before bacilli have appeared in the urine. Therapeutic inoculation and open-air treatment are the best means of dealing with these patients, except in a few cases where a nephrectomy or the removal of a tuberculous testicle may be indicated. In the former operation, the cystoscope, combined with improved methods of estimating a patient's renal efficiency, minimizes the risk of removing the less diseased of the two kidneys, an occasional surgical tragedy of the past.

SUMMARY.

I would thus summarize the treatment of these cases of surgical tuberculosis:

1. In all cases "open-air treatment" should be organized to meet the circumstances and requirements of the particular case.

2. The patient's powers of resistance to the disease should be periodically measured by suitable blood examination.

3. Where the resistance is found to be low and there is no evidence of excessive autoinoculation, use should be made of inoculations of Koch's new tuberculin, in doses that are accurately controlled, both as regards their amount and repetitions, by examination of the blood.

4. For patients in whom there is evidence of excessive autoinoculation, absolute rest, with, in the case of a limb, absolute fixity of the diseased part, should be prescribed.

5. In the cases of circumscribed tuberculosis, efforts should be directed to increase the circulation through the infected area. I have already indicated the means we have at our disposal to effect this object.

6. Operative procedures should be directed to the removal of the inert material, whether caseous glands, carious bone, or collections of pus, and allowing the access to the infected area of healthy lymph. The necessary operations should be conducted with the most scrupulous asepsis.

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A CASE OF ACTINOMYCOSIS (STREPTOTRICHOSIS) OF THE LUNG AND LIVER SUCCESSFULLY TREATED WITH A VACCINE.

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FORMERLY actinomycosis was regarded as a single disease occurring in man and cattle, caused by one definite organism—the ray-fungus (*Actinomyces bovis*, Harz)—the parasitic nature of which was first fully described in cattle by Bollinger in 1877. The disease was diagnosed by the discovery of the ray fungus in the affected tissues or discharges, but the parasites were not isolated in pure culture and studied, and, in spite of variations in structure, the identity of the ray-fungi in all cases of actinomycosis, whether in man or cattle, was assumed.

Bostroem in 1890 published an account of the characteristics of some ray-fungi isolated from cases of human and bovine actinomycosis, which he regarded as belonging to the same species; but Wolff and Israel in 1891 published an account of a ray-fungus isolated from a case of human actinomycosis, which differed in a number of characteristics from that of Bostroem, and evidently belonged to a different species. Since then a considerable number of species, more or less well defined, have been described. Some confusion was caused by the description of some of these species, which differed in various respects from *Actinomyces bovis*, as pseudoactinomycosis or pseudo-tubercle. It is now, however, admitted that there are many forms of actinomycosis, and the significance of the term has been widened so that it is used to designate a class of diseases each of which is caused by a distinct species, or at any rate variety, of parasite. Two generic names for these parasites are in use—namely, streptothrix and actinomycosis; the former was recommended for

adoption by a committee of the Pathological Society of London in 1899, and is generally used by British and American pathologists, but actinomycosis is still in use, especially on the Continent.

The following case seems worthy of being reported, as the organism obtained from it was isolated in pure culture, and its growth on various media studied, but especially because it is the first case, so far as I am aware, that has been treated with a vaccine prepared from the infecting organism according to the methods of Sir A. E. Wright:

F. G., a schoolboy, aged 14, was admitted to the General Hospital, Birmingham, under the care of Professor Saundby, on December 19th, 1906. He then complained of a troublesome cough, with abundant sputum having an offensive odour, and also of pain and swelling on the left side of the chest.

History.

The family history was unimportant. As long as he could remember he had suffered from bronchitis during the winter. Six years ago he had been in hospital with pneumonia, and in December, 1905, was again in hospital for eight days with a severe attack of bronchitis. At that time it was noticed that his sputum was abundant and very offensive; his fingers were also slightly clubbed. There is no record of a bacteriological examination of the sputum.

