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Etiological role of streptococci in diseases

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INTRODUCTION

The streptococci constitute a very large group of organisms made up of innumerable and indefinite species. It has been only through extensive and persistent research that so much has been discovered in showing the relationships between streptococci and disease.

The field proved to be so widespread that I was forced to limit the aspect of this thesis. My only hope has been to emphasize the very widespread influence of streptococci. Although the presentation is purely statistical this has seemed essential for unity of convincing proof. I have considered only those works pointing to streptococci as being the etiological agent.

CONTENTS

I. HISTORY

The name streptococcus comes from the Greek words streptos, meaning chain, and kokkos, meaning a berry. The term was introduced by Billroth in 1868 (73). Many observers early noted streptococci in pus during suppurative inflammation. Pasteur recognized the coccus in puerperal sepsis in 1878, and at the same time Koch saw these organisms in pus from wound infections (141). But it was Ogston in 1881 who first clearly differentiated between the staphylococcus and the streptococcus. His description was as follows: "Sometimes they were seen as chains from 3 or 4 cocci, up to much larger numbers. Generally 5 or 6 cocci were strung together, often 10-20 were found. In other specimens, again, no chains were seen at all; the cocci were grouped like the roe of fish, into clusters where there was neither beginning nor end." (97).

Pure cultures of streptococci were first obtained by Fehleisen in 1883 from lesions of erysipelas and by Rosenbach in 1884 (141). Thereafter the organisms were found in other specific pathological lesions and given the name of that disease, such as the names streptococcus erysipelatis, St. puerperalis, and so on. These findings of new species or strains led to much confusion

until various aids for differentiation were worked out.

Marmorek (1895) was the first to work systematically with streptococci and their uniformity of properties. One of these was the ability of the human pathogenic strains to produce lysis of the red blood cells (58). Bordet (1897) and Besredka (1901) also found that the filtrate of streptococci cultures produced lysis. But it was Schottmuller, in 1903, who classified the streptococci as follows: 1.-St. longus or erysipelatis (now hemolyticus), strains derived from acute and severe infections, and producing a clear zone surrounding each colony on blood media; 2.-St. viridans or mitior, characteristically found in normal throats and in subacute infections, and producing a greenish discoloration around the colony (58).

At first it was thought that hemolysis divided all pathogenic from the non-pathogenic types. A third group was added, when Zangemeister in 1910 described strains of streptococci whose growth produced no effect on red blood cells (58). Within recent years Smith and Brown have carried the studies further on standard blood agar plates and designated the three types as, alpha, beta, and gamma.

Differential sugar media was first used by Gordon

(62) in 1903-05. Holmans later classified streptococci by primarily differentiating the hemolytic and non-hemolytic strains on blood agar followed by classification on three sugars. (58).

The next problem to come up was the separation of the various strains into separate groups. Gay (58), stated that separate strains although indistinguishable by cultural methods could be grouped by appropriate immune reactions, as agglutination, fixation, and anaphylaxis. Swift and Thro (129) found that agglutination reactions were specific for streptococci, although they did not serve to separate the strains from one another. Whereas fixation reactions seemed to show that most strains produced a separate immune body. Howell (72) confirmed these findings in 1918, and found less specific fixation among the viridans than the hemolythic group.

In summarizing, the differentiation of the types has been made upon the fermentation of sugars, effects on red blood cells, pathogenicity, and on immunolotical reactions.

Now, another perplexing and debated question has arisen, the possibility of mutations. Bacteriology has

always depended on the constancy of bacterial species. But each new technic has enabled bacteriologists to further subdivide organisms which are a single species, though all evidence still points to the fixed cultural and pathogenic properties. On the other hand, it has been noted that minor variations in the physiological properties of bacteria occur with changes in environment. Ruediger (117) found that hemolytic streptococci lost their property of clearing blood agar after growing in glucose for two years. Anthony (2) reported that only 95% remained true to type.

Rosenow (108), in 1912, was able to transform the streptococcus epidermicus into the pyogenes by growth on agar. He further claimed to have transferred 17 strains of viridans into pneumococci and 21 hemolytic streptococcus strains into viridans (111). Other men have carried on studies to prove or disprove this theory of transmutation. The greatest evidence seems to rest with those who believe that such changes if they do occur under natural conditions must be exceptional. Smith and Brown (124, 17), say that under natural conditions they do not proceed rapidly enough to interfere. The objections to experimental production of these muta-

tions have been: 1.- One must deal with a pure-line culture; 2.- The injections of the cocci into normal animals and subsequent isolation of a different type of coccus may be due to a coccus normally present in that animal.

II. LOCAL INFECTIONS

The streptococci are parasitic organisms. Their greatest natural habitat is the animal body, and especially the mucous membranes of the digestive and respiratory systems. This relationship with the human body places them ready for invasion whenever the opportunity is offered.

Upon invasion ensues a struggle between the invading organism and the patient's body resistance. The end results depending upon such factors as the virulence of the organism, the number present, and the power of tissue defense. If the coccus is of low virulence and the tissue haw powers of defense, the infection is overcome with little tissue disturbance. If the coccus is more virulent and the tissue less resistant, the organism may grow in the tissue bringing about either a rapid or slow cellular response and producing thus an acute or chronic infection.

Acute Local Infections

The streptococci play a very important etiolotical role in many so called acute local infections. This may be either as the primary causal agent or only as secondary invaders.

Skin

Acute localized infections of the skin are usually caused by the staphylococci, though the streptococci may contribute. This is due to the fact that normally streptococci inhabit the skin in relatively a small number of individuals.

