassium Iodide as a lotion for the wound, and also the local application of the solid in the form of a stick. But NoCARD (107) found that one per cent solution of Potassium Iodide did not affect the growth of the organism in culture. Its action, therefore, cannot be a direct one.

(105) Wien. Klin. Woch. September 1895.

(106) Journ. Amer. Med. Assoc. May 11. 1901.

(107) Quoted by Malcolm Morris, Lancet. 1896. Vol. 7 p. 1553.

Gautier (108) believing that the drug acted in virtue of the free Iodine liberated in the tissues, injected the Potassium Iodide in solution into the lesion, and then passed a current through to decompose the Potassium Iodide. While Bevan (109) recommends the application of X-rays to the lesion while the patient is taking Potassium Iodide internally, stating that the X-rays liberate free nascent Iodine in the substance of the lesion in larger amounts than would occur if the rays were not used, having found experimentally that X-rays did liberate Iodine from Potassium Iodide outside the body. But it seems to me that if Iodine were liberated in sufficient amount to interfere with the growth of an organism with resistance so great as that of the streptothrix actinomycosis (Vid.sup.), the tissues would certainly suffer serious damage.

I think, then, that we must look for some other explanation than a direct action of the drug on the actinomycotic organism.

Lieblein (110) believes that the action of the Potassium Iodide is to bring about a solution of the cellular infiltration about the abscess cavity, and the consequent discharge of the ray fungus, in imitation of nature's own method of healing. Potassium Iodide is recognised as having this absorbent action,

(108) *Sémaine Médicale*. 1891. p.245.

(109) *Annals of Surgery*. May, 1905.

(110) *Beitz. f. Klin. Chir.* XXVIII. p.198.

as one might call it, on pathological tissues, and I think it seems quite possible that this action may have something to do with the beneficial effects sometimes seen during its administration.

But I would suggest that another action of Potassium Iodide has a much greater beneficial effect in actinomycosis - namely, its so-called lymphagogue action, whereby it causes a greater flow of lymph through the vessels. In connection with this point I examined the notes of the British cases with a view to ascertaining if any increase of discharge from the lesions had been noted, and found that in 4 cases (111) it was noted that the discharge was greatly increased - in three of the cases a profuse serous discharge was noted as occurring - with improvement in the local condition later. This increased flow affecting the actinomycotic mass has evidently been widely noted, as Wright (*loc.cit.*) recommends, as a preliminary to surgical treatment in extensive lesions (e.g. in abdominal actinomycosis) that Potassium Iodide should be administered because its effect on the lesion is to make the suppurative foci more evident. It may be taken for granted, then, that there is an increased flow of lymph through the actinomycotic lesion, and this increased flow would, in the cases where there is an

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- GIVEN
- (111) (1) Lancet. 1900. Vol. II. p. 255
(2) Lancet. 1896. Vol. I. p. 1553.
(3) Journ. of Dermat. 1906. Vol.33. p. 151.
(4) B.M.J. 1896. Vol. I p.1555.

open wound, perhaps aid to some extent in the discharge of the organism. But its main action, would, I think, be in bathing the foci throughout the lesion in fresh lymph rich in bacteriotropic substances, these antibacterial substances being - as pointed out by Wright (112) deficient in the neighbourhood of such organismal foci.

The drug would therefore be beneficial as well in those cases in which discharge could not escape to the surface. The increased absorption of Lymph from foci might also be of benefit, as suggested by Wright in connection with other means of producing such increase of absorption - the benefit resulting from an increased production of antibacterial substances following on the passage of the bacterial substances into the blood.

It might be said that any beneficial effects produced in this way - i.e. by the increased flow of lymph through the lesion - must necessarily be slight, but I think the benefit thus produced would probably not be less than that actually found in connection with the use of the drug.

Again it might be objected that in the somewhat similar condition of tuberculosis, no improvement is obtained by the use of Potassium Iodide. In connection with this, I would suggest that the difference in the ^{effect of the} drug in these two conditions might possibly depend

(112) Lancet. 1907 Vol.II. p.495.

on the involvement of the lymphatic apparatus in tubercle and its non-involvement in actinomycosis, and again that a more free passage of the blood stream to all parts of the actinomycotic lesion is present than in a tuberculous lesion, owing to the vascularity of the growth in the former.

