A CASE OF ACTINOMYCOTIC CEREBRO-SPINAL MENINGITIS.¹

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(PLATE II.)

CASE—CLINICAL HISTORY.—The patient, a male, æt. 26, was admitted to the surgical wards of the Sheffield Royal Hospital in December 1908, after having attended as an out-patient for a few weeks. He was a cabinetmaker by trade, and gave the following history :—

In June 1908, at a small village outside Glasgow, he had a carious tooth removed from the right upper jaw, cocaine being used as local anæsthetic. Immediately afterwards the right upper jaw became swollen, and he was treated as an out-patient at the Glasgow Western Infirmary, where two or three abscesses were incised through the mucous membrane.

On admission to hospital (Sheffield) he was found to have a large abscess over the right upper jaw. The lower jaw was fixed so that he could hardly move it, apparently by partial ankylosis of the right temporo-maxillary joint. There was some discharge from the right ear, but the tympanum was unruptured and the discharge seemed to come from a sinus opening into the external auditory meatus. The abscess was incised and the right superior maxilla was found bare for some considerable extent. The wound healed up partially, and the patient was discharged, only, however, to be readmitted again on 7th January 1909. He had then a submaxillary abscess, which was unconnected with bone or the previous condition, and due probably to suppuration in and around the submaxillary glands. Incision of this abscess was followed by a partially healed sinus, and he was discharged on 3rd February 1909.

On 29th March 1909 he was readmitted with an abscess over the right superior maxilla. There were signs also of deep abscess formation over the anterior temporal region on the right side. Free incision and scraping were again carried out.

Ten days later he complained of pain at the back of the head and neck. This was very severe and unrelieved by treatment. On 23rd April another collection of pus had formed in front of the right ear in the temporal region, and fluctuation could be detected in the tissues of the right cheek. Examination of the pharynx, of the right auditory meatus, and of the nose proved negative. He was again operated upon, and a sample of the pus then obtained was sent for examination to the University Pathological Laboratory.

From this time onwards the pain in the occipital and cervical regions increased in severity. He complained also of pain all down the spine, particularly in the lower lumbar and sacral regions. He vomited repeatedly, and the temperature reached 101° on several days.

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On 1st May he developed distinct signs of meningitis. He became restless and intolerant of attempts at examination. The knee-jerks were much exaggerated, and Kernig's sign was well developed on both sides. The neck was held rigid, and there was opisthotonos. His condition now became progressively worse. On 6th May there was retention of urine, considerable head retraction and apparent paraplegia. On this day blood cultures were taken and lumbar puncture was performed. The latter operation was one of difficulty, partly because of the opisthotonos and restlessness, but also because the exudate was apparently very thick and fibrinous. About 2 c.c. were obtained only after using a trochar of large diameter and employing vigorous suction.

On the evening of 6th May the patient died, the temperature just before death reaching 105°.

Post-mortem findings.—An autopsy was performed twenty hours after death. The body was poorly nourished. There was considerable rigor mortis, and post-mortem staining was present over the usual situations. The right side of the scalp had been recently shaved, and there were several operation scars over the right side of the head and neck. But for one or two small sinuses these wounds had completely healed, and there was no purulent discharge. The mesentery contained a group of old tuberculous glands. Otherwise the thoracic and abdominal contents showed nothing unusual; their description is therefore omitted. In removing the skull cap it was found that the right temporal bone and part of the frontal bone on the right side were stripped of periosteum and covered with a thin layer of brown blood-stained pus. It was impossible to ascertain the condition of the superior maxilla, or of the temporo-maxillary joint because of the mutilation it would have involved.

The convexity of the brain was normal except for some flattening of the convolutions and engorgement of the superficial veins. The structures about the base of the brain and the lower aspect of the cerebellum were hidden by yellowish purulent exudate. This had extended for a short distance along some of the fissures on to the outer aspect of both hemispheres. There was no odour of butyric acid, which is described as being marked in some cases of actinomycosis. The base of the skull was occupied by a large amount of liquid milky pus.

On removal of the vertebral laminae the whole of the subarachnoid space was found to be distended with thick viscid blood-stained material, which closely enveloped the cord throughout its whole extent. The exudate was particularly viscid and tenacious in the lumbar sac. There was no macroscopic evidence that the process had extended outside the dural sac. Subsequent section of the brain showed that there were no abscesses in the brain itself, nor had the lateral ventricles been invaded.

BACTERIOLOGICAL FINDINGS.

