TWO CASES OF MENINGITIS DUE TO *ERYSIPELOTHRIX MONOCYTOGENES*

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Meningitis due to *Erysipelothrix monocytogenes* (*Listeria monocytogenes*, Pirie) is generally considered to be a rare disease. Kaplan (1945), who reviewed the literature, collected records of 14 proved cases of meningitis due to this organism. Since then at least 14 others have been described, chiefly in the American literature. Murray (1955) believes, however, that human infection with *Ery. monocytogenes* is probably more common than is realized. He points out that German papers alone list some 150 described cases of meningitis and meningo-encephalitis, granulomatosis infantiseptica, septicaemia, and mononucleosis caused by this organism. Murray estimates that meningitis and meningo-encephalitis comprise roughly 33% of all published cases.

In this country only two cases of meningitis have been reported. Gibson (1935) described a fatal case in a 37-year-old labourer caused by a diphtheroid organism that was later identified by Webb and Barber (1937) as *Listerella monocytogenes*. In 1938 Wright and Macgregor (1939) cultivated the organism from the cerebrospinal fluid of a 17-month-old boy dying on the seventh day of illness. The purpose of this paper is to report two apparently unconnected cases of meningitis due to *Ery. monocytogenes* occurring in Leicestershire within the space of eight weeks, and to focus attention on the existence of a disease that may be more common in this country than the literature indicates.

Case Records

Case 1.—A man, aged 63, was admitted to the Leicester Isolation Hospital on November 12, 1955, with a severe progressive frontal headache of 12 hours' duration. He had pain at the back of the neck and his legs were stiff, with sciatic pain on flexion. There was no vomiting and no history of head injury. There was nothing relevant in the past medical history.

On examination his temperature was 102.6° F., pulse rate 68, and respirations 24 a minute. He had photophobia and was rational though drowsy. There was

stiffness of the neck, and Kernig's and Brudzinski's signs were positive. The pupils were equal and reacted normally. The optic fundi were normal. His blood pressure was 130/65 mm. Hg.

Lumbar puncture on admission produced a turbid cerebrospinal fluid (C.S.F.) under increased pressure, containing protein, 400 mg. per 100 ml., sugar, 52 mg. per 100 ml., and more than 2,000 leucocytes per c.mm. (neutrophils 80%, lymphocytes 20%). Gram-positive coccobacilli were seen in smears, and culture of the C.S.F. yielded a heavy growth of small transparent colonies on blood agar after 18 hours' incubation (Strain 1).

A blood count on admission showed 10,000 leucocytes per c.mm. (neutrophils 88%, lymphocytes 12%) and Hb 13.9 g. per 100 ml.

Treatment consisted of soluble penicillin, 1 mega unit intramuscularly, and sulphamezathine, 2 g., and chloramphenicol, 500 mg., orally every six hours. Penicillin was discontinued after seven days, and sulphamezathine and chloramphenicol after 10 days. Intrathecal soluble penicillin, 15,000 units daily, was also given for the first two days.

The patient's temperature fell to normal 72 hours after admission. Lumbar puncture on November 15 produced a slightly opalescent fluid under normal pressure. There was a decrease in the number of leucocytes (neutrophils 90%, lymphocytes 10%). No organisms were seen in smears and culture was sterile. Headache and drowsiness continued, but with diminishing severity, for six days. During this time the general clinical condition slowly improved, but neck stiffness did not disappear until the sixth day after admission. A blood count on November 21 showed 5,500 leucocytes per c.mm. (neutrophils 56%, lymphocytes 38%, monocytes 4%, and eosinophils 2%) and Hb 14.8 g. per 100 ml. A final lumbar puncture on November 22 produced a clear fluid under normal pressure containing protein, 180 mg. per 100 ml., sugar, 74 mg. per 100 ml., chlorides, 600 mg. per 100 ml., and 42 cells per c.mm. (neutrophils 10%, lymphocytes 90%). The Paul-Bunnell test on a sample of blood taken on the same day, the eleventh day of illness, was negative. Treatment was stopped on November 22 and the patient was discharged well on November 28.

