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Brain Abscess and Meningitis Caused by a Diphtheroid Resembling *Corynebacterium ulcerogenes.*

WILLIAM E. CLAPPER AND JOHN H. CARLQUIST. (Introduced by L. P. Gebhardt.)

From the Departments of Bacteriology and Pathology, University of Utah, School of Medicine, Salt Lake City, Utah.

Rare cases of meningitis and brain abscesses caused by other organisms than the meningococcus, pneumococcus, streptococcus, tubercle bacillus and Pfeiffer's bacillus have been reported from time to time. Topley and Wilson[1] mention *B. anthracis, E. coli,* and Friedlander's bacillus among others as an infrequent cause of meningitis. *Actinomyces bovis* has been found in an abscess of a child's brain,[2] and *Brucella suis* was incriminated by Hansmann and Schenchen.[3] *Bacterium enteritidis,*[4] as well as *Neisseria gonorrheæ,*[5] has been shown to be the cause of meningitis. In 1936, a filterable virus was suggested as the cause of suppurative meningitis.[6] Recently the supposedly non-pathogenic *S. marcescens* has been isolated from a case of meningitis.[7]

There are relatively few references in the literature to diphtheroids as the cause of meningitis. Two such cases have been reported[8,9] in which the causative organism was similar to the one herein described with respect to pathogenicity to laboratory animals, but was different in certain other important respects.

Kessel and Romanoff reported an organism which they classified as *Corynebacterium hoffmanni* as the cause of a case of meningitis.[10] Schultz, Terry, Bruce and Gebhardt[11] reported the isolation of an organism from a case of meningoencephalitis which they named *Corynebacterium parvulum,* but which later proved to be *Listerella monocytogenes.* This bacterium was fatal within 72 hours when given intravenously or intracerebrally to rabbits, mice, guinea pigs, and rhesus monkeys. Gibson[12] isolated a diphtheroid bacillus from a fatal case of meningitis which was highly virulent for guinea pigs, rabbits, rats, and mice when given intraperitoneally or intravenously.

Experimental. The organism to be described in this paper was isolated repeatedly in pure culture from a brain abscess and spinal fluid of a 7-year-old child who was under observation from December, 1943, to July 1, 1944, at which time she expired.

Pathology. Microscopic sections of the brain tissue showed only necrosis and a non-specific inflammatory reaction.

Bacteriology. Smears made from the abscess pus repeatedly showed the presence of organisms having the characteristics described below. No organisms were seen in eosin-hematoxylin stains of histological sections.

Aerobic and anaerobic cultures as well as guinea pig inoculations were made, using the pus from the brain abscess and spinal fluid. The guinea pigs remained normal. The only organism isolated was found growing aero-

1 Topley and Wilson, *Principles of Bacteriology and Immunology,* 2nd Ed., Wm. Wood and Company, p. 1146.

2 D'Ewart, John and Dawson, George D., *Brit. Med. J.,* 1927, **1**, 718.

3 Hansmann, G. H., and Schencken, J. R., *Am. J. Path.,* 1932, **8**, 435.

4 Stevenson, F. N., and Wells, L. K., *Lancet,* 1933, **225**, 1084.

5 Strumia, M. M., and Kohlhas, J. J., *J. Inf. Dis.,* 1933, **53**, 212.

6 Rivers, T. M., and Scott, T. F. M., *Science,* 1935, **81**, 439.

7 Aronson, J. D., and Alderman, *J. Bact.,* 1943, **46**, 261.

8 Dick, G. F., *J. A. M. A.,* 1920, **74**, 84.

9 Miller, M. K., and Lyon, M. W., Jr., *Am. J. M. Sc.,* 1941, **162**, 593.

10 Kessel, Leo, and Romanoff, Alfred, *J. A. M. A.,* 1930, **94**, 1647.

11 Schultz, E. W., Terry, M. C., Bruce, A. T., Jr., and Gebhardt, L. P., PROC. SOC. EXP. BIOL. AND MED., 1933, **31**, 1021.

12 Gibson, H. J., *J. Path. and Bact.,* 1935, **41**, 239.

bically, and was a Gram positive rod resembling those of the genus Corynebacterium.

The organism isolated repeatedly from the patient showed the following:

Morphological and Staining Characteristics. When grown on blood agar for 48 hours at 37°C and stained with methylene blue, rods varying from 1 to 5 μ long by 0.5 to 1 μ wide were observed. Some curved and coccoid forms were present, but most were straight rods. Clubbing was observed, the clubs appearing at one end only. Two to 3 beads were seen in many of the bacteria. The appearance closely resembled the true diphtheria bacillus. However, no palisade formation and but few V and W forms were observed.