In the discharge obtained from the various operation wounds about the head, in the cerebro-spinal exudate removed during life, and also in that obtained after death, there were present the typical granules or *drüsen* of actinomycosis. These were small oval or spherical bodies of a translucent or ground-glass appearance, varying from the size of a pin's head to those of microscopic proportions.

On examination the larger granules showed densely packed filaments with a varying amount of débris, whereas in younger colonies the filaments were more distinct, and there was little or no granular

débris. The ordinary laboratory stains, including carbol fuchsin and carbol thionine, stained these filaments but feebly, and the best pictures were obtained in all instances by using Gram's method. In the smaller *drüsen* the filaments, which showed frequent branching, stained well by this method, but in older colonies the filaments presented considerable granular degeneration of their protoplasm. They were never segmented, and no appearance at all comparable in size to coccal forms could be demonstrated. In addition to branching filaments, short bacillary and markedly spiral forms were frequent in all preparations. Club formation was not found either in films or in sections, but not uncommonly the extremities of filaments presented knobbed or flask-shaped swellings which took on Gram staining very strongly. No appearances suggestive of spore formation could be found, and repeated examination failed to reveal the presence of any acid-fast fragments.

CULTURES.—The blood cultures which were taken remained quite sterile after six weeks' incubation. A large number of culture tubes of the ordinary laboratory media were inoculated with pus obtained before death and also at autopsy. In some cases the pus as a whole was used for this purpose; in other cases the granules were picked out, washed several times in sterile water, and then inoculated. Under aerobic conditions no growth whatever occurred, with the exception of a few contaminating micro-organisms, which I shall refer to later. Successful cultural results were obtained only under anaerobic conditions and at blood temperature. The following cultural features have been noted :—

1. *Liquid media*.—Glucose broth (1·5 per cent.) proved to be the most favourable liquid medium. About the fifth or sixth day dense white irregularly shaped granules are found, the largest being pinhead in size. These clumps are aggregated on the bottom of the tube. There is no surface growth, and the medium remains quite clear. About the tenth day, in addition to the granular growth, there develops a faint flocculent deposit, which rises up as a thin cloud on shaking the tube. Usually no further growth appears, and even at its maximum the growth is but small in amount. In some instances, however, the granular material becomes more and more flocculent, and the flocculi adhere to the bottom and sides of the culture tube. In plain broth no growth occurs even after several weeks. In serum broth a few small clumps of growth may be seen after ten days. In glycerin broth a faint deposit may be found about the tenth day, but most tubes show no growth. The cultures obtained in liquid and in solid media are odourless.

2. *Solid media*.—Plain agar slopes and glycerin agar slopes show no growth. On glucose agar about the sixth day small white pin-point colonies are visible. By about the twelfth day they have attained their maximal size, being 1 to 2 mm. in diameter, and they appear as raised circular pearly-white nodules with smooth surface but sometimes having crenate margins. The colonies show no tendency to coalesce, are very friable, and do not at first stick to the medium. Growth into the agar is found in tubes incubated for three or four weeks, and occurs also in tubes which have first been incubated anaerobically and then allowed to come into contact with air.

Probably the best and most vigorous growth of the organism is obtained in glucose-agar shake-cultures. About the fourth or fifth day of incubation, colonies of varying size appear scattered throughout the medium, but in addition there develops, at a depth of 1 to 2 cms. from the surface, a clouded zone about 5 or 6 mm. in width. In a few days more this belt shows itself to be composed of a densely packed mass of minute colonies. Above, and more particularly below, this region isolated colonies are found, which appear as irregular opaque white masses and may attain a size of 2 mm. in diameter, whereas the colonies inside the zone remain small.

MORPHOLOGY IN CULTURES.—Films made from the growth on agar surface colonies show the presence of numerous straight or slightly bent bacillary forms. These average 4μ in length, but may reach 8μ or even more. Their thickness varies from 0.4μ to 0.5μ , thickened portions being met with either about the middle or at the extremities. T-shaped and Y-shaped arrangements of branching are common, without, however, any appearance of true branching such as is found in the filaments obtained from the tissues. The short plump forms, as a rule, stain well with Gram's method. The longer forms take on Gram's staining more irregularly, being often decolorised at the ends, sometimes in the centre. This irregularity in size and in staining, together with the general distribution of the bacilli about the microscopic field, reminds one strongly at first of some forms of diphtheria bacilli.