Whether the action of Potassium Iodide in these cases be, in a very small part, due to a raising of the antibacterial power of the blood to actinomycosis, or not - and I do not wish to press this point, - a more active method of increasing this ~~the~~ power has been attempted, namely by the inoculation with a vaccine prepared from the cultures of the streptothrix actinomycosis.

I may first, however, refer to the treatment which has been ^{carried} ~~held~~ out in some cases of actinomycosis by the inoculation of vaccines prepared from other organisms than the streptothrix actinomycosis. Billroth (113), Ziegler (114) and others used tuberculin in some cases of this disease with, it is stated, success: while Ziegler used the bacterial products from the staphylococcus aureus with temporary benefit in one case. The benefit in the latter might, of course, have been due to the relief of a possible mixed infection with the staphylococcus aureus.

(113) Wien. Med. Presse. 1891. p.350.

(114) Munich. Med. Woch. 1892.

But as regards the former, while it is agreed by most that inoculation with the specific organism for a disease benefits that particular disease, it is believed that ~~if~~ this action is a specific one - the view being generally held that the opsonins of normal serum are non-specific (115) but that the increase following the injection of a bacterial vaccine is a true specific one (116). One would hardly expect, then, that inoculation with Tuberculin would be followed by improvement, and Friedreich (117) states that Tuberculin is not a remedy for actinomycosis.

(In connection with this mention may be made of the fact that Illich (118) found that the tuberculin reaction was given for actinomycosis: while Erving (loc.cit.) states that a reaction somewhat similar to that in tuberculosis was given in one of the American cases, but no reaction followed its injection in two other cases.)

Lately Dr. Wynn (119) has reported a case in which a vaccine was prepared from the streptothrix found in the purulent discharge of a typical case of actinomycosis of the lung and pleura, and the patient was inoculated with this vaccine with immediately beneficial results. More recently still Dr. Wynn has given a fuller account of the case (120). This case

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- (115) Yorke & Smith Bio-Chemical Journal 1906. Vol. II. Dec. 19
(116) Series of Articles on Opsonins J. Hopk. Hosp. Bull. July 1907
(117) Deutsch. Med. Woch. 1896. XIV. p. 579.
(118) Beits., f. Klin. d'aktinomyose. Vien. 1892.
(119) B.M.J. 1907. I. 1119.
(120) B.M.J. 1908. March 7. p. 554.

an advanced pulmonary affection with cavity formation and involvement of the pleura leading to an empyema, showed no improvement after resection of a portion of rib for the empyema on December 19th 1906, and looked and felt very ill. The first injection was given about three weeks after the operation (i.e. on January 8th) and his condition began immediately to improve. In a few days the cough became less troublesome, and the sputum and discharge of pus diminished in a remarkable way. The temperature, which had varied between 99° and 100° both previous to and since the operation, dropped to normal on the day following the first inoculation, and remained normal for three days, subsequent slight rises ^{occurring for a day or two} being attributed to the removal of the drainage tube. The temperature subsequently did not rise above normal. Six inoculations in all were given. There was no sputum a week after the first inoculation, and the cough and discharge soon disappeared. The opsonic index, which stood at .3 before the inoculations, now stood at a higher level, the highest being 1.7. The patient put on weight rapidly, gaining a stone from December 29th to February 4th, and 6 lbs. from the latter date to March 27th. All active signs in the chest had early disappeared. He was last seen on February 20th 1908 i.e. over a year from the commencement of treatment, and 10 months from the time of leaving hospital - and it was ~~then~~ noted that the cavity in the chest was smaller, and there were

evidences that cicatricial contraction was taking place in the lung tissue: there were no moist sounds. Patient had gained 2 lbs. in weight since leaving hospital. The last injection had been given on March 27th 1907. This case, then, showed a very remarkable and rapid improvement, coinciding exactly with treatment by inoculations, and it would seem that the condition was cured - though it has been stated that no case should be considered as cured until a period of two years has elapsed. No other case, the notes of which I have read, has shown such rapid recovery from such a grave lesion; and this rapid recovery could not be attributed to the operation, and I think could not be considered a spontaneous one.