Smears made from Loeffler's medium and stained with methylene blue were more uniform in size than were those from the blood agar. The coccobacillary type predominated and there was no clubbing. Few granules were in evidence. Gram stains of smears from cultures on Loeffler's medium were Gram positive. A tendency to be in parallel pairs was noted in this and other stains. This seems quite characteristic for the organism. Neisser's stain showed nothing more than did methylene blue.

A Gram stain of the surface growth of a 48-hour Veillon agar stab showed coccobacillary forms predominating, many of which were in pairs. Granules at both ends of the rods were observed in many. The majority of the organisms retained the stain. A stain made from organisms taken from the bottom of the stab showed more rod-like bacteria, larger than those taken from the top, and with more clubbing and more bizarre forms in evidence.

The stained organism appeared about the same when grown on plain agar as when grown on Loeffler's medium. They are not acid fast, non-motile, non-capsule forming, and do not form spores.

Growth Characteristics. This organism is a facultative anaerobe with an optimum temperature for growth at 35-37°C, but will grow scantily at room temperature. It is not fastidious in its nutritive requirements and grows on all of the ordinary laboratory media. Growth was rather scant on plain agar after 24 hours, but in 48 hours, it was good. The colonies are small, round, and white. Microscopically they appear to have a granular surface. The edges are smooth and entire. There was no apparent change in colony formation after being transferred every week for several months on nutrient agar slants.

Colonial growth on Loeffler's medium was about the same as on plain agar, with pinpoint, discrete, white, entire colonies being produced. On blood agar, however, a somewhat larger colony was produced. These colonies are greyish white, moist, convex, and of a butyrous consistency. No zone of hemolysis was seen. Under low power the colonies appeared round and smooth. The colonies on chocolate agar showed little difference from those on whole blood agar. Tellurite agar allowed only slight growth, but the colonies were definitely blackened.

A Veillon agar stab was made which showed a thin, filmy villous growth along the stab in 48 hours. The growth became less toward the bottom of the tube. On gelatin a scant growth was seen on the surface after 9 days and no liquefaction took place.

Growth in plain broth was scant in 24 hours, but good in 48 hours. The broth was turbid with a stringy sediment. On first isolation in peptone media, no growth was seen. However, growth was obtained in this medium in 48 hours after the bacterium had been growing on other media in the laboratory for several months. Tryptose phosphate broth produced a cloudy, stringy growth in 24 hours at 37°C. A synthetic broth composed of glucose, $NaNH_4HPO_4$, $MgSO_4$, and K_2HPO_4 would not support visible growth. Stained smears showed swollen, oval, and other pleomorphic forms.

Biochemical Reactions. No indole was produced from peptone and nitrates were not reduced. The methyl red and V.P. tests were negative. Catalase was produced after 48 hours. Lead acetate showed no blackening. No active dehydrogenases for lactic acid, glucose, maltose, sucrose, or glycerol could be demonstrated. However, methylene blue was reduced in nutrient agar in 18 hours.

Litmus milk was neither coagulated, re-

TABLE I.

Mg/ml	Sulfanilamide .25	.12	.06	.006	Sulfamerazine .25	.12	.06	.006	Sulfasuxadine .25	.12	.06	.006	Sulfaguanidine .25	.12	.06	.006
24 hr	—	—	+	+	—	—	—	+	—	—	+	+	—	+	+	+
48	—	+	+	+	—	—	—	+	—	+	+	+	—	+	+	+
72	—	+	+	+	—	—	+	+	—	+	+	+	—	+	+	+
96	—	+	+	+	—	—	+	+	—	+	+	+	+	+	+	+

\+ equals growth as determined by visible cloudiness
— equals no growth.

duced, nor was acid or base formed in 10 days Of the carbohydrates, dextrose, and levulose alone were fermented, producing acid but no gas. Sucrose, lactose, maltose, galactose, salicin, dextrin, mannitol, and glycerin were not attacked. Starch agar plates when treated with iodine showed a reddish to clear zone around most of the colonies.

Inhibiting Agents. Penicillin produced in our laboratory when added to nutrient broth in a concentration of 6 units per ml, failed to inhibit the growth of this organism, while 0.03 unit per ml inhibited the growth of staphylococci.

Neither did 7 mg per ml of sulfanilamide nor 1 mg per ml of sulfaguanidine inhibit growth when added to nutrient broth. However, using peptone as the test medium, the results in Table I were observed.

All 4 of the sulfa drugs dissolved in peptone broth in a concentration of 0.25 mg per ml inhibited the growth of the organism for at least 72 hours. Sulfamerazine was the most effective and sulfaguanidine the least effective.

Pathogenicity for Animals. Intracerebral inoculation of mice with 0.03 ml of a 24-hour broth culture of the growing organisms produced no symptoms. The brains were removed after 3 weeks and no organisms could be demonstrated. The brains appeared to be normal. Similar results were obtained when .15 ml of the organism suspended in saline was injected intracerebrally into guinea pigs and hamsters.