When agar surface colonies are left in contact with air for a few days after being incubated anaerobically, films show the bacillary forms to have changed so that they are completely decolorised in Gram's method or retain the stain but feebly. Moreover, there are present in large numbers spore-like bodies situated often at one extremity of the bacilli, this giving rise to a drumstick appearance. These spore-like elements are spherical or oval structures, about 0.9μ in size transversely, and about 1.3μ longitudinally. They retain the Gram staining well, but are decolorised in the ordinary spore-staining methods. Cultures from these spore-like bodies give rise to vigorous growths in glucose-agar shake-cultures, and films from these show no spores but only bacillary forms of varying length, as in the agar surface growths.

In broth cultures the longer bacillary forms of the organism predominate. They appear thinner than on agar, and do not stain so readily by Gram: usually the more central parts alone retain the gentian-violet, while the end takes on the counter-stain. Here, too, as in agar growths, T-shaped and Y-shaped arrangements are met with. In some preparations one spherical or oval Gram-positive granule of the same diameter as the bacillus is found situated towards one extremity of the organism. In other preparations several granules of smaller size were discernible in each bacillus. Both these appear-

ances have no special significance, and may be attributed, I think, to the vagaries of Gram staining.

In the case of two cultures in glucose broth in which the amount of pus inoculated was large, and in which the growth seemed to pass rapidly from the granular to the flocculent condition, microscopical preparations showed the presence of two different elements—first, filaments about 0.9μ in thickness, staining well by Gram's method; and secondly, longer and more wavy filaments of less diameter, 0.4μ to 0.5μ in thickness, which always decolorise in Gram's method. These latter are seen to spring from the extremity of a thicker filament and to continue their growth in the same axis, the change in diameter being sudden and abrupt. In the hope of demonstrating that this luxuriant growth of thin filaments may take on Gram staining and increase in diameter when placed in the living tissues, I am making inoculation experiments which are not yet completed.

In no instance were elements found which were acid-fast, and attempts to demonstrate club formation by the methods first adopted by Homer Wright have proved unsuccessful.

VITALITY IN CULTURES.—Regarding the vitality of the organism in cultures I can say but little, inasmuch as investigations in this direction are so far incomplete. It is possible to get subcultures from growths in broth up to three weeks old, and cultures which show the spore-like bodies give vigorous growths after six weeks.

PATHOGENICITY.—Guinea-pigs have been inoculated both intraperitoneally and subcutaneously with the cerebro-spinal exudate, with pure broth cultures, and with one of the cultures rich in streptothrix formation. In the subcutaneous cases inflammatory nodules have developed at the seat of inoculation, but these have afterwards receded. In one case an abscess formed which burst on the skin surface on the twelfth day, and films from this showed a few branched filaments. So far none of the inoculated animals have died nor have they presented any signs of illness.

CONTAMINATING MICRO-ORGANISMS.—A brief reference with regard to the contaminating organisms is necessary. In tubes incubated aerobically there were found—

1. A Gram-negative diplococcus.
2. A Gram-positive coccus which gives in glucose cultures a strong butyric acid odour.
3. A Gram-negative bacillus which gives in growths a heavy musty odour.

Inasmuch as inoculation results with the various organisms isolated from cases of human and bovine actinomycosis have so frequently proved negative or inconclusive, I intend to carry out animal experiments with these contaminating organisms in combination with that which is the subject of this paper.

RECORDED CASES OF ACTINOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM.

Actinomycosis of the central nervous system is sufficiently rare to be worth recording. It is impossible here to do more than to make brief reference to the hitherto recorded cases.

Ponfick⁽¹⁾ in 1882 described a case of generalised actinomycosis in which the brain was affected. At the same time he recorded a second case in which the brain and meninges were invaded, the primary seat of the disease in both instances being the prevertebral tissues. Two years later Israël⁽²⁾ gave details of a patient in whom the disease appeared first in the lungs, the brain and meninges being secondarily involved. In the same year Köhler⁽³⁾ published the record of a man with generalised actinomycosis. In 1887 Bollinger⁽⁴⁾ described the case of a woman, æt. 26, who showed symptoms and signs of cerebral tumour. At autopsy an actinomycotic nodule was found occupying the third ventricle, but no other lesion could be discovered. The case reported by Naunyn⁽⁵⁾ in 1888 was that of a girl, æt. 16. At autopsy there were found vegetations on the mitral valve and small reddish-brown masses on the cerebral pia mater. Microscopic examination of material obtained from both these sources showed the presence of a streptothrix.

