Fatal Case of *Pasteurella pseudotuberculosis* Infection Associated with Hepatic Cirrhosis

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Human infection with *Pasteurella pseudotuberculosis* may appear as a benign acute mesenteric lymphadenitis or as a septic typhoid-like illness with enlargement of the liver and spleen and an almost uniformly fatal outcome. The benign form was first described by Knapp and Masshoff (1954) and numerous cases have since been recognized. There are few reports of the septicaemic disease, the first and for a long time the only recognized form of the infection in man. Knapp (1959) could find records, chiefly by American and Continental workers, of only some 15 authenticated cases between 1910 and 1952. Mollaret *et al.* (1964) traced one more case and added one of their own. So far as we know the case described here is the first to be reported in Britain.

CASE REPORT

The patient was licensee of a public house from 1956 until his death on 9 February 1965 at the age of 51. He was first admitted to hospital on 21 February 1962 with a three-months history of anorexia, flatulence, abdominal swelling, and occasional vomiting and epistaxis. During the previous four years he had drunk 5 pints (2.8 litres) of beer daily.

Examination showed massive ascites with a paraumbilical hernia and oedema of the lower abdominal wall and legs. The liver was enlarged four fingerbreadths below the right costal margin, hard, and irregular but not tender. The spleen was palpable.

Investigations.—Liver-function tests were compatible with the clinical diagnosis of hepatic cirrhosis, probably alcoholic. (Serum bilirubin 2.2 mg./100 ml., thymol turbidity 8 units, colloidal gold strongly positive, alkaline phosphatase 10.5 King-Armstrong units/100 ml., serum albumin 2.6 g./100 ml., serum globulin 4.6 g./100 ml., prothrombin concentration 52%.) The fasting blood sugar was raised to 210 mg./100 ml., with glycosuria but no ketonuria; blood urea was 20 mg./100 ml. Paracentesis abdominis yielded a litre of straw-coloured fluid.

He was discharged on 5 March 1962 on a high protein and carbohydrate diet with salt restriction; treatment with chlorothiazide was continued at home. He was strongly advised to abstain from alcohol, but did not do so.

He was readmitted in coma on 17 December 1963 and again on 21 January 1964. After discharge on 21 February he remained well until his next admission as an emergency case on 2 January 1965, having developed a sore throat, cough, and rigors three days previously. He was drowsy and disorientated, with a temperature of 102.8° F. (39.3° C.) and a purulent tonsillitis. There was faint icterus and minimal finger tremor, but ascites was not marked. (Blood urea 100 mg., serum bilirubin 1.3 mg., thymol turbidity 2.4 units, colloidal gold negative, alkaline phosphatase 7.5 K.-A. units, serum albumin 2.7 g., serum globulin 2.8 g., prothrombin concentration 50%.) He responded to treatment with benzylpenicillin and tetracycline, followed by cloxacillin, and returned home on 11 January 1965.

His final admission was on 2 February 1965, when he was referred because of drowsiness, confusion, and anorexia. He was icteric, with palmar erythema, spider naevi, and gynaecomastia. The ascites had increased and he had a flapping tremor. (Blood urea 67 mg., serum bilirubin 3.0 mg., colloidal gold strongly positive, alkaline phosphatase 8.0 K.-A. units, serum albumin 2.3 g., serum globulin 3.6 g., W.B.C. count 23,000/cu. mm., with 88% neutrophils.) He was treated with intravenous glucose, diuretics, tetracycline for two days, followed by cloxacillin for four days and finally neomycin. Six days after admission he suddenly collapsed with an unrecordable blood pressure and pulse. Despite

blood transfusion and stimulants he died 24 hours later, on 9 February 1965.

NECROPSY REPORT

Necropsy was performed 14 hours after death. The body was that of a well-nourished male. The skin was deeply jaundiced and the abdomen protuberant. No free fluid was present in the pleural cavities and pericardial fluid was not increased. The heart was of normal size; myocardium, valves, and coronary arteries seemed normal. The air passages and lungs appeared normal apart from pulmonary venous congestion. The abdomen contained a large effusion of straw-coloured slightly turbid fluid. The gastrointestinal tract was normal apart from the presence of fluid faeces in the colon. The liver showed moderately advanced portal cirrhosis complicated by the presence of multiple abscesses up to 1 cm. diameter and containing greenish pus; these were randomly distributed throughout the organ. The gall bladder contained several small mixed calculi but was not inflamed, and the common bile duct showed no evidence of obstruction or inflammation. The portal vein appeared normal. The spleen was moderately enlarged and softened. The kidneys were swollen, congested, and oedematous.