Dr. Wynn states that in his case there was not much difficulty in preparing a vaccine, as the organism was isolated and grown in pure culture: but that in many cases it is difficult or impossible to isolate the organism. Dr. Wynn also remarks that it will in future be important to determine whether a vaccine prepared from one of the easily grown species or from a stock laboratory culture, will have any effect upon an infection caused by another species of streptothrix.

It has been noted previously that observers have failed to cultivate the streptothrix actinomycosis from the lesion, or that they were unable to obtain a pure culture. In many cases in order to obtain a

pure culture a very considerable time must elapse during which the lesion may be progressing steadily, rendering a cure more difficult to obtain. So that, although undoubtedly the injection of a vaccine prepared from the actual organism infecting the case to be treated is more liable to be followed by good results, recourse has to be made - as in the case of Tuberculosis - to a stock preparation. It may be noted in connection with Tuberculin that the apparent failure of the vaccine in some cases of Tuberculosis is attributed to the possibility of differences between the organism infecting the patient and that from which the vaccine has been prepared.

The case which I saw treated with a vaccine prepared from a stock laboratory culture, and the notes of which I have given, certainly did not show such marked improvement as the case quoted above in which the organism from the lesion was utilised for the preparation of the culture. But there was undoubtedly a fairly marked improvement under its use, the improvement dating from the time of commencement of treatment with the vaccine and lasting till the patient left hospital, when the condition suffered a relapse - most probably due largely to the advent of mixed infection in some virulent form, judging by the local condition of the lesion and by the temperature. The improvement in this case was certainly quite coincident with the commencement of the vaccine treatment, the boy's condition previously showing a steady advance of the disease.

I think, however, that the treatment hardly obtained a fair trial in this case. It seems to me that the dosage with which the treatment was commenced should have been continued, or have been increased only slightly - unless a careful watch were kept on the opsonic index. Again the patient - in a Hospital reserved practically for acute diseases - could unfortunately not be kept in bed for as long a period as seems to me to have been very desirable. It seems to be to be certainly advisable, then, in a disease so intractable to other methods of treatment, that vaccine therapy should be further tried, as there would appear to be some hope of its proving of considerable advantage.

The difficulties regarding observations on the opsonic index may be raised as an objection to its use. Now the value of close observations of the opsonic index as a guide to the time and amount of dosage, while strongly urged by many, is not admitted by all. Thus in a series of papers devoted to opsonin and vaccine therapy by representative American workers (121) the conclusion is come to that Wright's method of determining the amount of opsonin present, although better than the method of taking the phagocytic index - the proportion of cells containing organisms in the specimen of blood under observation to those containing them in a specimen of normal blood - is too

(121) Johns Hopkins Hosp. Bull. July 1907.

inaccurate to be of any real value: and again, that in the treatment of disease by vaccines it is unnecessary and indeed useless to follow the opsonic index curve as determined by Wright's method. In the case of actinomycosis inaccuracies are, of course, more liable to occur in the operation of counting.

One reason given for the observation if the index curve is in order that individual inoculations may be given at the summit of the curve, thus attempting to produce a cumulation of positive phases. But this cumulation of positive phases, it is generally held (122) is unattainable in tuberculosis; each injection has to be conducted as if a new case were being begun, it being customary to allow the good effects of one injection, produced by the resultant positive phase, to take full effect before again inoculating. This means, as a rule, an interval of about three weeks between successive inoculations. Another reason for these observations, is, of course, the danger of administering the vaccine during the negative phase, when an additional dose of toxin might just suffice to overtax the powers of resistance: but this does not apply, I think, so much to actinomycosis as to for example Tuberculosis, as the toxins certainly do not seem to be so virulent in the former; and by allowing an interval of three weeks to elapse between each successive dose, I think the danger would be

(122) Wright. (Lancet 1907. II. 494) and others.

inappreciable.

I think it would be permissible, then, in a chronic disease like actinomycosis to employ the method of vaccine treatment which is adopted by some institutions for Tuberculosis in connection with out-patients - namely the administration of small doses (.001 Mgr.) at regular intervals of about three weeks. At the same time it is probable that better results would be obtained by observing the opsonic index curve, so that a gradually increasing dose might be given until that dose is found which produces the best resultant positive phases - which is the method recommended by Wright (loc.cit.)