Sabourand considers the following skin disease as due to the streptococcus: impetigo, certain forms of intertrigo--especially those involving the area behind the fold of the ear, pityriasis alba, and dermatitis of the scalp. The last three due to anhemolytic streptococci (74).

Kinear (74) in a study of 176 cases of streptococcic dermatitis (including intertrigo and pityriasis) found streptococci absent in only 15 cases that presented involvement of the posterior auricular fold.

Bier and Hoffman (8) reported a seasonal dermatitis from which both staphylococcus aureus and St. hemolyticus were isolated in equal numbers.

Meleny (29, 90), who in the past few years has done a great deal of work on chronic underming ulcer, was the first to report such a condition and to show it was due to a hemolytic streptococcus. His further studies showed that the organism was intermediate between the

anaerobes and aerobes, and so he called them hemolytic micro-aerophilic streptococci. Meleny (89) was also the first to report in 1924, an acute gangrene of the skin due to hemolytic streptococcus.

The direct cause of impetigo is a streptococcus, though it may be symbiotic with staphylococcus. Those most frequently found are the St. pyogenes, infrequens and anginosus (59).

Erysipelas

Erysipelas, an acute inflammatory process involving chiefly the skin lymphatics, has been described clinically since the early days of medicine. It is probably the first disease known to be caused by the streptococcus. Hunter and Volkmann, as early as 1869 (59), both described streptococci in the lesion. But it was Fehleisen, who isolated streptococci from erysipelas in 1882 and was the first to grow them in pure culture--to which he gave the name St. erysipelatis. Fehleisen began his work in 1881 (60) and in 1883 demonstrated that erysipelatous lesions could be produced experimentally in the skin of laboratory animals by intradermal inoculation of hemolytic streptococci.

Experimental erysipelas was probably first produced by Orth in 1873 (60), who, before the knowledge

of the causative organism in this disease, produced a spreading and fatal abscess by subcutaneous inoculation on the back of rabbits of the contents from a human erysipelas bleb.

Gay and Rhodes (60) produced erysipelas in rabbits by giving intradermal inoculations of St. hemolyticus. Recently Rivers and Tillet (107) have done likewise.

Since 1883 investigators have made numerous attempts to establish the etiology of erysipelas by both cultural and morphological studies of hemolytic streptococci isolated from erysipelatous lesions. But these offered no adequate criteria by which a differentiation could be made between strains of erysipelatis and non-erysipelatis hemolytic streptococci. Since, active investigations have been conducted on the biology of streptococcus hemolyticus, particularly by means of serological methods. Important work on opsonins and agglutinins by Tunnicliff suggested that a specific group of hemolytic streptococcus was the etiological agent causing erysipelas. Tunnicliff (131) in 1920, showed that serum of sheep immunized with a streptococcus from acute cases of erysipelas was found to con-

tain opsonins and agglutinins for streptococcus of this disease, but not for streptococci from other infections.

Birkhaug (11) showed that it was possible to differentiate by immunological methods a group of hemolytic streptococci causing erysipelas from the group causing scarlet fever and other infections. In 1925, he reported that 91.5% of his 34 strains agglutinated with each of 7 monovalent erysipelatous immune sera. While only 20% of the 45 strains isolated from other sources were agglutinated by the immune sera. This antigenic relationship demonstrated by agglutination test was later confirmed with regularity by in vivo local passive immunity experiments carried on by Birkhaug (12, 13, 14).

Stevens and Dochez (126) pointed out that erysipelas immune sera would agglutinate scarlatinal strains, but that strains from erysipelas agglutinated in a much higher percentage of instances. They also showed that strains from miscellaneous pyogenic infections would agglutinate in these sera, but the percentage of positive reactions was low, and a strain usually was agglutinated in but one of the several

sera. Whereas in the case of erysipelas, when agglutination occurred in one serum, the strain usually agglutinated in all other erysipelas sera.

Singer and Kaplan (121) showed that the sterile toxic filtrate of a broth culture of streptococcus erysipelatis possessed the properties of a true toxin. When injected into man, this toxin was capable of exciting the formation of a neutralizing substance. The antitoxin produced by injections of the toxin alone seemed to compare in its protective qualities with the antierysipelas serum obtained by others from animals.

Rivers and Tillet (106, 107) successfully demonstrated that skin infiltrated with an immune monovalent streptococci serum produced local protection against cultures of streptococcus hemolyticus employed for the serum production. Birkhaug previously had showed the same results. He further mentioned that intradermal, intravenous and intramuscular injections of immune erysipelatas serum in cases of erysipelas seemed to offer promise for a specific treatment.

In 1926, Birkhaug (14) demonstrated clinically in 60 moderately severe cases of erysipelas that intramuscular injections of the anti serum, when given during the first 3 days of the disease, caused a prompt im-

provement of toxic symptoms and prompt fading of the lesion with absorption of the blebs and edema. In late cases the results were also striking, although repeated injections were necessary to completely neutralize the toxin in the patient's blood.

A year later, Birkhaug (15) confirmed the view that streptococcus erysipelatis produced a toxin, and further showed that a source of active immunization against recurrent attacks by means of intramuscular injections of the toxin rapidly increased the antitoxin concentration of the blood in 24 patients.

Though good results, following the use of antiserum, have been reported by many, others give results to the contrary. So, as in other fields, further investigations are needed.

Gastro-intestinal System

In acute local infections of the mucous membranes, the streptococci are the chief offenders. Of the three types, the beta hemolytic streptococci are the most important, though frequently associated with them are the alpha and gamma types.