Intraperitoneal inoculations of guinea pigs and mice with 1 ml of 24-hour broth culture were without effect. Inoculation of a rabbit intravenously with 0.5 ml of a 24-hour broth culture showed negative results. There was no evidence of infection at the point of inoculation. This organism appears to be of a very low order of pathogenicity.

Discussion. Repeated examination of the purulent material from the brain abscess failed to show acid-fast organisms. Examination of tissues showed no evidence of tuberculosis or actinomycosis. The organism described was isolated in pure culture several times from the abscess of the brain and finally from the spinal fluid. The evidence available indicates that this organism was the causative agent of the abscess and the meningitis.

Although the organism resembles *C. diphtheriæ* in some of its morphological and cultural characteristics, it differs in the following important respects:

(1) No clubbing and little granule formation was seen when the organism was grown on Loeffler's medium. This is the medium of choice for morphological comparison within this genus.

(2) This diphtheroid grows readily on plain nutrient agar, while the true diphtheria bacillus does not.

(3) No pellicle was produced by the diphtheroid.

(4) No zone of hemolysis was shown when grown on human or rabbit blood agar. Some strains of the true diphtheria organism also show no hemolysis.

(5) This organism resembles the mitis type of diphtheria organism most when grown on tellurite, but is a uniform black with no gray portion.

(6) The fermentation reactions were not typical of the diphtheria organism.

(7) This organism was non-pathogenic to laboratory animals.

It is in accord with all the properties which Bergey's manual lists for *Corynebacterium ulcerogenes* with the exception of sucrose fermentation. *C. ulcerogenes* is listed as pro-

ducing acid with sucrose. The organism herein described does not. *C. ulcerogenes* was once isolated from ulcers of the skin in a man. It was non-pathogenic for animals. This is apparently the first time an organism with the characteristics given has been isolated from a brain abscess or a case of meningitis. It is of peculiar interest because of the low order of pathogenicity exhibited in the case described and in the laboratory animals, but yet possesses what was apparently the ability to cause an abscess and meningitis in a child.

Summary. An organism resembling *Corynebacterium ulcerogenes* was isolated repeatedly in pure culture from a brain abscess and spinal fluid of a 7-year-old child. The morphological and biochemical characteristics of the organism were determined, and found to be culturally identical to *C. ulcerogenes*. It was found to be resistant to penicillin, *in vitro*, but inhibited in growth by sulfanilamide, sulfamerazine, sulfasuxidine, and sulfaguanidine. Sulfamerazine was the most effective. The organism was non-pathogenic to guinea pigs, white mice, rabbits, and hamsters, irrespective of the route of inoculation.

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Fumaric Acid Salts as Hydrogogue Cathartics.*

CHARLEY J. SMYTH, ROBERT BRUNDAGE, JAMES M. ORTEN, AND ARTHUR H. SMITH.

From the Department of Medicine, Wayne County General Hospital, and the Department of Physiological Chemistry, Wayne University College of Medicine, Detroit.

The alkali metal salts of certain organic acids, notably tartaric and citric acids, have been used for many years as cathartics and for certain other therapeutic purposes. Since the beginning of the present war, tartaric acid has become difficult to obtain and the supply of other commonly used organic acids has been somewhat curtailed. Hence, a search for satisfactory substitutes has been instituted and fumaric acid has been suggested as a likely possibility. It is similar in chemical structure to tartaric acid, is available in large amounts at a moderate cost, and is a "physiological" substance in the sense that it occurs naturally in animal tissues.[1]

The present study was undertaken to determine the laxative effects of fumarates and is a part of a larger study designed to determine the general effects of the administration of fumarates, in varying doses, to different species of animals. The only other extensive published data on the laxative effects of fumarates found in the literature are those of Gold and Zahm[2] who compared the laxative potency of fumarates, sodium tartrate, and magnesium acid citrate in constipated human subjects and showed that the laxative efficacies of the fumarates of sodium, calcium, and magnesium are approximately the same and that these 3 also possess approximately the same laxative potency as sodium tartrate and magnesium acid citrate, gram for gram.

Methods. The subjects chosen for this study were either ambulant or bed patients hospitalized for chronic disease at the Wayne County General Hospital. Many of them had hypertrophic or rheumatoid arthritis, heart disease, Parkinson's Disease, or other afflictions which required institutional care. All the patients volunteered for this study. Each patient had chronic constipation with a long history of dependence on some form of laxative. The patients were considered constipated after 3 or more days without a bowel movement.

The 4 preparations studied, magnesium fumarate, calcium fumarate, sodium fumarate, and Rochelle Salts, were administered by dis-

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[1] Annau, E., *et al., Z. f. physiol. Chem.*, 1935, **236**, 1; 1936, **244**, 105.

[2] Gold, H., and Zahm, W., *J. Am. Pharm. Assn.*, 1943, **32**, 173.