He remained fairly well until May, 1906, when he suddenly began to cough and bring up much fetid sputum, and was feverish. After three weeks in bed he improved, and was able to get about again until the first week of November, 1906, when he complained of severe pain in the left side of the chest. Since then he had remained in bed, and on December 15th he had another severe attack of coughing, and is said to have brought up "nearly two pints of offensive matter." He felt bad all over, and on the day before admission a rounded tender swelling appeared on the left side of the chest, just below and outside the nipple. For some days he had been unable to lie down for fear of choking, and for three or four months he had been losing weight, and often had night sweats.

Condition on Admission.

He was a well-developed boy, showing signs of slight recent wasting. Respiration was shallow and rapid, the left side moving less than the right. There was a well-marked Harrison's sulcus, and the left side was more prominent than the right. On the left side, below and to the left of the nipple, was a rounded swelling, the most prominent part of which corresponded with the sixth intercostal space. This swelling was red, tender, and fluctuating, and was evidently a pointing abscess. The lower half of the left side of the chest anteriorly and laterally below the fourth intercostal space was absolutely dull on percussion, no breath sounds could be heard, and vocal fremitus and resonance were absent; posteriorly resonance was impaired, and moist râles were heard. Elsewhere the lungs were free from dullness or abnormal sounds.

The cardiac impulse could not be felt, and the outline of cardiac dullness was difficult to determine. The liver was just palpable below the ribs, but the spleen could not be felt. The abdomen otherwise was normal. The urine was scanty and had a specific gravity of 1028, acid reaction, many urates, but no albumen and no sugar. He passed about 30 oz. a day. The fingers and toes show slight clubbing but no bony enlargement. The diagnosis of an empyema pointing through the chest wall was made.

Operation.

The patient was operated upon on the evening of the day of admission. Chloroform was given, and an incision made over the fluctuating swelling. About 8 oz. of very offensive pus at once squirted out. The seventh rib was felt beneath the incision, and about 1 in. of it was removed. A ragged cavity could then be felt with the finger running upwards to the axilla and apparently in the lung itself.

Examination of Pus and Sputum.

The pus and sputum were sent to me on the following morning for examination. The pus was very thick and tenacious and had the colour of pale anchovy sauce. It contained large numbers of small yellow granules. The sputum consisted of similar pus mixed with mucus. On staining by the Gram method an enormous number of mycelial threads were revealed, in places forming dense masses. Numerous spores were seen but no clubs. Here and there the "ray-form" was present, but the organism was mostly in the form of a diffuse mycelium. No portion of the threads could be stained by the Ziehl-Neelsen method. In the pus the organism was apparently present in pure culture, but the sputum also contained various cocci and bacilli. No tubercle bacilli could be found. Both sputum and pus had a feculent odour. The staining and cultural characters of the organism will be described in detail later.

Diagnosis.

From the characters of the pus there was no doubt that we were dealing with a case of streptotrichosis of the lung and pleura.

Vaccine Treatment.

Having had experience of the manufacture and use of vaccines in other bacterial infections, and considering the close relationship between tuberculosis and streptothrixosis, the success which has attended the vaccine treatment of the former, and the almost invariably fatal result of streptothrixosis of the internal organs, even when treated with large doses of potassium iodide, I determined, with Dr. Saundby's permission, to see whether it were possible to make a vaccine from the streptothrix in this case.

Agar cultures of less than forty-eight hours old were taken, the growth was scraped off, sterilized, and dried for one hour at 60° C. It was then ground up in an agate mortar with normal saline solution containing 10 per cent. glycerine. The vaccine was standardized by weight, 1 c.c. of the emulsion containing 1 mg. of "actinomycotin." This was diluted a thousand times, and the dose used for inoculation was 0.001 mg. of the solid substance.

