THE ENTEROCOCCI: WITH SPECIAL REFERENCE TO THEIR ASSOCIATION WITH HUMAN DISEASE

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During the past 15 years, when beta hemolytic streptococci of Lancefield's (1933) groups A and C were subjects of investigation in this laboratory, strains of group D were acquired from time to time and were included in the comparative studies. In this paper they will be called enterococci, a term first used by Thiercelin (1899).

Because the enterococci have been found to be resistant to the sulfonamides and to penicillin, and because the doctor wants to know as early as possible in the course of a disease what kind of treatment is indicated, the importance of the recognition of the enterococci has increased in recent years.

Sherman and his collaborators (1931, 1937, 1943) studied the enterococci extensively, and Sherman (1937) published a review of the literature. Their studies included few pathogenic strains, and the review did not include a full consideration of the incidence of enterococci in human disease.

THE HARDINESS OF ENTEROCOCCI

Sherman (1938) reported other distinguishing characteristics of the enterococci in addition to precipitation in serum of group D—namely, the ability to grow at 10°C and 45°C; survival at 60°C for 30 minutes; and tolerance for inhibitory substances, as shown by ability to grow in the presence of 6.5 per cent sodium chloride, 0.1 per cent methylene blue, or 40 per cent bile.

The tolerance of the enterococci for inhibitory substances is of practical importance. A high degree of resistance to the sulfonamides was reported by Bliss and Long (1937), Long and Bliss (1938), Neter (1938, 1940), Helmholz (1937, 1941), Francis (1941), Rantz and Kirby (1943), and MacNeal and Blevins (1945).

In his original paper on the inhibitory action of penicillin on many species of bacteria, Fleming (1929) noted that enterococci were resistant to it. This finding was confirmed by later investigators (Bornstein, 1940; Heilman and Herrell, 1942; McKee and Rake, 1942; Watson, 1944; White and Sherman, 1944; MacNeal and Blevins, 1945).

THE SOURCES OF THE STRAINS OF OUR COLLECTION

Our collection contained 23 strains from human pathologic sources and 11 strains from other sources, included for comparison. Three of the latter were from the stools of normal human subjects; one was from a normal human throat; two were from different pooled lots of human plasma; one was from an unknown human source; one was isolated from milk powder and one from pasteurized...
milk; one was from the diseased lung of a dog; one, received from the American Type Culture Collection, had a history of having been isolated from pus from a horse with strangles. The authenticity of this origin is questionable, because the strain came indirectly from the original investigator and was labeled "S. equi."

Some of the strains listed in table 1 are duplicates from the same patient. It appears that more than one of the strains (nos. 1188, 1308, 1355, and 1357) that were received from Dr. Sherman may have been isolated at different times from the same patient, because, according to Sherman, Stark, and Mauer (1937), S. zymogenes was isolated on various occasions from one subject. Strains 1332 and 1333 were originally the same strain, one of the branches having had a history of undergoing variation in its ability to hemolyze blood.

THE CHARACTERISTICS OF THE ENTEROCOCCI

The strains included in table 1 belonged to group D, according to Lancefield's precipitin test; all grew at 10 C and 45 C; all grew in media containing 6.5 per cent NaCl and in media having an initial pH value of 9.6; all tested strains (31) grew in media containing 40 per cent bile; all hydrolyzed esculin; none hydrolyzed starch; all attained a final pH of 4.4 or lower in glucose broth, except one (no. 945) which produced a final pH of 4.6; all strains fermented maltose; of 27 strains tested, all fermented salicin; of 29 strains tested, all fermented trehalose. None of 25 tested strains fermented dulcitol or inulin.

The characteristics which were common to all strains are omitted from table 2, which includes those reactions which showed interesting differences between strains. Omitted from the table are the following reactions: hydrolysis of sodium hippurate, production of ammonia in 4 per cent peptone, and virulence for mice. These reactions appeared not to be correlated with significant characteristics.

Though not considered in table 2, a general statement in regard to the virulence of the enterococci for mice may be of interest. Mice were injected intraperitoneally with broth cultures, which had been inoculated very lightly by platinum needle and incubated for about 11 hours. Two strains killed mice in $10^{-2}$ dilution; 22 killed in $10^{-1}$ dilution but not in higher dilutions; 9 strains failed to kill in the $10^{-1}$ dilution. According to these results, the virulence of enterococci for mice is low as compared with the virulence of many strains of streptococci of groups A and C.