Case 2.—A man, aged 40, was admitted to the Leicester Royal Infirmary on January 8, 1956, with

violent frontal and retro-orbital headache which had begun two days previously. Twenty-four hours before admission, double vision, photophobia, and some deafness were noticed. There had been no vomiting. There was nothing relevant in the past medical history.

On examination his temperature was 102° F., pulse rate 90, and respiration 22 a minute. He was ill, restless, obviously disturbed by severe headache and had photophobia. He was conscious and well orientated, but drowsy. There was stiffness of the neck, pain on turning the head to either side, and a positive Kernig's sign. The pupils were equal with normal reflexes. There was complete paralysis of the left external rectus and weakness of the left side of the face. There was deafness in the right ear and moderate deafness in the left ear. There was no evidence of otitis media. No other cranial nerve lesions were noted. The tendon reflexes were all present and equal, and the plantar responses were flexor. There was a palpable spleen. His blood pressure was 160/90 mm. Hg.

Lumbar puncture on admission revealed a turbid fluid under increased pressure containing protein, 180 mg. per 100 ml., sugar, 14 mg. per 100 ml., and 800 leucocytes per c.mm. (neutrophils 95%, lymphocytes 5%). No organisms were seen in smears. Culture of the C.S.F. produced no apparent growth on overnight incubation, but when the blood agar plates were re-examined after 36 hours there were several small, semi-opaque colonies of Gram-positive cocco-bacilli (Strain 2).

A blood count on January 8 showed 10,300 leucocytes per c.mm. (neutrophils 72%, eosinophils 1%, lymphocytes 19%, and monocytes 8%) and Hb, 10 g. per 100 ml.

A blood culture taken on January 8 was sterile after 10 days' incubation.

The patient was given soluble penicillin, 1 mega unit intramuscularly every four hours for four days, an initial dose of streptomycin, 1 g. intramuscularly, followed by 1/3 g. intramuscularly four-hourly for four days, and soluble penicillin, 20,000 units plus streptomycin 100 mg. intrathecally once daily, for three days. After the first four days the combined penicillin-streptomycin therapy was stopped and chloramphenicol was given orally, 500 mg. six-hourly for 11 days.

The response to treatment was rather slow. The fever was continuous, but with a gradual fall for the first five days, during which time headache and neck stiffness were severe, and there was occasional delirium. The C.S.F., which became sterile after the first day, remained under increased pressure until January 13. A blood count on the same day showed 9,600 leucocytes per c.mm. (neutrophils 80%, lymphocytes 12%, monocytes 8%) and Hb 11.6 g. per 100 ml. Thereafter, although the temperature remained at about 99° F. there was gradual improvement with diminishing neck stiffness and drowsiness. Headache persisted until January 18 when a lumbar puncture produced a fluid containing protein 400 mg. per 100 ml., sugar 115 mg. per 100 ml., and 180 leucocytes per c.mm. (neutrophils 60%, lymphocytes 40%). Bilateral facial weakness and nystagmus on both sides appeared on January 18 and were still present when the patient was

discharged to the convalescent home on January 30. The deafness, however, was improved. The left sixth nerve paralysis was still present on discharge. A blood count on January 29 showed 8,200 leucocytes per c.mm. (neutrophils 86%, eosinophils 1%, lymphocytes 12%, monocytes 1%) with Hb 10.8 g. per 100 ml.

Bacteriology

Morphology.—The organism as seen in the smears from the C.S.F. of Case 1 appeared as a small Gram-positive cocco-bacillus occurring singly and in pairs end-to-end, and was at first mistaken for a pneumococcus. In stained preparations from blood agar cultures both strains appeared as small, straight, or slightly curved, Gram-positive rods arranged singly and in pairs. Granules and swollen forms were not seen. There was no evidence of branching. Spores were not formed. Both strains were non-motile at 37° C., but when grown in broth at room temperature they showed characteristic tumbling motility. Polar flagella were demonstrated with difficulty using Kilpatrick's method (Fig. 1).