After the operation on December 19th there was a considerable discharge of pus through the drainage tube; this gradually lost its feid odour; the sputum remained abundant, frothy, and offensive; coarse râles were heard all over both lungs. The temperature for the first week was irregular, with evening rises to 99° and 99.5°; the pulse-rate was 100 to 120, and the respirations, which were 32 to 36 on December 20th, fell to 20 to 24 by the end of the week. On December 28th the patient was transferred to the Jaffray Suburban Hospital. The temperature from December 28th to January 8th, the date of the first inoculation, was pyrexial, showing evening rises to 100°, and once to 102.3°. With the rise in temperature the rate of respiration increased to 28 or 34, the pulse remaining at 100 to 120. The patient now looked and felt very ill, the cough was troublesome, and there was an abundant discharge from the drainage tube, the sputum was also considerable in amount. The day following his removal to the Jaffray Hospital he complained of pain in the region of the liver, which was found to extend downwards to within 1 in. of the umbilicus, and to be very tender on pressure; the spleen could also be felt. It seemed probable that the removal had produced an autoinoculation with extension of the infection to the liver. The organisms in the pus and sputum were still active, and grew readily on culture media.

An attempt was made to estimate the opsonic index to the streptothrix. Obviously from the nature of the organism such an estimation could not have the same accuracy as the estimation of the opsonic index to tubercle bacilli or staphylococci. Young agar cultures were used, and the growth, after drying and sterilizing at 60° C., was ground up in an agate mortar with normal saline solution. A very fair emulsion was obtained, which on microscopic examination showed spores, bacillary forms, and here and there longer threads or portions of threads. The chief difficulty arose from the fact that the growth was stiff and tenacious, the organism being apparently surrounded by a homogeneous substance. The estimations were made in the usual way, my own serum being used as a control. At the first attempt the preparations were incubated for twenty minutes at 37.5° C., and on examination it was found that phagocytosis had been active, the leucocytes treated with my own serum being densely packed with threads and spores, while very few had been taken up by the leucocytes

treated with the patient's serum. At the next attempt a more dilute emulsion was used, and the preparations incubated for only ten minutes; 100 to 150 leucocytes were counted in each preparation. On January 3rd the index was estimated at 0.3, and on January 7th at 0.5.

On January 8th the first inoculation of 0.001 mg. of "actinomycotin" was given. Twenty-four hours later the negative phase was apparently over, as the index had risen to 0.7, and by January 16th was 1.2. The patient had a good night after the inoculation, and in a few days the cough became less troublesome, and the sputum and discharge of pus diminished in a remarkable way. The temperature dropped to normal the day following the inoculation, and remained normal for the next three days. On January 12th the discharge had so diminished that the drainage tube was removed; this caused a slight irregularity of temperature for a day or two.

On January 18th a second inoculation of 0.001 mg. was given, and on January 21st the temperature fell to normal, and afterwards remained so. The respirations had decreased to 22 to 24 and the pulse-rate to 96 to 108. The patient was allowed to get up for a short time on January 19th. Inoculations of 0.001 mg. were given on February 11th and 25th, and March 11th and 27th, six inoculations altogether being given.

The opsonic index was estimated at intervals, the highest point reached being 1.7. A negative phase was never observed to last more than twenty-four hours, and the positive phase reached its maximum on the eighth to tenth day. Generally the temperature taken a few hours after an inoculation showed a slight fall, but on one occasion there was a rise to 99.2°. I do not wish to attach too much importance to the actual figures given for the opsonic index, as the difficulties in the way of making a satisfactory emulsion were great, but the difference between the films made from preparations with my own serum and those made from preparations with the patient's serum were very marked before inoculation was begun, afterwards there was no doubt that the patient's serum had a much higher opsonic power than my own, and with practice the difficulties of technique were largely overcome and a fairly accurate count could be made. The improvement in the patient's condition after inoculation was very marked. There was no sputum a week after the first inoculation, the cough had disappeared by January 22nd, and the sinus rapidly closed, the discharge by the first week in February being very little. Attempts were made on several occasions to grow the organism from the pus; after the second inoculation these attempts were unsuccessful. There was a steady increase in weight from 4 st. 8 lb. on December 29th to 5 st. 8 lb. on February 4th, and on leaving hospital on March 27th the weight was 6 st., a gain of 1 st. 6 lb. in three months. The moist sounds in the lungs disappeared, and examination on the day before leaving hospital showed some flattening of the left side of the chest in the lower axillary region, slight dullness on percussion, and a large area below the angle of the left scapula over which cavernous breathing was heard. This cavity was quite dry, and no moist sounds were heard here or elsewhere. The liver had slowly decreased in size until it could not be felt below the ribs. It was evident that the condition had left behind thickened pleura with a large cavity in the lung. There was then no sputum, and only

Fig. 1.—Photomicrograph of pus from empyema stained by Gram's method, showing dense mycelium of branching threads.