Andrewes (1) in 1906 found streptococci to be the bacteria most frequently found in the mouth. Thomson and Thomson (59) showed that streptococcus viridans

occurs in the nose and throats of practically all normal people and outnumbers the hemolytic type. Gay (59) states that the streptococci predominate in dental and oral infections, though they are usually not the primary factors.

The lymphoid tissue of the upper respiratory and digestive tract offers a favorable medium for streptococci existence. And so with lowered resistance and a virulent coccus, the result may be an acute tonsillitis, abscess, pharyngitis, adenitis, sinusitis, otitis media, or mastoiditis. From any of these infections there may be extension to any of the other sites. Or the extension may be to the brain causing a streptococcus meningitis or abscess formation. Or the extension may be to the remaining respiratory system producing pneumonia, lung abscess, pleurisy, empyema, pericarditis and so on.

Tonsillitis, a frequent precursor of other diseases, is generally agreed to be caused by essentially the hemolytic streptococcus. As early as 1895, Frankel and Macintyre (57) called attention to this fact. Davis (37) in a series of cultures from extirpated tonsils found virulent streptococcus hemolyticus to be the predominant organism. Experimental streptococcic tonsillitis has been produced in man with secretions from

active cases. Rickey (105) reports such experiments made by the medical officers of the United States in their studies of the epidermiology of influenzae in 1919. Further studies shall be taken up under the heading--septic sore throat.

Acute streptococcal infections of the remaining alimentary system and its associated organs occur less frequently. The hemolytic streptococci while sometimes the primary cause of these acute infections are not often found alone. Associated with them may be the staphylococci, the B. coli group, and so on, but more frequently than all are the alpha and gamma types of streptococci.

Genito-urinary System

In the genito-urinary tract primary as well as secondary streptococcus infection may occur, such as urethritis, cystitis, cervicitis, and nephritis. Commonly, clinical bacteriological studies of these various infections place streptococcus as only a minor offender. But Culver (35) in his report emphasizes the importance of streptococcal infections.

The tract, excepting the anterior urethra, is normally sterile. While the anterior urethra, according to Culver (35), harbors some 30 odd bacteria

including several varieties of streptococci. But this probably plays only a minor role in other infections of the urogenital organs.

Young, Colston, and Hill (140) recovered streptococci in 11% of 600 cases of bladder infections. In slightly less than one-half of the cases streptococci were in pure culture. The same proportion of streptococcus infections was found in kidney specimens.

Bumpus and Meisser (19) emphasized the importance of streptococcus from focal infections in several instances of pyelonephritis.

Barry and Mintz (4) in analyzing 143 kidney infarcts, found streptococci in 72.2% of the positive cases.

although streptococci play an important role in genito-urinary infections, cystitis probably represents the lone streptococcal infection with evidence of specificity.

Nephritis

Acute nephritis is one of the fields of medicine in which experimental methods of study have been extensively employed. It is nearly always due to some acute infection, usually a streptococcic infection. The cocci gain access to the blood and it is probable that

the injury is produced by the direct action of their bodies on the glomerular endothelium. The various clinical and patheological types depend upon the degree and extent of permanent injury.

MacNider (86), in a brief review, states that with the recognition in the early eighties of the importance of bacteria as the cause of disease, it was only natural that they should be looked upon as a likely cause of the various types of nephritis. He points out that as early as 1884 Ernst suggested that a true nephritis was an inflammatory process caused by an infectious agent. Pernice and Scagliosi in 1894 inoculated ribbits, dogs and guinea pigs with a variety of organisms, and claimed to have induced a glomerulonephritis. They further considered the toxins to have much less effect on the kidney than the bacteria (86).

The Dicks (45) in 1915 reported that bacteria isolated from the urine of nephritis were capable of producing both urinary and anatomic findings of nephritis.

In 1917 Ophuls (99) inoculated rabbits intravenously with streptococci and obtained a definite glomerulo-nephritis which also involved the tubules. He concluded that the majority of cases in man were due to streptococci but that other bacteria could cause

similar lesions.

Faber and Murray (55) employed not only streptococci but the colon bacillus and straphylococcus. They failed to produce typical pure glomerulo-nephritis even when immune antibodies could be demonstrated in the serum.

Bell and Hartzell (7) in a study of 32 cases of acute glomerulo-nephritis confirm the prevailing opinion that acute nephritis is closely associated with an infectious process. Of the 32 cases, 12 showed endocarditie, 6 streptococcic septicemia, 5 empyemia, 3 peritonitis, 4 septic sore throat, 3 erysipelas, 2 puerperal sepsis, 4 acute arthritis, 2 pneumonia, and so on. The frequency of acute endocarditis in the series was very impressive. And they showed that it was not accidental, by the fact that in over 3,300 consecutive necropsies, not including those with acute nephritis, there were only 63 with acute endocarditis, or only 1.9%. This relationship has also been observed by others. Councilman (34), as early as 1897, found 10 instances of acute endocarditis in 28 cases of acute nephritis. Klotz (77) also found endocarditis and nephritis in frequent association.

The relationship of tonsillitis to acute glomerulo-nephritis has been discussed by many. And many have

shown tonsillitis to be followed by acute nephritis.

Bell, Clawson, and Hartzell (6) produced experimental nephritis in 5 out of 14 monkeys by the intravenous injection of streptococci. In one case the glomerulo-nephritis was characterized by epithelial cresents, fusion of glomerular lobules to the capsule, swelling with occlusion of the capillaries, and atrophy of tubules associated with occluded glomeruli.