Delépine⁽⁶⁾ in 1889 recorded a case of generalised infection with multiple cerebral abscesses. In the following year Almquist⁽⁷⁾ published the description of a case of cerebro-spinal meningitis occurring in an artilleryman. Plate cultures of material obtained at the post-mortem examination yielded numerous colonies of bacillus proteus and of cocci together with one colony of a streptothrix. This grew readily on gelatin subcultures at room temperature. There is no record that the same micro-organism was found in the pus or in the meninges, and one may, I think, justly conclude it to be an aerial contamination. The case described by Keller⁽⁸⁾ showed meningitis and a small cerebral abscess, and the ray fungus was found in the pus.

In Eppinger's⁽⁹⁾ case there was a large brain abscess together with cerebro-spinal meningitis. The organism isolated from this case was first described as a cladothrix, but more recently it has been classified as streptothrix asteroides. Stuart M'Donald⁽¹⁰⁾ has described a case of generalised infection due to an identical or closely similar organism.

Sabrazès and Rivièrè⁽¹¹⁾ record the case of a woman, æt. 31, in whom one kidney and the meninges were involved. Anaerobic gelatin cultures gave a single colony of a streptothrix, but subcultures and animal inoculations were unsuccessful. West⁽¹²⁾ quotes two cases of cerebral actinomycosis—one recorded by Sammt⁽¹³⁾, the other by Mallory⁽¹⁴⁾. Both of these were secondary to lung lesions. A case of epileptiform convulsions due to a so-called primary abscess is described by Ferré and Faguet⁽¹⁵⁾. The streptothrix isolated in this instance grew particularly well on potato, and was not pathogenic to guinea-pigs. The authors claim that their organism was nearly related to Eppinger's streptothrix, but their description is meagre and their experimental results do not warrant the conclusion.

Dolore⁽¹⁶⁾ gives a short account of a case of cervical and facial actinomycosis which ended in cerebro-spinal meningitis; and Martin⁽¹⁷⁾ has described from Chiari's laboratory in Prague two cases of cerebral abscesses which were metastases from actinomycosis of the lungs.

Schlegel⁽¹⁸⁾, in Kolle and Wassermann's *Handbuch*, refers to cases published by de Quervain⁽¹⁹⁾ and by Nikitin⁽²⁰⁾. Chiari⁽²¹⁾ has described two cases in males, æt. 43 and 37 years respectively, who suffered from bronchiectasis. Multiple abscesses of the brain and spinal cord with cerebro-spinal

meningitis were found post-mortem. Cultures and inoculations were, however, negative.

In 1901 Habershon ⁽²²⁾ described a generalised infection occurring in a male. Musser, Pearce, and Gwyn ⁽²³⁾ in the same year gave an account of an apparently primary abscess in the cerebrum due to a streptothrix. In 1903 Howard ⁽²⁴⁾ published a somewhat similar case. Cultures were unsuccessful. A rabbit inoculated with the pus died in twelve days with purulent peritonitis. Microscopical examination of the exudate showed "no branching forms, but numbers of long and short threads, bacillus and coccus forms." Cultures from the peritoneum gave *Streptococcus pyogenes*, but no other organism. Although the case is published as one of actinomycosis there is no mention whatever of granules.

Buday ⁽²⁵⁾ found an actinomycotic nodule situated between the anterior pillars of the fornix. The specimen was shown before a Medical Society, but no description of the case clinically, or of the specimen, has ever been published.

By the kindness of Dr. Arthur Hall I am permitted to make mention of an unrecorded case which has occurred more recently. A man, æt. 35, was operated upon in Aberdeen in 1904 for an abscess in the neighbourhood of the kidney. The diagnosis of actinomycosis was made in Aberdeen and subsequently also in Newcastle. In 1906 he came under treatment in Sheffield for compression paraplegia. Laminectomy was performed by Mr. Pye-Smith, who found pachymeningitis and necrosis of the seventh and eighth dorsal vertebræ. On microscopical examination branched filaments were found in the portions of softened bone removed at operation, but no cultures or inoculations were made. The man died the day after operation, and a post-mortem examination was not obtained.

I have thus been able, in a survey of the literature at my disposal, to obtain descriptions of, or references relating to, twenty-five possible cases of actinomycotic infection of the central nervous system. This number includes several cases on the identity of which one must cast considerable doubt, together with other cases of suppurative disease described as pseudo-tuberculosis, or streptothrix or cladothrix infections. If one limits the term actinomycosis to a process in which there occurs the formation of granulation tissue and of pus containing granules or *drüsen*, these latter being composed of a felted growth of branched filaments together with their degeneration products, then the recorded cases of real actinomycosis of the central nervous system are considerably fewer in number.