Uncorrelated with characteristics which appeared to be significant for classification purposes are the following, listed in table 2: type of hemolysis; liquefaction of gelatin; sensitivity to bacteriophage D$_2$-1188; production of acid from lactose, arabinose, and raffinose. The characteristics of distinction were found to be agglutinative reactions, sensitivity to phage D-693, growth in milk containing 0.1 per cent methylene blue, survival at 60 C for 30 minutes, and production of acid from sucrose, mannitol, and sorbitol. In the study of a larger series of strains, the production of acid from glycerol might be found to be of some significance.
## TABLE 1

*Histories of streptococcal strains of group D*

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*Note: *Strangles?* indicates a possible designation for Strangles.*
TABLE 1—Continued

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* The authenticity of the source of strain 945 is questioned (see the text).
† Strains 1332 and 1333 were from the same patient.

TESTS FOR THE DIFFERENTIATION OF ENTEROCOCCAL SPECIES

According to the key in the fifth edition of *Bergey’s Manual* (1939) liquefaction of gelatin and hemolysis are considered to be distinctive characters, on which the differentiation of enterococcal species is based. Sherman, Stark, and Mauer (1937) mentioned the “thin and shaky boundaries” which separate the “supposed” enterococcal species, but Sherman (1938) recognized 3 species which he differentiated on the basis of the two characteristics mentioned above.

Durand and Dufourt (1923) reported that they found a precise correlation between liquefaction of gelatin and agglutinative reactions. According to other investigators, however, liquefaction of gelatin is an unstable property of no significance in classification. Houston (1934) noted that the action of bacteriophage may alter the gelatin-liquefying property. Elser and Thomas (1936) found gelatin-liquefying strains of enterococci which agreed well with nonliquefying strains in cultural and biochemical properties. Wheeler and Foley (1943) stated that biologic characteristics of enterococci could not be correlated with serologic type.

Lack of correlation between liquefaction of gelatin and significant characteristics may be noted in table 2. For example, strains 1278 and 1600 gave almost identical reactions in all tests excepting that for liquefaction of gelatin.

Gordon (1922) found that hemolytic and nonhemolytic strains of enterococci behaved alike in agglutinin absorption tests. Frobisher and Denny (1928), Elser and Thomas (1936), and Sherman and Stark (1931) found that hemolytic and nonhemolytic strains resembled each other in every respect excepting the reaction on blood. The literature records many instances of the loss of hemo-
<table>
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*S. durans* (Sherman and Wing)

* Strong reduction in milk containing 0.1 per cent methylene blue.
† The titers are expressed as reciprocals of the highest serum dilution which agglutinated.
‡ Strain 945 was peculiar in that the final pH was only 4.6.
lytic power in streptococci (Grinnell, 1928; Todd, 1928; Fry, 1933; Lancefield, 1934). That this phenomenon may occur in enterococci was observed by several investigators (Gordon, 1922; Stein, 1933; Noël, 1934). Our strain 1333 was originally a hemolytic strain which, when it was received, had a history of having produced a green variant from a pure line culture. In our laboratory neither strain 1333 nor the substrain 1332 produced beta hemolysis. The reverse change, the acquisition of hemolytic power by enterococci of the alpha type, was reported by Meyer (1926).

In our laboratory repeated changes in type of hemolysis were observed in strain 693. This strain had been isolated by Kendrick and Hollon (1931) from feces in a case of intestinal hemorrhages. They noted that when first isolated it was strongly hemolytic, but that it soon lost its hemolytic power and became alpha hemolytic. After transmission to our laboratory, however, it produced beta hemolysis. Because it did not behave in accordance with its previous history, another subculture of the strain was requested. It also produced beta hemolysis in our laboratory when first received, and it has done so consistently. However, a subculture of our beta hemolytic 693 was given to another laboratory of the National Institute of Health, and it was reported as having changed to an alpha hemolytic strain. A subculture of this alpha strain was returned to our laboratory. It was tested for type of hemolysis on agar containing rabbit blood, which was in general use in our laboratory, and on sheep blood, which was in use in the other laboratory. On rabbit blood agar, beta hemolysis occurred, but on sheep blood, alpha hemolysis occurred. This observation of differences in the type of hemolysis dependent on the source of blood was made also by Kobayashi (1940), who reported that the enterococcus does not hemolyze the blood corpuscles of the goat or sheep, although it may hemolyze the corpuscles of man, horse, cow, or rabbit.