In conclusion Hartzell (6) offers three hypothesis to explain the origin of glomerulo-nephritis: "First, there is a specific etiological agent, some special strain of streptococci. Secondly, many types of streptococci may produce the disease but only certain individuals are susceptible. Third, there must be repeated injury to the glomerular endothelium, and this last seems to be gaining ground."

Chronic Focal Infections

The importance of the etiologic relation of focal infection to systemic disease is a subject that has received much clinical and bacteriological study. Continually new findings are being reported.

A focus of infection may be defined as a circumscribed area of tissue infected with pathogenic organ-

isms. The foci may be primary or secondary. Primary foci are usually located in tissues communicating with a mucous or cutaneous surface. Secondary foci are the direct results of infection from other foci by direct extension or by way of the vascular or lymphatic systems.

The primary foci of infection may be anywhere in the body. Billings (9, 10), who has done a great deal of work on focal infections, gives the following account of possible sites: "Infection of the teeth and jaws, with the especial development of pyorrhea dentalis. And alveolar abscess, infection of the tonsils and sinuses are the most common forms of focal infection. Submucous and subcutaneous abscesses are occasional foci. Chronic infection of the bronchi and bronchiectasis; chronic infection of the gastro-intestinal tract and auxiliary organs, including cholecystitis, appendicitis, ulcers and intestinal stasis; chronic infection of the genito-urinary tract are not uncommon forms."

Many kinds of bacteria have been accused of causing localized infections and of gradually producing, through absorption, pathological changes in distant parts of the body. But by far the most common group in-

volved is the streptococcus, particularly the alpha and gamma streptococci of low virulence. These streptococci have been found most frequently in chronic teeth, tonsillar and sinus infections, in subacute endocarditis, peptic ulcers, in chronic arthritis, and other conditions.

The factors determining the localization of bacteria in these specific areas are obscure. Gay (58) explains it in two general ways. First, by a lowering of resistance of the affected part in the individual; and secondly, by a specific affinity of the particular culture in question for a given tissue in the body. Rosenow (113) emphasizes the organotropic effect of bacteria rather than the decreased resistance. He has apparently been able to show that streptococci obtained from particular lesions have a particular affinity for the tissue. Thus he has shown from the standpoint of etiology that streptococci are not only present in rheumatic fever and endocarditis, pericarditis, and myocardial lesions as well as the joints affected in this disease complex but also in other deverse affections as appendicitis, peptic ulcer, herpes zoster, and so on.

Rosenow's work has received much criticism, although some men have reported confirmatory results. It is yet

too early to make deductions as to the true significance and value of such work.

III. IN GENERAL INFECTIONS

Septicemia is an infection characterized by the presence of bacteria and their toxic substance in the blood stream. The microorganisms enter the blood stream through a wound or during the course of a specific local infection.

Tileston (24) states that it is a common disease of all ages and that the streptococcus is the organism most commonly found.

We classify septicemias as primary, and secondary.

Primary Septicemia.

When a septicemia occurs as an independent process, it is designated a primary septicemia. The microorganisms and their products enter the blood stream without producing marked local symptoms. These infections occur seldom, for the source of such infection is usually very carefully handled.

Smith (123) reports an epidemic of streptococcus hemolyticus septicemia, occurring in a nursery home, involving 17 infants ranging from the age of 1 month to 8 months. The epidemic was characterized by sudden onset, absence of vomiting or diarrhea, absence of any apparent localized infection, and an uniformity of positive blood cultures.

Okell (98) has shown that within a few moments after extraction of teeth from an obviously septic mouth, a transient streptococcal bacteremia may be observed in 75% of cases. Even in patients with no obvious gum disease, extraction is followed by a transient bacteremia in 34% of cases.

The fate of such organisms has been studied by Hopkins and Parker (70). They injected streptococci into the circulation of insusceptible cats and susceptible rabbits. They found that in the cats, the streptococci are quickly withdrawn from the blood and are found most numerously in the lungs, less numerously in liver and spleen, and in small numbers in bone marrow, lymph, muscle and kidneys. While in the susceptible rabbits, they are quickly removed, but are distributed in different proportions--the liver and spleen absorbing almost as many as the lungs, and the muscles also absorbing many. In both animals, the organisms taken up by the lungs and liver were promptly killed. But those taken up by the rabbit muscle multiplied rapidly, and then reappeared in the blood stream. The bactericidal action was demonstrated to apparently depend upon the action of living cells, for the action was demonstrated in excised lung tissue but not in lung extracts.

Puerperal Septicemia.

Puerperal septicemia is a wound infection in which the organisms are brought from without into the general canal sometime during the puerperium. The majority are classed as primary. The name "puerperal sepsis" was suggested by Morton (118) in 1692 to apply to a febrile condition in puerperal women. Holmes and Semmelweiss early established the contagiousness of this disease. In 1843 Holmes (22) published an essay on the contagiousness of puerperal fever, stating in his own words: "The disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physician and nurses. About the particular mode of infection, whether it be by the atmosphere the physician carries about him into the sick chamber, or by the direct application of the virus to the absorbing surfaces with which his hand comes in contact."

That the streptococcus is the etiologocal agent in the majority of severe cases has been known since Mayrhofer (118) in 1865 found the organisms in smears and Pasteur in 1878 cultivated it from fatal cases.

It is still quite undecided what types of streptococci may be the etiological agents. Although it is known that the pyogenes strain of the hemolytic type

produce severe puerperal infections. Harris and Brown (67), in a study of 113 cases, found streptococci of various types in the uterine cavity of 67% of the cases. About one half of the streptococci found were of the beta hemolytic variety, and of these the majority were St. pyogenes. They further showed in their series that streptococci of fecal origin were rarely agents of puerperal infection.