Fig. 2.—Photomicrograph of mycelium in sputum, showing branching and beaded threads, spores, and short rods.

occasionally a dry cough. On April 26th, 1907, the patient was shown to the members of the Pathological and Clinical Section of the Birmingham Branch of the British Medical Association. He then had not received an inoculation for a month, and looked well and robust.

No other treatment besides that described above was given except from January 11th to 18th, when 10 grains of potassium iodide were given three times a day without my knowledge; this was stopped as soon as I became aware of it.

The patient has been seen since at intervals of about a month as an out-patient. He has continued well, and has been free from pain or cough except for a slight attack of bronchitis during the first fortnight in December, 1907. He was seen for the last time on February 20th, 1908; there was then more flattening of the chest at the left base; the cavity was smaller and no moist sounds could be heard; occasionally he had a dry cough, but there was no sputum and the breath was not offensive. The liver and spleen could not be felt. His weight then was 6st. 3lb. No inoculations of "actinomycotin" have been given since March 27th, 1907.

BACTERIOLOGY.

The organism is a typical streptothrix. The pus or sputum, when stained by Gram's method, showed enormous numbers of delicate, thread-like filaments of fairly uniform thickness. Some of the filaments were straight and unbranched, others were bent at acute angles, the majority were wavy and sinuous, twisting and intertwining in all directions. Branching was common, the branches passing off laterally from the parent stem, sometimes at right angles, more often at acute angles. Occasionally an appearance of dichotomy was seen, but on tracing the branches they were seen to be unequal. The filaments were arranged in dense, irregular masses, from which threads passed out irregularly on every side, or in the form of a diffuse network of threads here and there aggregated together in denser masses. No definite clubs were found, but the ends of a few filaments were slightly swollen. The filaments were mostly stained irregularly, their contents being broken up by more or less regularly-spaced unstained intervals, so that the appearance of a chain of short, stout rods, or of a row of beads, was given. In these intervals a faintly-stained sheath could be made out. Some of the filaments showed uniform staining, and there was also considerable variation in the depth of staining, as though some of the threads were degenerated.

Besides the long threads there were numerous bacillary forms resembling in size the rods contained in the threads; most of these showed irregularity of staining, so that they had a beaded appearance.

Among the filaments were large numbers of oval cocciform bodies, singly, in pairs, end to end or side by side, or in short chains of three or four, or in irregular dense masses. Many of the leucocytes had ingested threads or the cocciform bodies.

Cultural Characters.

It grows readily on ordinary media at 37° C., much less readily at room temperature. It grows under both aerobic and anaerobic conditions, but more freely under the former. The growth on media inoculated with the fresh pus was more diffuse than in subcultures, for the colonies on solid media were very adherent and difficult to break down and spread on the surface of the media, so that the resulting growth was often in the form of heaped-up masses. Growth seemed to occur more readily after several generations of artificial culture. No odour was detected in any of the cultures.

Agar.—At 37° C. growth appears after twenty-four hours as small greyish discoid colonies, later becoming confluent and raised. A separate colony has a raised centre and flat wrinkled margin. The growth as a whole is raised with a fimbriated edge. After a few days a pale yellow colour appears.

Glycerine agar.—Growth rather more free than on plain agar, surface raised and shiny, and at bottom of the slope culture has the appearance of fresh honey, being semi-fluid, pale yellow, and translucent.