Cultural Characteristics.—Both strains grew readily on the usual media, producing on blood agar, after 24 hours' incubation at 37° C., small, circular, domed transparent colonies with a smooth, shining surface and entire edge. On ageing the colonies had a tendency to become opaque and the edge fimbriate. On primary culture both strains were non-haemolytic, but after two or three subcultures definite zones of β -haemolysis appeared round the colonies. Both strains have since remained haemolytic. Growth occurred on MacConkey's medium after 48 hours at 37° C. and after four days at room temperature. On Hoyle's tellurite medium small, black, smooth, circular colonies were visible after 48 hours at 37° C. Gelatin stab cultures produced filiform growth with no liquefaction. In digest broth both strains produced a uniform turbidity with a slight deposit which disintegrated on shaking. Growth occurred at 4° C. and in broth containing 10% NaCl.

Biochemical Characteristics.—The biochemical characters of both strains were identical. Acid but no gas was produced in glucose, salicin, laevulose, dextrin, and rhamnose after overnight incubation, in maltose after two days, in sucrose after five days, and in lactose after eight days. Mannitol, dulcitol, xylose, galactose, and inulin were not fermented after 28 days. The methyl red test was positive and the Voges-Proskauer reaction weakly positive. Indole was not formed. There was no production of H₂S. Nitrates were not reduced to nitrites in seven days. Both strains were catalase positive.

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Smear showing polar flagella of *Ery. monocytogenes*. Kilpatrick's stain, $\times 720$.

FIG. 2.—Lesion in mouse liver showing area of necrosis, inflammatory exudate, and infiltration of hepatic cells with polymorphs and monocytes. Haematoxylin and eosin, $\times 300$.

FIG. 3.—Mouse liver showing *Ery. monocytogenes* in large numbers in the inflammatory exudate. Gram's stain, $\times 1,150$.

Haemolysin Production.—Neither strain showed evidence of soluble haemolysins for horse or sheep red blood cells.

Agglutination and Agglutinin Absorption Tests.—Specific antisera were prepared in rabbits against both strains, and against a type specific strain of *Ery. monocytogenes* No. 7974 obtained from the National Collection of Type Cultures. The results of cross-agglutination tests are shown in Table I, in which the titre of each serum for its homologous strain as well as for the heterologous strains is recorded. Readings were made after four hours in a 53° C. water-bath, and again after standing overnight at room temperature. No change in end-point was detected at the second reading. Two strains of *Ery. rhusiopathiae* did not agglutinate with any of the specific antisera.

TABLE I
RESULTS OF AGGLUTINATION TESTS

Antiserum	Antigen		
	Strain 1	Strain 2	7974 (N.C.T.C.)
Strain 1	10,000	10,000	10,000
" 2	10,000	10,000	10,000
" 7974	5,000	5,000	5,000

Absorption of agglutinins was carried out for each strain. The absorption experiments, as is shown in Table II, indicate that, while strain 1 and type specific strain 7974 are antigenically similar, strain 2 shows some antigenic difference.

TABLE II
RESULTS OF ABSORPTION EXPERIMENTS

Antiserum	Absorbing Antigen	Agglutinable Antigen		
		Strain 1	Strain 2	7974 (N.C.T.C.)
Strain 1	Strain 1	0	0	0
" 1	" 2	1,000	0	1,000
" 1	" 7974	0	0	0
" 2	" 1	0	0	0
" 2	" 2	0	0	0
" 2	" 7974	0	0	0
" 7974	" 7974	0	0	0
" 7974	" 1	0	0	0
" 7974	" 2	1,000	0	1,000

Pathogenicity.—A rabbit inoculated with approximately 90 million organisms of strain 2 died overnight with confirmed septicaemia. A similar dose of strain 1 gave rise to a prolonged illness followed by recovery. Instillation of pure suspensions of the strains into the conjunctivae of rabbits produced a severe conjunctivitis within 36 hours.

Intraperitoneal inoculation of white mice gave varied results. Mice which received approximately

9 million organisms were not affected. When the inoculum was increased ten-fold death occurred in from 24 hours to six days. The organism was readily recovered from the heart blood, spleen, and liver. Several mice which survived for more than two or three days showed at necropsy multiple focal necroses of the liver. On histological section these lesions were surrounded by a rim of neutrophils and monocytes with numerous intra- and extra-cellular Gram-positive cocco-bacilli (Figs. 2 and 3).