The inconstancy of hemolysis in strain 693 illustrates the unreliability of the hemolytic property as a character of specific significance. The lack of correlation between type of hemolysis and other characteristics is illustrated in table 2 by strains 914 and 1275, which gave almost identical reactions in all tests excepting that for hemolysis.

*Enterococcal bacteriophage.* That enterococcal bacteriophage may be more widespread than phages attacking other streptococci is suggested by the more frequent mention of it in the literature. Beckerich and Hauduroy (1922), and also Hadley and Dabney (1926), studied this phage. Bagger (1926) reported the sudden appearance of bacteriophage in a plate culture of a strain of enterococcus which had been under cultivation for a long time, many similar plate cultures having been made previously. According to Houston (1936), an active enterococcal phage can often be isolated from the stools in cases of ulcerative colitis. This author also reported (1934) that in a septic focus the enterococcus usually occurs in a phage-infected form. He believes that the action of the phage results in variation in the characteristics of the organism. Graham and Bartley (1939) found that 34 of 36 strains of enterococci were sensitive to all three phages which they studied. In our experience, enterococcal phage could be readily obtained from sewage.
Kendrick and Hollon (1931) noted the parallelism between serologic and bacteriophagic relationships in a group of fecal streptococci. One of us (A. C. E.) studied their phage, and reported (1934) that sensitivity to this phage, designated D, differentiated the enterococci from other streptococci, and that on the basis of bacteriophagic reactions the grouping of enterococci corresponded with the grouping recognized on the basis of other characteristics.

During the course of our studies on bacteriophage, a race designated D2 was found in a sample of sewage taken in Washington, D. C. It lysed enterococci, but differed from phage D in that the antilysins prepared against the two phages behaved differently. Antilysin D2 neutralized phage D as well as phage D1, whereas antilysin D neutralized the homologous phage but not the phage D2.

Each phage was prepared by propagation on a strain of enterococcus found to be highly sensitive. Phage D was propagated on strain 693, and phage D2 was propagated on strain 1188. The techniques of isolating the phage, preparing the filtrates and the antilysins, making the serologic tests, and determining the sensitivity of the streptococci to the phages were described in previous publications (Evans, 1934, 1942; Evans and Sockrider, 1942). All strains of enterococci were tested for sensitivity to filtrates of both phages, D and D2, with results as shown in table 2.

Serologic relationships. A number of investigators (Gordon, 1922; Durand and Dufourt, 1923; Meyer and Löwenstein, 1926; Takeda, 1935; Meyer, 1937) reported that the majority of enterococci from various sources fall into a few well-defined groups according to agglutinative reactions, which were confirmed by agglutinin absorption tests in the studies of some of the investigators.

Saunders (1930) reported that in a large series of cases enterococci from the tissues of resected gastric and intestinal ulcers and from certain types of ulcers in other parts of the body exhibited similar serologic characteristics. Torrey and Montu (1936) found that enterococci serologically related to Saunders' strains occurred more frequently in patients showing intestinal lesions than in normal adults. A few of Saunders' strains (nos. 1275, 1276, and 1277 of tables 1 and 2) and a few of Torrey and Montu's strains (nos. 977, 978, 979, and 980) were available for the present study. It was found that the strains from cases of ulcer, received from Saunders and from Torrey and Montu, resembled strains from other pathologic as well as nonpathologic sources in serologic behavior as well as in physiologic and biochemic reactions.

That the commonest serologic types of enterococci are widely distributed is suggested by the studies of the following authors: Houston (1936) reported that type 1 of the "Belfast classification" was identical with one of Meyer's types of continental European strains, and Meyer (1937) reported that his type 1 agreed with Takeda's (1935) type 1 of strains isolated in Japan.

Agglutinating serums were prepared against three strains, 894, 1130, and 1188, strain 1188 having been selected because it was the strain previously utilized for the propagation of phage D2. Strain 1130 was selected to represent strains which failed to agglutinate in antiserum 1188; strain 894 was selected to represent strains which failed to agglutinate in either serum.
Rabbits were injected with antigen prepared from fresh broth culture heated at 56 C for 1 hour. The cultures were centrifuged and the sediments were suspended in saline solution containing 0.2 per cent tricresol. The first 3 doses, injected subcutaneously on successive days, each consisted of 0.5 ml of antigen of a turbidity equivalent to 2,000 ppm of the silica standard. They were followed by 2 intraperitoneal doses of 1 ml, 400 ppm, on successive days. Intraperitoneal injections were made with increasing doses 3, 4, or 5 times during the following 2 weeks, the largest being 1.0 ml, 1,000 ppm. Trial bleedings were then made 6 days after the last injection. If the serum did not show a good titer of agglutinins, further injections were made.