The disease is one which would appear to affect adult males, and in each case the invasion of the central nervous system has been the determining cause of death. The lungs and bronchial glands are the common seat of the primary lesion, and in only three cases—Ponfick's two and Dolore's one—has the infection resulted by direct extension from the tissues of the neck and face. In none of the recorded cases have cultures or inoculation experiments proved successful, and the diagnosis has been furnished, in the majority of the cases, only by microscopical examination of the pus.

A search through the literature on actinomycosis reveals much that is confusing. The first full description of the causal organism is that given by Boström ⁽²⁶⁾, and published by him in 1890. He

emphasises the necessity of inoculating a large number of culture tubes in each case, and he himself found only twelve colonies of growth in seven hundred tubes taken from eleven cases of actinomycosis of the jaw in cattle. The organism was grown under aerobic conditions and showed itself as a streptothrix. Subcultures from these original colonies flourished on all the ordinary laboratory media even at room temperature. No positive results, however, were obtained by inoculation. All these facts, namely, the low percentage of positive cultures, the luxuriant growths in subcultures at room temperature, and the absence of pathogenic action, point to the inadvisability of considering Boström's organism as of ætiological significance. Homer Wright (²⁷) goes so far as to suggest that the organism thus isolated is nothing more than an aerial contamination. Results agreeing with Boström's have been published by Rossi-Doria (²⁸), Domec (²⁹), and many others, some of whom have obtained positive inoculation results.

Wolff and Israel (³⁰), on the other hand, isolated from two cases of actinomycosis an organism which flourished best under anaerobic conditions and at body temperature. This organism was accepted by Kruse (³¹), in Flugge's *Handbuch*, as the probable cause of some cases of actinomycosis, but so violent was the opposition of Boström and his followers that the description of the Wolff-Israel organism was removed from those text-books in which it had found a place. The results of later investigators, however, have done much to establish the existence of the anaerobe. Aschoff (³²) isolated it from a case of lung actinomycosis, and was successful with his inoculation experiments. Levy (³³) too has found it in five cases of human actinomycosis. Lignieres and Spitz (³⁴) have isolated it from bovine cases, and Dean (³⁵) found what was probably the same organism in a jaw abscess in a horse. More recently Homer Wright (²⁷) has obtained an organism which is essentially an anaerobe in thirteen cases of human actinomycosis, and in two of the bovine disease.

The organism in the present case is more strongly anaerobic than those hitherto described, but it is to be classed as nearly related to, if not identical with, the Wolff-Israel organism.

If one accepts an organism which grows best under anaerobic conditions and at blood temperature as the causal agent in at least some cases of actinomycosis, then one's conception as to the etiology of the disease must be altered; for it is improbable that such an organism exists widespread outside the body,—as has been found in the case of Boström's streptothrix,—and one may reasonably suppose, as Wright has suggested, that its normal habitat is the alimentary tract, and that it gains entrance to the tissues not on foreign bodies, but rather that it finds a suitable nidus for development as the result of traumatism exercised by these bodies.

I must thank Dr. Wilkinson for his kind permission to use the

case, also Professor Macdonald for placing at my disposal his photo-micrographic apparatus, and Professor Beattie for numerous valuable suggestions. I am also under obligations to Dr. Wilson and Dr. Holburn for clinical details of the case.

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Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

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* Reference by Howard (24) not personally verified by author.

DESCRIPTION OF PLATE II.

- FIG. 1.—Section showing a streptothrix colony in the exudate surrounding the spinal cord ; stained by Gram's method. (× 750.)
- FIG. 2.—Film preparation of cerebro-spinal exudate obtained during life, and showing branched filaments ; stained by Gram's method. (× 2250.)
- FIG. 3.—Film preparation of agar-surface growth, after twelve days' incubation under anaerobic conditions ; stained with carbol gentian-violet. (× 2250.)
- FIG. 4.—Film preparation of growth shown in Fig. 3 after contact with air for four days. It shows the spore-like bodies. Stained with carbol gentian-violet. (× 2250.)
- FIG. 5.—Film preparation of unusual growth in glucose broth, three weeks old. It shows thin Gram-negative filaments springing from thick Gram-positive filaments. (× 2250.)
- FIG. 6.—Growth in 1·5 per cent. glucose agar-shake culture, after eight days' incubation.