Meleny (91) and his co-workers, report a series of 24 cases occurring in the course of one month. This constituted a small epidemic caused by a single strain of hemolytic streptococcus, of unusual virulence, as determined by reciprocal agglutination and absorption of agglutinins. They also observed that the organism could be carried in the nose without producing clinical symptoms.

Since the time of Holmes and Semmelweiss it has been known that the source of infection was exegenous, but that due to gamma, non-hemolytic streptococcus is probably endogenous in many cases.

Murray and King both stress that the spread of hemolytic streptococcus from the throats of carriers to women in labor as a big factor in the etiology of puerperal sepsis. King (75) points out that while the

rate of puerperal sepsis remains quite constant throughout the year, puerperal infections by hemolytic streptococci are higher in the winter. Infections of the throat by the same type of organisms are also most common during winter. Murray (95) admits that throat carriers of St. hemolyticus are very prevalent, and that apart from a negation of surgical and aesthetic principles they are not a danger to parturient women.

An interesting study by Burt-White (20) showed that women who react positively to intradermal inoculation of scarlatinal toxin are more liable to develop puerperal sepsis than the non-reactors. Of 100 cases tested, 27 were found sensitive and 30% developed puerperal sepsis while only less than .03% of the non-reactors developed the infection. This has been debated by many and requires further investigation.

In closing this short discussion, we may conclude that streptococcus pyogenes is an accepted causal agent.

Secondary Septicemias

The secondary septicemias are much more frequent than the primary, and usually follow as complications of the acute infectious diseases. They may be divided into acute or chronic infections.

The chronic types are due to the streptococcus

viridans and streptococcus indifferens, or according to Brown's classification--the alpha and gamma types. These are related to the rheumatic state and shall be discussed under that heading.

The acute septicemias are secondary to some local infection and generally follow the acute infectious diseases as scarlet fever, diphtheria, pneumonia, measles, and the like. As such it is clearly noted that upper respiratory infections play a very important role. Children are more susceptible to upper respiratory infections, and consequently septicemias are found more frequently in children. But contrary to the incidence, the mortality rate is greater in adults as was shown by Shwartzman and Goldman (120) in their studies of 168 cases over a period of 5 years.

These secondary septicemias may be due to the invasion of streptococci alone or accompanied by other bacteria. Cooke (32) reports the following observations made at a childrens hospital during a period of 5 years. Of a total of 104 cases giving positive blood cultures, streptococcus hemolyticus was found alone in 48, and accompanied by staphylococcus aureus in 3. Streptococcus non-hemolyticus was found alone in 7, and

accompanied by staphylococcus in 2 cases. The lungs proved to be the portal of entry in the majority of cases.

Dennett and Allen (44), in a study of 115 cases with positive blood cultures, found the streptococcus to be the most commonly detected blood stream infection. There were 86 cases of streptococci septicemia, 33 in children and 53 in adults. Of the children 61% recovered, while only 22.6% of the adults recovered. The type of streptococci represented were 53 hemolyticus and 33 viridans. The apparent causes of the hemolytic septicemias were mastoiditis, osteomyelitis, meningitis, peritonitis, tonsillitis, etc. Among the children mastoiditis was responsible for about 50% of the cases. Among the adults, however, there was no one disease preeminently responsible.

Warren and Herrick (135), in an analysis of 134 cases of bacteremia, found streptococci in 72. They also noted that the majority occurred during the winter and early spring months which is coincident with upper respiratory infections.

A bacteremia secondary to an acute or subacute throat infection is not always easily demonstrated. This was shown by a study of 93 throat infections by Ballen-

ger, Rubin, and Werner (3). Of the blood cultures they had taken, only 4 were positive. Streptococcus hemolyticus was found more frequently in acute throats and viridans in the subacute.

IV. RESPIRATORY INFECTIONS.

Hemolytic streptococci are intimately associated either directly as causative agents or indirectly as secondary invaders in a number of diseases which involve the throat and respiratory tract.

Septic Sore Throat

Septic sore throat is an acute tonsillitis of unusual severity, due to a streptococcus, which often assumes epidemic proportions. It is only rather recently that it has been considered as comprising a definite clinical entity.

Swithinbank and Newman (137), as early as 1903, made the statement that it was safe to assume that a year never went by in which there was not an outbreak of sore throat or tonsillitis due to milk. The first outbreak recognized in the United States was the Boston epidemic of 1911 reported by Winslow (137), and caused by an infected milk supply.

Since 1900, streptococci have been more or less regularly reported as present in septic sore throat. But no evidence was given that possibly only one species caused these epidemics until the work of Rosenow and Davis in 1912. Rosenow and Davis (39, 43) came to the conclusion that the hemolytic streptococcus they

found was a separate species and the cause of epidemic sore throat in practically all cases. They found the following characteristics: the coccus occurred in short chains and surrounded by a definite capsule; on blood agar, the colonies were larger and more moist than those of the common hemolytic streptococcus (pyogenes). They gave it the name--streptococcus epidemicus. Miller and Capps (21) further substantiated the work by finding the same coccus in 28 cases in the same epidemic.

Davis and Capps (41) succeeded in infecting the cow udder and milk by rubbing the coccus culture into the teats. They further proved that there were five times as many cases of sore throat among customers receiving infected milk than among those receiving non-infected milk (42). Davis and Capps also showed that mastitis produced by hemolytic streptococci lasted for several weeks in cows. This time roughly corresponding to the duration of milk-borne epidemics.