In the case of strain 1188, a satisfactory serum was obtained after treatment of the rabbit for 3 weeks; strain 894 required 4 weeks. In the case of strain 1130, the serum was unsatisfactory, when tested against the homologous strain, after treatment for 6 weeks. It agglutinated in 1:10 but not in higher dilutions. However, it agglutinated many heterologous strains in a titer of 1:100 or 1:1,000 (table 2). Torrey and Montu (1936) reported that some of their strains lacked agglutinogenic properties.

Distinguishing characteristics of the enterococci. In table 2 the 34 strains of enterococci are arranged in 6 groups, primarily according to agglutinative reactions. It may be noted that certain other characteristics are more or less correlated with agglutinative reactions.

The first group includes 17 strains, one of which, no. 1308, was labeled Streptococcus zymogenes when received from Dr. Sherman. All strains of this group agglutinated in serum 1188; all but two agglutinated in serum 1130, and all but another two agglutinated in serum 894. All strains were sensitive to phage D-693; all grew in milk containing 0.1 per cent methylene blue; all survived 60 C for 30 minutes; all produced acid from sucrose, lactose, mannitol, and sorbitol. The strains varied in sensitivity to phage D1-1188, hemolysis, liquefaction of gelatin, and production of acid from glycerol. Only one strain produced acid from arabinose, and it was also the only one which produced acid from raffinose. The table shows that liquefaction of gelatin and type of hemolysis are uncorrelated with other characteristics. According to all available evidence the 17 strains of the group belong to one species. In agreement with priority of nomenclature the group should be designated Streptococcus zymogenes (Mac-Callum and Hastings, 1899), and the names faecalis and liquefaciens should be eliminated.

The last group in table 2 includes only one strain, no. 1309, which was received from Dr. Sherman with the designation "S. thermodurans." Afterwards Sherman and Wing (1937) changed the specific name to Streptococcus durans. These authors reported that S. durans does not have as strong a reducing action as other strains of group D; it lacks the ability to produce acid from glycerol and sorbitol; usually it does not attack mannitol or sucrose. These distinguishing characteristics of S. durans were confirmed in our studies (table 2), which show, further, that strain 1309 does not agglutinate in the serums which
agglutinate the strains of *S. zymogenes*, and that it is resistant to phages D-693 and D+1188.

Between the widely different species *S. zymogenes* and *S. durans* are strains of intermediate characteristics (see table 2). These intervening groups show a gradation of divergence from the characteristics of *S. zymogenes* toward the characteristics of *S. durans*. Group 2 differs from *S. zymogenes* chiefly in the failure to agglutinate in antiserum 1188, and in the failure of most of the strains to produce acid from sucrose and sorbitol. Group 3 diverges further in that the strains fail to agglutinate in antiserum 1130. The strains of group 4 agglutinate in none of the sera, but in other characteristics they resemble those of *S. zymogenes*.

The data in table 2 are insufficient to determine whether any one or more of the groups 2, 3, and 4 or any combination of them should be regarded as a separate species. However, the failure of production of acid from sucrose and sorbitol appears to have some significance. Possibly a new species should be recognized largely on the basis of those characteristics.

The strains of group 5, one of which was derived from the other, are clearly differentiated from the two recognized species, *S. zymogenes* and *S. durans*. They differ from *S. zymogenes* in their failure to react in the three agglutinating serums, in their resistance to phage D-693, and in their failure to survive 60 C for 30 minutes. They differ from *S. durans* in their strong reduction of methylene blue, in their failure to survive 60 C for 30 minutes, and in their production of acid from sucrose, mannitol, and sorbitol.

Graham and Bartley (1939) mentioned a variety of enterococcus which lacked the property of resistance to heat. Another author mentioned strains which resisted 60 C for 10 minutes, but not for 30 minutes. This report was seen by one of us (A. C. E.), but the reference was lost. If group 5 is found to be of numerical significance, it should be given a specific name.