Gelatine.—Growth slower, but after four days discoid colonies form. In stab cultures, heaped-up yellow mass on surface, closely-set discs radiating from a central core along line of stab, with separate colonies in deeper part. No liquefaction or tinting of the medium.

Broth.—Greyish, semitranslucent, flocculent masses. Broth remains clear. No odour.

Glucose-broth.—Growth similar, but more abundant.

Litmus-milk.—Turned pink after four days, and milk coagulated by the seventh day, forming a dense, pink clot.

Potatoes.—Give a striking growth. Appears after twenty-four hours at 37.5° C. and abundant in forty-eight hours. Growth dry, considerably raised, and heaped up in irregular masses. Colour ochreous or brick-red.

Serum.—Growth resembles that on agar, but less vigorous. Serum not liquefied.

Diastatic Action.—None manifested after seven days' incubation at 37.5° C.

Morphology and Development.

The organism in artificial culture is highly pleomorphic. Examination of a twenty-four hours old culture shows a large number of short bacillary forms staining either homogeneously or in beaded fashion, and sometimes slightly thickened at one end. These forms were either single, in pairs, or placed end to end in short or long chains. The chains were sometimes straight, but more often wavy, and bent in graceful curves. Branching was uncommon, but here and there were short lateral branches on some threads. Often branching was simulated by an accidental arrangement of the rods. Many spores were present, but usually in dense masses, and were probably remains of the original growth with which the medium was inoculated. Longer threads were found in the broth cultures, and especially in glucose broth, than on solid media. For the next few days similar appearances were seen, but there was more variation in the length of the threads, long uniform threads being more common. After about a week's growth many branched, irregularly-stained threads were seen, and also short rods and spores. The threads now resembled those found in the original pus, being broken up into chains of short rods or spores, the latter being most frequently seen at the ends of the threads with the rods in the intervening portions. After one month's growth on glycerine agar or potato, dense masses of spores were found, with short, badly-staining rods and a few long branched threads. These threads stained very irregularly with Gram's stain, and at first sight apparently consisted of rods placed end to end with intervening spaces of varying length, but closer examination showed that they were surrounded by a homogeneous sheath which crossed the gaps between the rods. In some of the wider gaps the sheath appeared to be dilated. No clubs were seen in any of the cultures examined at various ages.

The organism from cultures of all ages, from a few days to 9 months, was stained by Ziehl-Neelsen's method, but no acid-fast portions were found. After staining with hot carbol-fuchsin for five minutes some of the rods and spores retained the stain after immersion for three minutes in methylated spirit, but they were decolorized by 5 per cent. sulphuric or hydrochloric acid in one minute.

Identity of the Organism from this Case.

From its morphology and appearance in culture I have not been able to identify the streptothrix from this case with any of those of which full descriptions have been published. The most frequent organisms found in cases of pulmonary streptotrichosis belong to the "acid-fast" group, in which are included those described by Eppinger, Aoyama, MacCallum, M'Donald, Sabrazés, and Rivière, Birt and Leishman, and others. The streptothrix from this case is at once distinguished from these by the absence of "acid-fast" characters. It differs from *Streptothrix bovis communis* in its more vigorous growth, in its inability to liquefy gelatin, and in its power of coagulating milk. *Streptothrix bovis* has not been described in cases of pulmonary streptotrichosis hitherto, and is apparently a rare form in human disease.

It has most in common with the organisms described by Wolff and Israel, Norris and Larkin, Krause, and Levy. These agree in growing under an aerobic as well as aerobic conditions, in not being "acid-fast," in not liquefying casein, gelatin, or serum, but in coagulating milk. It differs from them, however, in its more rapid and vigorous growth.

SOURCE OF INFECTION.

The source of infection in this case could not be traced. The patient had always lived in the town, and had not been associated with cattle or in the habit of chewing straw or grain. We are at present ignorant of the common sources of infection, and a wider knowledge of the natural

Fig. 3.—x, Injection of "actinomycin"; O, operation; D, drainage tube removed.

distribution of streptotrichae is much needed. *Streptothrix bovis* is the only species which has been found both in man and lower animals, and since the organisms from cases of human streptotrichosis have been isolated and studied this species has been rarely found. Saprophytic species are common in the air, water, and soil, and parasitic species have been found living on grasses, attached to the roots of leguminosae, and in animals they have been found in the oyster, pig, fowl, horse, dog and rabbit. At present we have no certain evidence that these species can become pathogenic for man.