In 1915 Smith and Brown (124) made the statement that streptococci causing epidemic sore throat were not necessarily the same in different epidemics. They also advanced the theory that such epidemics were not caused by the streptococcus which usually causes bovine mastitis, but by a streptococcus of human origin which

occasionally gains entrance to the udder of the cow.

Brown, Frost and Shaw (18) in 1926 stated that the streptococcus epidemicus differed very strikingly and constantly from St. pyogenes in two major particulars, namely St. epidemicus possesses a striking capsule and its colonies are large, moist and have a tendency to grow on the surface.

In 1929, Davis (40) concluded that the St. epidemicus seemed to be the specific cause of the disease and so regarded by those who had most carefully studied it. From his studies of recent epidemics, all work indicated that the usual if not the only route of transmission of the coccus was, from a human to the udder of a cow, through contact. Here they incubate and rapidly multiply, then to pass out in the milk supply directly to the throat of the consumer.

The question as to whether the characteristics claimed by Davis and Rosenow as distinctive of a St. epidemicus, show a constant differential relationship to other streptococci as to constitute a species is still under discussion. Williams and Gurley (136) reported that neither of the species characteristics holds sufficiently to be used in designating a species. And that the present strains of hemolytic streptococci

from septic sore throat, not otherwise placed by agglutinin absorption, should be termed simply St. hemolyticus. They concluded that milk-borne epidemics of septic sore throat and scarlet fever may be caused respectively by one or more agglutinative types of hemolytic streptococci.

Pilot (102), who has carried on extensive studies on septic sore throat, makes the following summary. "The bacteria most often found are the hemolytic streptococci. The most severe types of infections are due to the St. epidemicus, and in milk-borne epidemics these streptococci have always been the source of mastitis in the cow. In sporadic cases due to St. epidemicus, the mode of infection is not through milk but carriers or active cases. A number of streptococci causing sore throat are not identified with St. epidemicus or St. scarlatinae. But little is known about their epidemiology and distribution. They may have considerable virulence and may cause sore throat and complications like that of the specific streptococci."

Scarlet Fever.

Scarlet fever is an acute infectious disease caused by the streptococcus scarlatinae, and characterized by an abrupt onset, with vomiting, fever, sore throat, and

a punctate rash on the skin and in the mouth, followed by desquamation.

Sydenham in 1875 (79) gave this disease the name scarlet fever. Loeffler, as far back as 1884 (101) observed streptococci in smears from the throats of scarlet fever patients. Later other bacteriologists found similar results. This led to the opinion of a close relationship between streptococcus and this disease entity. Though the majority thought them to be only important secondary invaders.

Klein claimed that a milk clotting streptococcus was the primary cause of scarlet fever in an English epidemic in 1886, and named it streptococcus scarlatinae (1).

In 1892, Park (100) reported the finding of peculiar streptococci in pseudo-membranes of the throat. By far the most frequent was a streptococcus showing similar traits to the St. pyogenes and erysipelatis. It was found to be present in all scarlatinal cases during eruption.

Moser reasoned that if streptococcus was the cause, a curative serum might be produced. In 1902, he (101) published a report of the good therapeutic results obtained by the use of an antiserum produced in the horse

after repeated injections had been made of living streptococci together with the broth in which they developed so that antigenic value of any toxin could be used.

Savchenko went a step further in 1905 (101) to show that the serum contained both scarlet fever antitoxin and streptococci bactericidal bodies. He also proved that the filtered broth in which the culture had grown contained a strong toxin.

In 1903, Hektoen (68) found streptococci in 12% of his scarlet fever cases.

Andrewes and Horder (1) in 1906 reported that scarlet fever was caused by either St. pyogenes or St. anginosus.

Gabritschewsky in 1907 (59) showed that a toxic vaccine from scarlet fever strains produced a fever and scarlatiniform rash in children who were immunized.

In 1911, Hektoen (69) attempted to produce scarlet fever in monkeys by feeding throat swabbings from active cases. But his results were very unsatisfactory, as were those of other investigators.

The Dicks who have contributed so much to the study of scarlet fever, first reported in 1914 (52) the finding of anaerobic organisms in scarlet fever patients. But in 1916 (46), they state that it was

not clear whether the organisms caused scarlet fever or were only secondary invaders.

During the same time, Mair (87) demonstrated St. scarlatinae in the throats of scarlet fever patients during the first week of the disease in 87%. He was able to produce in monkeys a disease which in many respects resembled scarlet fever. He also claimed that the streptococci were confined to the region of primary invasion, where they produced a toxin which was responsible for the generalized symptoms.

Schultz and Charlton, in 1918 (88) described the following phonemenon in connection with scarlet fever: "If one injects intracutaneously into the skin of a scarlet fever patient with a bright rash, 1 cc. of serum from a normal person, or from a convalescent case of scarlet fever, there appears, after a time, at the site of the injection, a characteristic change--consisting of a complete blanching of the rash."

Moser and Pirquet, as early as 1902 (52), found serum from scarlet fever patients agglutinated scarlet fever streptococci in low dilutions. But the importance of these tests was not clearly worked out until 1920. At this time, Tunnicliff (132) reported that the serum of immunized sheep contained opsonins and agglutinins

for hemolytic streptococci from scarlet fever patients, but not for streptococci from other sources. The results of absorption tests also indicated that the streptococci from scarlet fever formed a distinct group. She further stated that possibly the serum produced with this scarlatinal streptococcus group might prove of use in the diagnosis and treatment. In the same year, Bliss (16) showed that a great majority (80%) of strains of St. hemolyticus isolated from the throats of patients belonged to a specific biological type as determined by agglutination reactions. Stevens and Dochez (127) reported that strains of hemolytic streptococcus, from cases of scarlet fever throughout the United States, all interagglutinated with immune sera prepared with these strains.