*Enterococci in various animal hosts.* The hardiness of the enterococci enables them to multiply under a wide variety of conditions. They are found in health and disease, not only in various species of mammals, but also in lower forms of animal life. Steinhaus (1941) isolated enterococci from 5 species of insects; Sherman (1937) quoted several authors who considered the so-called *Streptococcus apis*, which is associated with European foul brood of bees, to be an enterococcus. Plummer (1941) isolated an enterococcus from the eye of a ferret; Sylvester and Benedict (1941) isolated it from the viscera of foxes and minks; and Elser and Thomas (1936) isolated it from the cervix of guinea pigs. Orcutt (1926) found enterococci in the digestive tract of normal calves and in calves suffering from diarrhea or scours. Torrey and Montu (1936), and also Plummer (1941), studied enterococci which had been isolated from milk in cases of bovine mastitis. Two of our strains, nos. 1309 and 1359, were probably of bovine origin, not associated with disease.

Hont and Banks (1944) cultivated enterococci from a pig which died of endocarditis, and they produced disease in a young pig from a healthy herd by
inoculating the culture intravenously. Thomson and Thomson (1927) mentioned the isolation of enterococci from the respiratory tract of dogs suffering from distemper. One of the hemolytic strains of our collection, no. 894, was isolated from the diseased lung of a dog, where it was associated with a non-hemolytic streptococcus which the writers did not have an opportunity to study.

The sources of the enterococci found in human infections. The data in tables 1 and 2 indicate that strains of enterococci similar to those found in pathologic lesions of man may be derived from the flora of the normal human intestines, or from animal sources. Takeda (1935) also was unable to find differences between the enterococci of the healthy and those of diseased intestines.

Among the 17 strains designated *S. zymogenes*, one was apparently of bovine origin, having been isolated from pasteurized milk; 2 were apparently from nonpathologic human sources, pooled normal plasma; 3 were from normal stools; and the remaining 11 were from human pathologic sources. Among the 8 strains of group 2, one was from a normal throat, one was from an unknown human source, and the remaining 6 were from human pathologic sources. Among the 4 strains of group 3, 2 were from animal sources, and 2 were from human pathologic sources. It may be noted that strain 894, from the diseased lung of a dog, behaved in every reaction like strain 979, from a human case of chronic ulcerative colitis.

No evidence that *S. durans* is pathogenic for man has yet appeared. None of our 23 strains from human pathologic sources showed the characteristics of this species. Brown and Schaub (1945) reported finding one strain of *S. durans* among 386 strains of group D isolated from autopsy material, but they did not state that they found evidence that it had been involved in any disease process.

The enterococci in human disease. The literature on enterococci in human disease contains many extensive reviews (Schmitz, 1912; Meyer and Schönfeld, 1926; Thomson and Thomson, 1927; Dible, 1929). The German literature on the pathologic significance of the enterococci was reviewed by Ehrißmann (1935). In the following review reference will be made to Ehrißmann but not to the authors whom he quotes. This review will omit references to papers in which the description of strains leaves doubt as to whether they were enterococci.

That enterococci are more frequently associated with human disease than they were formerly believed to be is indicated by the report of Brown and Schaub (1945), who stated that nearly 50 per cent of strains of streptococci isolated from autopsy material belonged to group D. These investigators were of the opinion that many of the strains were derived from post-mortem enterococcal invasion, but that many were associated with disease. Rantz and Kirby (1943) reported the finding of many enterococcal infections.

Enterococci in the human digestive tract. That the enterococci are common inhabitants of the normal human intestines was demonstrated by Andrews and Horder (1906) and by many subsequent investigators. Rantz and Kirby (1943) reported that they found enterococci to be constantly present in the normal bowel. On the other hand, Schmitz (1912) failed to find them in normal stools.
Thiercelin (1899) found enterococci involved in enteritis and concluded that they are important in most affections of the digestive tract. Sherman, Stark, and Mauer (1937) investigated the occurrence of S. zymogenes in a subject who harbored the organism. It could not always be isolated from the stools, but it could be isolated frequently, and usually with ease, during periods of intestinal disturbance (strain 1188 of tables 1 and 2 was from this case). Ross and Peckham (1920) reported finding enterococci in the stools during an outbreak of 12 cases of severe dysentery, 5 of which were fatal.

Linden, Turner, and Thom (1926) were the first to report outbreaks of food poisoning due to streptococci in cheese. Others have been reported more recently. The streptococci from one of the early outbreaks was identified with Lancefield's group D by Sherman, Smiley, and Niven (1943). According to Sherman (1945), symptoms similar to those in man may be produced in cats by feeding them with milk in which enterococci have grown.