Sections from the lungs showed pulmonary venous congestion with a few very small areas of early bronchopneumonia.

Sections from the liver showed a coarse multilobular cirrhosis, the portal tracts presenting fibrosis and bile-duct proliferation. The hyperplastic liver-cell nodules showed numerous small abscesses containing pus cells and remains of necrotic liver cells. There were occasional large foci of liver-cell necrosis surrounded by a zone of infiltration by neutrophil leucocytes. In the centre of some abscesses masses of organisms were seen staining bluish with haematoxylin; with methylene blue they were seen to be very short rods. There was no evidence of haemochromatosis, pylephlebitis, or cholangitis, though there was apparent agonal clotting in some small veins.

BACTERIOLOGY

Past. pseudotuberculosis was isolated in pure culture from one of the liver abscesses. The organisms were small oval Gram-negative rods, motile at 22° C. but not at 37° C. Growth was good on nutrient agar, horse blood agar, and MacConkey agar at 37, 30, and 22° C. On deoxycholate-citrate agar growth was poor at 37° C. but better at 30 and 22° C. Growth on blood agar produced no haemolysis but some browning of the medium. Colonies at 22° C. were smaller and emulsified more smoothly than growth at 37° C. In nutrient broth at 37° C. there was a stringy deposit with slight turbidity and a ring of growth at the top, while at 22° C. growth was more diffuse.

Biochemical reactions: acid without gas formed after 18 hours at 30° C. in glucose, maltose, mannitol, rhamnose, laevulose, mannose, dextrin, trehalose, and xylose, and later in sorbitol, glycerol, galactose, arabinose, and salicin; lactose, dulcitol, sucrose, inositol, inulin, adonitol, cellobiose, and raffinose not fermented after 14 days; fermentation of glucose in Hugh and Lefson's (1953) medium; methyl-red positive, Voges-Proskauer negative, no growth in Koser's citrate or Møller's KCN broth; indole, H₂S, and decarboxylases for lysine, ornithine, and arginine not produced; gelatin not liquefied; oxidase negative (Kovács, 1956); catalase and urease produced; nitrates and methylene blue reduced, and aesculin hydrolysed. With the use of Mast sensitivity disks the culture was sensitive to ampicillin (10 µg.), chloramphenicol (25 µg.), and streptomycin (10 µg.); less sensitive to tetracycline (10 µg.) and benzylpenicillin (1 unit); and resistant to sulphafurazole (200 µg.). Serological tests showed that the strain belonged to type 1A.

A guinea-pig inoculated intramuscularly with 0.5 ml. of an overnight broth culture died six days later. At necropsy there were enlarged lymph nodes near to the site of injection in the leg and also in the abdomen; innumerable white nodules were present in the spleen and liver and a few nodules in the lung. No organisms were seen on direct smears of the spleen and liver, but culture yielded a heavy growth of *Past. pseudotuberculosis* type 1A from both organs. Histological examination of the liver, spleen, and lung showed miliary abscesses with central clumps of organisms surrounded by polymorphs and mononuclear cells.

EPIDEMIOLOGICAL INVESTIGATION

The patient's family comprised his wife, aged 55, and two married daughters, aged 25 and 21, both living away from home but visiting their parents frequently. The patient kept a dog—a Lakeland terrier—and budgerigars. The dog had been with the family three years, had no history of illness, but frequently bites, and had bitten the patient some time before his last illness. A budgerigar bought in the summer of 1964 was kept at the patient's home until a month after his death, when it was taken to the home of his elder daughter and has remained there. This bird had always been healthy. About a year before the patient's death another budgerigar, which had been kept at his home, was also given to his elder daughter. This budgerigar was found dead three or four days after the patient died; no specimens were available for examination.

Faeces specimens from his wife, the elder daughter, the dog, and the healthy budgerigar were cultured for *Past. pseudotuberculosis* with negative results on deoxycholate-citrate agar and on a selective medium (Morris, 1958). Agglutination tests with serum from the wife, the two daughters, and the dog were carried out by the technique described by Mair *et al.* (1960) against suspensions of a stock strain of *Past. pseudotuberculosis* 1A and that isolated from the patient (see Table). Negative results were obtained from the wife and the younger daughter. The serum of the elder daughter and the dog showed significant titres against both suspensions. Two members of the family—the wife and elder daughter—were inoculated intradermally with *Past. pseudotuberculosis* skin-test antigen. The wife showed no reaction after 24 and 48 hours, but the elder daughter had a positive result (erythema 22 mm.; induration 10 mm.) 24 hours after the injection. A month after the intradermal test, serum from the elder daughter showed a slight rise in titre (see Table). Both the elder daughter and the dog were perfectly well, and gave no history of recent illness.