The vaccine should be prepared from the actinomycotic organism present in the lesion, when this is possible and when not much time would spent in the process, as undoubtedly this would afford the best chances of success. But if this be impossible, or the process should be long, then I think one ought to try a stock laboratory culture for the purpose, selecting one which in its morphological appearances in cultural and staining characteristics, most resembles that present in the lesion.

Undoubtedly, along with the vaccine treatment, active and radical surgical measures should be adopted in every possible case, but in many such treatment is quite impossible. Care should be taken to guard

against mixed infection. The patient should be kept at rest if the lesion be extensive, or should involve the thorax or abdomen; and, generally, those measures found valuable in Tuberculosis should be adopted, the patient being given the best hygienic surroundings, preferably open air treatment when possible, and plenty of nourishment.

The administration of Potassium Iodide internally, and possibly the application of X-rays, have already been mentioned as being of some benefit.

There is good reason to believe that, with earlier diagnosis and with more active treatment on the lines suggested above, this disease, which would appear to be not nearly so uncommon* as is generally believed and which is characterised by so high a mortality, would be afforded a much better chance of a successful termination.

* See page 129.

APPENDIX.

The cases which I have referred to were reported as follows:-

I. Those apparently primary in the Head and Neck.

- (1) Lancet, 1906. Vol. I. p. 1397.
- (2) Lancet. 1906. Vol. II. p. 1213.
- (3) Lancet, 1906. Vol. II. p. 1307
- (4) Ib. 1905. Vol. II. p. 157
- (5) Ib. 1904. Vol. II. p. 1204
- (6) Ib. Ib. Ib. p. 1205. (case 3.)
- (7) Ib. 1904. Vol. I. p. 1126
- (8) Ib. 1904. Vol. I. p. 1656. (Case 2.)
- (9) Ib. 1902. Vol. I. p. 306
- (10) Ib. 1901. Vol. I. p. 3. (Case 14)
- (11) Ib. 1901. Vol. I. p. 3. (Case 15)
- (12) Ib. 1901. Vol. I. p. 125
- (13) Ib. 1900. Vol. II. p. 255
- (14) Ib. 1900. Vol. II. p. 1138.
- (15) Ib. 1900. Vol. I. p. 1210;— and B.M.J. 1901.
Vol. I. p. 12.
- (16) Trans. Clin. Soc. Lond. 1900. Vol. 33. p. 196; and
Lancet, Nov. 4. 1899.
- (17) Lancet. 1898. Vol. II. p. 1061
- (18) Ib. 1897. Vol. I. p. 311. (Case 1)
- (19) Ib. 1897. Vol. I. p. 311 (Case 2)
- (20) Ib. 1897. Vol. I. p. 734
- (21) Glas. Med. Journ. 1896. Vol. 45. p. 382; and
Lancet, Jan. 1896.
- (22) Lancet, 1896. Vol. II. p. 1553.
- (23) Waring, Trans. Path. Soc. May 21. 1895; and
Lancet, May, 1895.
- (24) Lancet, 1891. Vol. II. p. 1101. (Case 3)
- (25. & 26) B.M.J. 1906. Vol. I. p. 322 (Two cases)
- (27) B.M.J. 1904. Vol. II. p. 1696.
- (28) B.M.J. 1903. Vol. II. p. 1460
- (29) B.M.J. 1901. Vol. I. p. 18
- (30) B.M.J. 1896. Vol. I. p. 1553.
- (31) B.M.J. 1896. Vol. I. p. 1554. (Case 5)
- (32) B.M.J. 1896. Vol. I. p. 1554. (Case 6)
- (33) B.M.J. 1896. Vol. I. p. 1555.
- (34) B.M.J. 1890. Vol. I. p. 709
- (35) Glas. Med. Journ. 1894. Vol. 64. p. 277.
- (36) Glas. Med. Journ. 1898. Vol. 50. p. 378.
- (37) Practitioner. 1898. Vol. 60. p. 398.

- (38) Journ. of Dermat. 1906. Vol. 33. p. 151. Dr. Eddowes.
- (39) Lancet. 1902. Vol. II. p. 671.
- (40) Lancet. 1886. Vol. II. p. 342.