Saunders (1930) reviewed the literature on the association of streptococci with ulcers of the digestive tract, and he reported finding the constant occurrence of enterococci in the tissues of resected gastric, duodenal, and gastrojejunal ulcers. His observations were confirmed by Torrey and Montu (1936).

According to Felsen (1936), after an acute infection with "Bacterium dysenteriae" a secondary infection with enterococci and "B. coli" sometimes takes place at the site of the mucosal ulcerations, presumably originally produced by the toxin of the dysentery organism.

Strain 693 of our collection (see the tables) was isolated from feaces in a case of intestinal hemorrhage.

Purulent abdominal infections with enterococci. Thiercelin's findings (1899) led him to believe that enterococci are important in the production of appendicitis. A number of more recent investigators have confirmed this association. (Meyer and Löwenstein, 1926; Ehrismann, 1935; Elser and Thomas, 1936; Lodenkämper, 1937; Muroi, 1938).

Enterococci are sometimes associated with purulent infections resulting from a damaged intestine or bladder (Schmitz, 1912; Rantz and Kirby, 1943; Wheeler and Foley, 1943; Brown and Schaub, 1945). Strain 1130 of our collection was from a case of peritonitis.

The streptococci of wounds. Fleming (1915) was of the opinion that the streptococci as well as other bacteria of wounds inflicted during war are generally of intestinal origin. Burnet and Weissenbach (1918) reported finding enterococci in 30 per cent of osteomuscular war wounds of less than 7 days' duration. Dible (1921) quotes a number of authors who noted the presence of enterococci in wounds studied during the First World War, and other more recent investigators have reported enterococcal infection of wounds (Morin, Caudière, and Certonciny, 1924; Takeya, 1938; Francis, 1941).

Infections of the urinary tract. Enterococcal infections of the urinary tract were reported by Andrews and Horder (1906), Meyer and Löwenstein (1926), Ehrismann (1935), and Elser and Thomas (1936). That enterococci occur frequently in genitourinary infections was shown by Porch (1941), who found
that 73 out of 100 strains of streptococci isolated from specimens of urine belonged to group D. Hollander (1942) found that 22 out of 40 (55 per cent) of streptococci from infections of the genitourinary tract belonged to group D. Rantz and Kirby (1943) found 27 per cent of streptococci isolated from specimens of urine belonged to group D. From 5 of their cases which presented signs of pyelonephritis they isolated enterococci in pure culture.

Puerperal sepsis. A good many authors have reported finding enterococci associated with puerperal sepsis (Meyer and Löwenstein, 1936; Ehrismann, 1935). Gordon (1922) found them in 8 cases, Ramsay and Gillespie (1941) in 6, and Rantz and Kirby (1943) in 2. Witebsky and his coworkers (1939) isolated a strain of enterococcus from the blood in a case of septicemia following abortion.

Takezawa (1937) found 50 strains of enterococci among 216 strains of streptococci from female genital organs in various diseases. Hare and Colebrook (1934) isolated streptococci with the characteristics of enterococci from 7 of 34 women who had low-grade fever during the puerperium, but in only a few instances were the organisms isolated in pure culture. Lancefield and Hare (1935) found no streptococci of group D among 46 strains from cases of severe infection of the uterus, but they found 8 strains of group D among 18 strains from “minor infections.” Brown and Schaub (1945) found that 9 per cent of 232 strains of streptococci from the uteri of patients with febrile puerpera were enterococci.

Otitis media, mastoiditis, and meningitis. Thiercelin (1899) isolated enterococci from cases of meningitis, and Andrewes and Horder (1906) found them in cases of otitis media, mastoiditis, and meningitis. Subsequent investigators have confirmed those early reports. Ehrismann (1935) quoted two authors who reported cases of meningitis due to enterococci; Lang, Lode, and Schuttermayer (1937) reported 2 cases; Wheeler and Foley (1943), 1 case. Rantz (1942) reported 1 case in which meningitis followed a prolonged ear infection. Rantz and Kirby (1943) found that about 10 per cent of streptococcal infections of the middle ear were caused by enterococci.

Among the strains of our collection, no. 1132 was from a case of ear infection following measles; no. 1181 was from a case of meningitis following mastoiditis; and no. 1574 was from a case of otitis media.