Agglutination Reactions of Blood Serum from Family Contacts and Dog

Sera	Date of Test	Serum Agglutination Titre with <i>Past. pseudotuberculosis</i> Type 1A	
		Stock Strain	Patient's Strain
Wife	15/3/65	< 20	< 20
	27/4/65	< 20	< 20
	25/5/65*	< 20	< 20
Elder daughter ..	15/3/65	320	1,280
	29/4/65	80	160
	25/5/65*	160	320
Younger daughter..	15/3/65	< 20	< 20
	29/4/65	< 20	< 20
Dog	17/3/65	160	640

* Serum taken a month after intradermal test.

COMMENT

Diagnosis of *Past. pseudotuberculosis* infection during life is not easy. The clinical picture is that of an acute septicaemic disease. Subicterus or frank icterus has been noted in about half the cases and a painful hepatomegaly in about three-quarters. In a few cases *Past. pseudotuberculosis* has been cultivated from the blood during life, but more often the diagnosis has been made at necropsy when, as in the present case, the organism has been isolated from the numerous

abscesses found in the liver (Knapp, 1959). It is likely that earlier diagnosis could be made and more cases of this infection recognized if the blood of patients suffering from obscure septicaemic disease was examined for antibodies to *Past. pseudotuberculosis*.

In contrast to the benign mesenteric form which shows a predilection for children and young people, the septic form affects the elderly, particularly males, and may be associated with alcoholism, diabetes, and haemochromatosis (Mollaret *et al.*, 1964). In the above case it was associated with cirrhosis of the liver, mild diabetes, and alcoholism.

The epidemiology remains obscure, though the occurrence of infection in a variety of animals suggests an animal source (Thal, 1954; Girard and Chevalier, 1955; Mair, 1965). In the septic type of pseudotuberculosis no association with animals has hitherto been established, whereas in the family outbreak of acute mesenteric lymphadenitis described by Randall and Mair (1962) serological evidence of infection was found in the pet dog as well as in three other members of the patient's family. The family of one of the three cases reported by Mair *et al.* (1960) kept a budgerigar. In the case we have reported, a daughter of the patient and the dog, which had bitten the patient some time before his death, showed serological evidence of infection.

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- J. D. MACAULAY,* M.A., B.M., B.CH., D.PATH.,
Assistant Pathologist, Salford Royal Hospital, Salford.
J. A. C. WILSON, M.B., CH.B., M.R.C.P., M.R.C.P.ED.,
Consultant Physician, Salford Hospital Group, Salford.
J. D. ABBOTT, M.D., DIP.BACT., M.C.PATH.,
Consultant Bacteriologist, Public Health Laboratory,
Withington Hospital, Manchester 20.
N. S. MAIR, M.B., CH.B., D.C.H., D.P.H., DP.BACT., F.C.PATH.,
Director, Public Health Laboratory, Groby Road Hospital,
Leicester.

* Present address: Cornwall General Hospital, Cornwall, Ontario, Canada.

REFERENCES

- Girard, G., and Chevalier, A. (1955). *Ann. Inst. Pasteur*, **88**, 227.
Hugh, R., and Leifson, E. (1953). *J. Bact.*, **66**, 24.
Knapp, W. (1959). *Ergebn. Mikrobiol.*, **32**, 196.
— and Masshoff, W. (1954). *Disch. med. Wschr.*, **79**, 1266.
Kovács, N. (1956). *Nature (Lond.)*, **178**, 703.
Mair, N. S. (1965). *J. Path. Bact.*, **90**, 275.
— Mair, Hélène J., Stirk, E. M., and Corson, J. G. (1960). *J. clin. Path.*, **13**, 432.
Mollaret, H. H., Temkine, J., Prade, M., Pieron, R., Destombes, P., and Guillon, M. C. (1964). *Presse méd.*, **72**, 2671.
Morris, E. J. (1958). *J. gen. Microbiol.*, **19**, 305.
Randall, K. J., and Mair, N. S. (1962). *Lancet*, **1**, 1042.
Thal, E. (1954). *Untersuchungen über Pasteurella pseudotuberculosis*, Lund.