Production of Monocytosis.—Both strains produced a circulating monocytosis in rabbits. Intravenous inoculation of strain 1 produced a monocytosis rising from 6% (pre-injection count) to 30% in four days. With strain 2 the monocyte count rose from 6% to 22% in five days.

Antibiotic Sensitivity.—The strains were tested by the serial-dilution method and were found to be resistant to sulphamezathine (> 20 mg. per ml.) and sensitive to penicillin (0.2 unit per ml.), chloramphenicol (5 µg. per ml.), chlortetracycline (0.4 µg. per ml.), oxytetracycline (0.5 µg. per ml.), and streptomycin (5 units per ml.).

Discussion

Ery. monocytogenes was first isolated in July, 1924, by Murray, Webb, and Swann (1926) from a rabbit and guinea-pig epizootic in Cambridge. In August, 1925, Pirie (1927) in South Africa cultivated a similar organism from a plague-like disease of gerbilles. Since then *Ery. monocytogenes* has been isolated from 27 animal species and its presence has been recorded in 26 countries. It is the cause of a specific infectious and often fatal disease in sheep, cattle, rabbits, guinea-pigs, and chickens. It has also been isolated from the canary, fox, pig, goat, chinchilla, racoon, lemming, ferret, vole, and rat. In ruminants the disease is characterized by encephalitis, and in rodents and chickens by septicaemia.

Although the organism appears to be of worldwide distribution and enzootic in the United States, England, New Zealand, and Germany, relatively few cases of human infection have been recorded. The part played by animals as a reservoir of infection for human beings has not been determined. With the exception of the placenta and vagina as probable routes of infection in the newborn, little is known of the mode of transmission in man.

As in previously recorded cases, we were unable to ascertain the source of infection. No connexion could be found between the two cases, and, since the strains showed some antigenic difference, it is

unlikely that they had a common source. Case 1, who worked as a packer for a pharmaceutical firm in Loughborough, stated that although he had bred rabbits 20 years previously he could not recall having had any contact with pets or domestic animals within the few months preceding his illness. He admitted, however, that there were one or two mole runs in his garden, and that on November 5, five or six days before the onset of his illness, he had been examining with his fingers the ramifications of a hole made by a mole. It was not possible to obtain any moles from the patient's garden, but one of us (N. S. M.) examined 50 moles from different parts of the county without finding any evidence of infection. Case 2, an engineer, lived in lodgings in Leicester and had not been out of the city for one month before his illness. His landlady's grandson had bought a golden hamster at Christmas from a pet shop. The animal was kept at home, partly in the front room and partly in a shed in the garden, where it died early in January. The hamster was put in a sealed container and buried in the garden. Although the patient had never personally fed or handled it, the animal was exhumed on January 15 and dissected with negative results. There was no evidence of rodents in the house or at his place of work, and he had no known contact with other birds or animals.

Both cases presented with classical signs of meningitis. The intensity and duration of the headache (six days in Case 1 and 10 days in Case 2) were striking features, and together with the drowsiness give a picture of an illness which was pursuing a slightly different course from the usual case of bacterial meningitis under treatment.

Summary

Two cases of meningitis due to *Ery. monocytogenes*, affecting adult males and occurring in Leicestershire within the space of eight weeks, are described.

Both cases recovered after treatment with penicillin, streptomycin, chloramphenicol, and sulphamezathine.

The bacteriological findings are described.

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REFERENCES

- Gibson, H. J. (1935). *J. Path. Bact.*, **41**, 239.
- Kaplan, M. M. (1945). *New Engl. J. Med.*, **232**, 755.
- Murray, E. G. D. (1955). *Canad. med. Ass. J.*, **72**, 99.
- Webb, R. A., and Swann, M. B. R. (1926). *J. Path. Bact.*, **29**, 407.
- Pirie, J. H. H. (1927). *Publ. S. Afr. Inst. med. Res.*, **3**, 163.
- Webb, R. A., and Barber, M. (1937). *J. Path. Bact.*, **45**, 523.
- Wright, H. A., and Macgregor, A. R. (1939). *Ibid.*, **48**, 470.