It is difficult to determine how long the patient had been infected as he had suffered from childhood from bronchitis. The earliest lesion of pulmonary streptotrichosis appears to be purulent bronchitis. In Canali's case this alone was present, and in Leith's case this condition was found *post mortem*. The disease is rarely recognized in this stage during life. In December, 1905, the patient was admitted to hospital with a severe attack of bronchitis, and it was then noticed that his sputum was abundant and had a feculent odour. This odour has been frequently recorded in cases of pulmonary streptotrichosis, and it is possible that examination of the sputum at that period would have revealed the streptothrix. It seems probable that the feverish attack with paroxysmal cough and increase in sputum occurring in May, 1906, marked the extension of the disease from the bronchi to the lung tissue, and that the severe pain in the left side complained of in November, 1906, marked the extension to the pleura with subsequent development of an empyema, which, as is usual in pulmonary and, indeed, other forms of streptotrichosis, showed a marked perforative tendency and gave rise to the external abscesses noticed on admission in December. While in hospital the disease appeared to spread to the liver, but whether by direct extension through the diaphragm or by the blood-stream it is impossible to say, most likely the former.

The case shows the importance of the systematic examination of the sputum, especially in cases resembling tuberculosis in which no tubercle bacilli can be found, and of the pus in all cases of empyema, especially those which show a perforative tendency. It is probable that some of these cases would be diagnosed earlier by a careful bacteriological examination of the sputum in cases of fetid bronchitis. At present we do not know how early the organism can be detected in the sputum of these cases. The sputum and pus should always be stained by Gram's method, as this stains all the known species except the degenerated portions. If the sputum is only stained by Ziehl-Neelsen's method the organism may easily be overlooked, especially if it belongs to an "acid-fast" species. Too much importance has been attached to the presence of clubs. These are very variable in appearance, and

their absence must not be taken to exclude the possibility of actinomycosis. Branched forms even are not always present, as in old abscesses the parasite may have undergone complete segmentation, and so would be difficult to distinguish from bacilli. Careful search, however, would probably reveal short branches and a few long filaments. Another source of difficulty I have found in some cases is that the parasite is surrounded by a gritty material which stains deeply and conceals the threads contained in it.

Pulmonary streptotrichosis is one of the less common forms of the disease. Rührh found 92 instances of pulmonary disease in 632 cases of streptotrichosis reported in the literature—a proportion of 14.5 per cent. In 18 of 34 cases collected by Hordenpyl the diagnosis was made during life—in 9 by examination of the sputum, and in 9 by examination of the pus from a lung abscess. The average duration of the cases was about ten months. In a few cases a cure has been reported, but such a result cannot be expected with any confidence, as it appears to be only a little less fatal than streptotrichosis of the brain or liver, from which no case of recovery, according to Acland, has been recorded.

The case reported in this paper is especially interesting, as it adds one more to the number of infections which have been successfully treated with a specific vaccine prepared from the infecting organism. In this case there was not much difficulty in preparing a vaccine, as the organism was isolated and grown in pure culture; but in many cases it is difficult or impossible to isolate the parasite. In these cases it will be important in the future 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. In this connexion it is worth while recalling that temporary benefit was found in Ziegler's case of severe actinomycosis of the

head and neck after injections of "bacterial protein" obtained from *Staphylococcus aureus*, and in Billroth's case after tuberculin injections.

In conclusion, I should like to express my indebtedness to Professor Saundby for enabling me to deal with the case, and to Professor Leith for the use of the excellent photomicrographic apparatus in his laboratory.

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Fig. 4.

Potato culture
three weeks
old.

Glycerine-agar
culture three
weeks old.