Endocarditis. MacCallum and Hastings (1889) obtained an organism which they called Micrococcus zymogenes from the blood in a case of endocarditis, and Sherman (1937) was convinced that their organism was an enterococcus. Subsequently many authors reported the isolation of enterococci in cases of endocarditis (Andrewes and Horder, 1906; Hicks, 1912; Gordon, 1922; Meyer and Löwenstein, 1926; Dible, 1929; Wallach, 1934; Houston, 1934; Baum, 1935; Ehrismann, 1935; Elser and Thomas, 1936; Reiners, 1936; Fox, 1936; Waaler, 1937; Clements, 1937; Otto, 1938; Moran, 1938; Rohleder, 1938; Williams, 1939; Lederle, 1940; Skinner and Edwards, 1942; Rantz and Kirby, 1943; Wheeler and Foley, 1943; MacNeal and Blevins, 1945; Brown and Schaub, 1945). Two strains of our collection, nos. 1332 and 1333, were from one case of malignant endocarditis.
Some of the investigators mentioned reported on the frequency of occurrence of enterococci in their cases of endocarditis. Elser and Thomas encountered enterococci "not infrequently" in the blood of patients suffering from a subacute form of endocarditis. Andrewes and Horder found 4 strains of enterococci among the streptococci from 24 cases of malignant endocarditis; Dible reported that 1 strain out of 6 isolated from the blood in cases of ulcerative endocarditis was an enterococcus; Moran found it in 5 out of 20 cases; Lederle in 8 out of 10 cases; Rantz and Kirby in 3 out of 16 cases; and MacNeal and Blevins in 6 out of 36 cases.

The portal of entry was determined in a number of cases of endocarditis reviewed by Skinner and Edwards (1942). Enterococci obtained from the blood stream were derived from an infected finger in 1 case, infected tonsils in 1, the gall bladder in 2, the urinary tract in 2, septic abortion in 3, and the gastrointestinal tract in 5.

Miscellaneous diseases. Rantz and Kirby (1943) called attention to the fact that the enterococci are rarely found associated with infections of the respiratory tract. They reported 8 cases; Wheeler and Foley (1943) reported 1 case. Brown and Schaub (1945) found enterococci in mixed cultures in cases of pneumonia. One strain of our collection (no. 702) was from a case of sore throat.

The enterococcus is occasionally reported to be associated with various diseases not mentioned above. Meyer and Löwenstein (1926) found it in cholecystitis, osteomyelitis, and pancreatitis; Houston (1934) found it in septic tonsils, the root canal of septic teeth, postnasal catarrh, septic antra, excised gall bladders, abscesses in various parts of the body, certain forms of acne and other skin lesions, and invariably in chronic onychia; Wheeler and Foley (1943) found it in dermatomyositis and in emphysema. Our collection includes strains from empyema (no. 696), an infected tooth (no. 912), osteomyelitis (no. 1121), and septicemia following smallpox vaccination (no. 1131).

There is an extensive literature on the association of enterococci with rheumatic diseases. It is omitted here because, if the association should be proved to be significant, this literature should be treated separately.

SUMMARY

The literature on human infections with enterococci is reviewed, and the results of a study of 34 strains, 23 from human pathologic sources and 11 from other sources, are reported.

Enterococci have been found in a great variety of human ailments. They appear to be important causal agents in some cases of endocarditis, intestinal disorders, abdominal infections due to injury of the intestinal tract, infections of wounds inflicted during war, and infections of the urinary tract.

The following characteristics distinguish the enterococci from other streptococci: reaction in serum of group D according to Lancefield's precipitin test, growth at 10 and 45 °C, growth in media containing 6.5 per cent sodium chloride, growth in media having an initial pH value of 9.6, and growth in media containing 40 per cent bile.
The hardiness of the enterococci is of practical significance in that they are resistant to the sulfonamides and penicillin.

The following characteristics are useful in distinguishing subgroups or species of enterococci: agglutinative reactions; sensitivity to bacteriophage D-693; growth in milk containing 0.1 per cent methylene blue; survival at 60 C for 30 minutes; and the production of acid from sucrose, mannitol, and sorbitol.

The type of hemolysis and liquefaction of gelatin, characteristics on which the differentiation of species hitherto have been based, were found to be uncorrelated with other significant characteristics.

The data indicate that enterococci pathogenic for man may be derived from the flora of normal human intestines or from the tissues or intestines of various species of animals.

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