In 1923, the Dicks (48) reported the results of swabbing the throats of 5 selected volunteers with 4 day old cultures of hemolytic streptococcus from cases of scarlet fever. Three were entirely negative, one developed a sore throat and fever without rash, and one developed a typical mild scarlet fever. Into 5 others a filtered culture was inoculated. After 10 days, all were well. And on the 11th day, 4 were inoculated with an unfiltered culture and one developed

scarlet fever. This result proved that there was no virus in the culture in addition to streptococci. Previously, in 1921 (47), they reported negative results with inoculations of blood serum, whole blood and filtered throat mucus.

In 1924 the Dicks (49) reported that a filtrate of St. scarlatinae culture, when used in proper dilution, gave positive skin tests in 42% of persons who had no history of scarlet fever. All the convalescent patients tested showed negative or only slight positive reactions. The action on the skin was inhibited by convalescent serum mixed with the filtrate before injection. In 2 cases in which it was possible to observe the tests before and after an attack of scarlet fever, it was positive before and negative during the convalescence.

In a study of 100 cases, they (50) found St. hemolyticus in all. They further pointed out that these organisms could be divided into 2 groups according to their effect on mannite. Sixteen percent of the strains fermented mannite, and 84% did not. Two volunteers were selected, one showing a negative skin test and the other a positive. Hemolytic streptococci not fermenting mannite were isolated from the throat of a scarlet fever

patient, and part of a 48 hour culture was swabbed on the throat of each volunteer. The negative remained well and the positive developed scarlet fever. So they concluded that the streptococci used in these experiments fulfilled all of Koch's laws and was the cause of scarlet fever.

In the same year they (51) showed that a scarlet fever antitoxin could be obtained by immunizing a horse with scarlet fever toxin.

Dochez and Sherman (53) stated that the streptococcus causing the fever constituted a specific biologic type and was not found in septic conditions other than scarlet fever. By inoculating guinea pigs with this streptococcus, they were able to produce a disease resembling scarlet fever.

Tunnicliff (133) further reported that experiments indicated that concentrated convalescent serum and the serum of rabbits properly immunized were equally specific and helpful in identifying scarlatinal streptococci in doubtful cases of scarlet fever and in discovering carriers.

Extensive investigations have been carried on regarding the number of types of hemolytic streptococci

in relation to scarlet fever. An essential step in this research was the immunological classification of scarlatinal streptococci which has been shown by Griffith (64) to comprise four chief serological types and a heterogenous group. In a series of 222 strains, 10 reacted with type I serum, 57 with type II, 45 with type III, 44 with type IV, and the remaining 66 were heterogeneous.

A year later Griffith and Gunn (65) reported similar results in a study of 100 cases of scarlet fever. They also found that there was evidence of correlation between the serological type of streptococci on the one hand and the severity of the scarlatinal attack and occurrence of complications on the other hand.

Bronchopneumonia.

Bronchopneumonia has no specific bacterial etiology, almost any pathogenic bacteria may cause it. We all know the high incidence of bronchopneumonia complicating the contagious diseases of childhood, the infectious diseases of adult life, and the cardio-renal disease of middle and old age. And it is an accepted fact that hemolytic streptococci are the chief cause of this complicating or terminal pneumonia.

Eyre (54) was one of the first investigators to

note the frequency of streptococci in cases of bronchopneumonia following the infectious diseases.

During a severe bronchopneumonia epidemic in scattered army camps (58), hemolytic streptococci were found in all or nearly all instances of the disease. Kendall (58), under auspices of the National Research Council, found that about 80% correspond to the pyogenes strain and 20% to the infrequens strain. Various camp reports showed that from 15 of them as high as 70% of the individuals harbored St, hemolyticus. Those especially susceptible to bronchopneumonia harbored as high as 89%.

Many investigators have reported a similar high incidence of secondary streptococcal pneumonia. And since most cases of bronchopneumonia are secondary, it is only natural that we assume that streptococci play an important role.

V. INFECTIONS OF THE CIRCULATORY-LOCOMOTOR SYSTEMS.

Infections may involve either the circulatory or locomotor system alone, or jointly. These infections comprise a large and very important group. They have been classified under the general term rheumatic state (rheumatism), which includes rheumatic fever, chronic arthritis, fibrositis or myositis, and endocarditis. Although streptococci are looked upon as the exciting cause by many, they are as yet not universally accepted.

Rheumatic Fever.

Rheumatic fever is an acute infection characterized by polyarthritis and a pronounced tendency to involve the endocardium, pericardium and myocardium.

It is only recently that the vast economical importance of this disease has been realized. Consequently intensive investigations have been carried out, enabling investigators to point to a specific organism as the causal agent in rheumatic fever.

The clinical importance of sore throat and rheumatic fever was probably the first step in the etiological study, and this was mentioned by Trousseau and Fowler in 1880 (103). But the earliest streptococcus to be reported was that by Netter in 1892 (103) from a single case of rheumatic fever.