II. Apparently primary in the Lungs.

- (1) Lancet. 1906. Vol. II. p. 158
- (2) Lancet. 1904. Vol. II. p. 1204. (Case 2).
- (3) Lancet. 1904. Vol. II. p. 1216. (Case 1).
- (4) Lancet. 1904. Vol. II. p. 1449.
- (5 to 8). Lancet. 1901. Vol. I. p. 3. (Case 1, 2, 3 & 4)
- (9) Lancet. 1897. Vol. I. p. 311. (Case 3).
- (10 & 11). Lancet. 1897. Vol. I. p. 1025. (Cases 1 & 3)
- (12) Lancet. 1894. Vol. II. p. 1155.
- (13) Trans. Path. Soc. Lond. 1894. O. 233; and
Lancet. Jan. 1894.
- (14) B.M.J. 1907. Vol. I. P. 1119.
- (15) B.M.J. 1905. Vol. II. p. 1168.
- (16) B.M.J. 1891. Vol. II. p. 124.
- (17) B.M.J. 1890. Vol. I. p. 709. (Case 2).
- (18) B.M.J. 1889. Vol. I. p. 357.
- (19) St. Bart. Hosp. Rep. 1895. p. 23.

III. Apparently primary in the Abdomen.

- (1) Med. Chir. Trans. 1905. April 11. Mayo Robson.
- (2) Lancet. 1904. Vol. II. p. 1216. (Case 2)
- (3) Lancet. 1904. Vol. I. p. 1656.
- (4) & (5) Lancet. 1902. Vol. II. p. 671, (Case 2); and
p. 672. (Case 3).
- (6 to 12). Lancet. 1901. Vol. I. p. 3. (Cases 5, 6, 7, 8,
11, 12, 13).
- (13) Lancet. 1900. Vol. II. p. 1137. (Case 1).
- (14) Lancet. 1897. Vol. I. p. 741.
- (15 & 16) Lancet. 1897. Vol. I. p. 1025. (Cases 2 & 4).
- (17 & 18) Lancet. 1891. Vol. II. p. 1100. (Cases 1 & 2).
- (19) B.M.J. 1907. Vol. I. p. 984.
- (20) B.M.J. 1906. Vol. II. p. 137.
- (21) B.M.J. 1902. Vol. II. p. 1588.
- (22) B.M.J. 1896. Vol. I. p. 1553. (Case 7).
- (23) Trans. Path. Soc. Lond. 1889. Vol. 40. p. 405.

- (24) B.M.J. 1887. Vol. I. p. 331.
- (25) Med.Chir.Trans. 1886. p. 135.
- (26) Trans. Path. Soc. Lond. 1885. p.254.
- (27) Duſſ. Med. Journ. 1905. Vol.119. p. 457.
- (28) Guy's Hosp.Rep. 1897. Vol. 54. p. 303.
- (29) Journ. Path. & Bact. 1898. p. 182.
- (30 to 36) H.J.Waring. St.Bart.Hosp.Rep. 1905.p.197.
(Seven cases).
- (37) Waring. St.Bart.Hosp.Rep. 1891. p. 173.
- (38) Edin. Hosp.Rep. Vol.II. 1894. Leith.
- (39) Guy's Hosp.Rep. 1891. Vol. 48. p. 311.

IV. Apparently primary in Skin.

- (1) Lancet. 1905. Vol.II. p. 157.
- (2) B.M.J. 1906. Vol.II. p. 1128.
- (3) Trans. Path.Soc. Lond. May 21. 1889. Delepine.
(doubtful).

V. Apparently primary in the Reproductive System.

- (1) B.M.J. 1899. Vol.II. p. 1704.
- (2) Edin.Hosp.Rep. Vol. II. 1893. Grainger Stewart
and Muir. (in Ovary).

VI. Undetermined.

- (1) Trans.Path.Soc. 1885. p. 254. Museum specimen -
liver.

[over.

Other cases have been referred to, but not reported, pointing to the fact that the number of cases which have been recognised is considerable. Certain observers, too, in this and other countries, who have been on the look out for cases of this disease, have met with a considerable number of cases in their experience. Thus in this country, Godlee (loc. cit.) met with five cases in one year: Mr. Kellock⁽¹²³⁾ stated that during the preceding three years seven cases occurred in the region of the caecum and appendix in the Middlesex Hospital: and others, including Ransome and Waring, report a considerable series of cases. These facts would point to the disease being much more common than is generally thought, this being the opinion of many observers in this and other countries.

(123) B.M.J. Oct. 1906.