Dana (36), in 1894, isolated a small diplococcus from a case of chorea following rheumatism. In 1898, Triboulet and Coyon (27, 5) cultured cocci from 11 cases of rheumatic fever and succeeded in producing endocarditis in rabbits by intravenous inoculation, This focused the attention on the mocrococcus to be the infective agent. Then the following year, Wassermann, Westphal, and Malkoff (27) isolated a streptococcus from a fatal case and produced multiple arthritis in rabbits with this organism. They stated that the freshly isolated organism appeared as a diplococcus, but in culture it grew as a streptococcus.

In 1900 Poynton and Paine (103) produced convincing evidence by demonstrating diplococci in rheumatic nodules, valves, pericardium and tonsils of 8 cases. They described the organism as minute gram positive cocci associated in pairs and growing as small chains on culture media. They were successful in producing polyarthritis, valvulitis and pericarditis in rabbits by intravenous injections.

Three years later, Beaton and Walker (5, 134) isolated the same micrococcus in 15 cases. They described it as a tiny gram positive micrococcus arranged in pairs and short chains and being non-capsulated.

It was not until 1908 that a positive joint culture was obtained. Loeb (85) by taking cultures on 45 cases, obtained 10 positive blood and one positive joint culture of streptococci.

Camisa in 1910 isolated a diplo-streptococcus from the blood of 6 out of 9 patients with chorea following rheumatic fever (115). Collins (31), also isolated cocci, which grew in pairs or chains, from the blood of a patient with severe chorea.

Coombs and Miller (33) succeeded in producing lesions histologically identical with human lesions by inoculating rabbits with streptococci from cases of rheumatic fever.

In 1913-14, Rosenow (110) isolated streptococci from joints in 7 out of 8 cases and from the blood in 4 out of 7 cases. He claimed to have isolated 3 types of cocci, each of which could be converted into the other. Two of the types, one a long chain coccus and the other a micrococcus, were obtained from cases with no muscle involvement. The third type, a diplococcus with short chains, was obtained from cases of rheumatism with definite muscle involvement.

Herry in 1914 made an elaborate study of 60 cases, 43 yielded positive blood cultures, 4 out of 5 joint

cultures were positive for streptococci, and 7 pleural fluids gave streptococci. Altogether 47 of the 60 cases (78.3%) gave positive streptococci. He also produced myocardial, endocardial and joint involvement readily in rabbits by injections of these streptococci (27).

Then, Cecil (23) further showed that destruction of the articular surfaces followed the intravenous injection of St. viridans into rabbits.

Swift and Kinsella (130) in 1917 concluded that no type of streptococcus was constantly found in acute rheumatic fever. For in their series, joint cultures were uniformly sterile and only 19% of the blood cultures were positive for non-hemolytic streptococci.

Clawson (29) isolated streptococci from the blood in a high percentage of 20 well defined cases of rheumatic fever or chorea. The majority belonging to the viridans group, though it did not seem to be a specific strain.

In 1926, Swift, Derrick and Andrewes (128) published the report that 62 out of 122 patients gave a history of sore throat. And they further reported that 13 strains of hemolytic streptococci isolated did not show any evidence of being related serologically.

In 1927, Small (122) reported that a serologically

specific non-hemolytic streptococcus was isolated from both the blood and throat cultures of rheumatic cases. Rabbit inoculations resulted in characteristic lesions identical with those found in humans. He offered the name St. cardioarthritis, for it was found in both rheumatic fever and chronic arthritis.

At the same time, Suranyi and Forro obtained St. viridans in 68% of their blood cultures (27).

Cecil, Nicholls and Stainsby (27) published their extensive results in 1929. They reported that 35 out of 60 cases gave positive blood cultures for streptococci. Of the 35 strains recovered, 33 were classified as alpha streptococci (viridans), one as beta (hemolytic), and one as gamma (anhemolytic). They also found that 5 out of 7 joint cultures were positive for St. viridans, and further that 3 of these were serologically identical to those obtained from the blood. And lastly they showed that agglutination, and absorption tests indicated that a specific biological group of streptococci were responsible for rheumatic fever.

In 1936, Goldie and Griffiths (61), in an investigation of 500 cases of rheumatic diseases reported that previous hemolytic streptococcal infections were more common in patients with rheumatic diseases than

in a control series of healthy individuals of similar circumstances.

In conclusion it is self-evident that it is difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the viridans type.

Chronic Infectious Arthritis.

Chronic infectious arthritis is a chronic inflammatory condition of the joints and periarticular tissues, characterized in the earlier stages of migratory swelling and stiffness of the joints, and in the later stages by more or less deformity and ankylosis (26). The condition has several synonyms, among which are arthritis deformans, rheumatoid arthritis, and atrophic arthritis.

Billings (9) was probably the first to contribute important facts bearing upon the etiology of chronic infectious arthritis, when he reported that a definite relationship existed between focal infections and arthritis (1912). At the same time, Davis (37) reported his studies on the bacteriology of tonsils with special reference to chronic arthritis. He showed that tonsils contained streptococci in a very high percentage of cases, and could account for the joint manifestations.

These reports naturally focused attention on the streptococci as a possible cause of chronic infectious arthritis.

In 1913, Davis (38) was able to produce experimental arthritis in rabbits with hemolytic streptococci isolated from focal infections. But he was unable to get positive blood or joint cultures. The following year, Rosenow (112) isolated St. viridans from the enlarged lymph nodes of several patients with chronic infectious arthritis. He also obtained a few positive joint cultures.

Moon and Edwards, in 1917 (92), reported that they obtained non-hemolytic streptococci in 6 out of 10 cases from joint effusions, and 18 out of 83 from the blood.

Richards (104), in 1920, claimed that 14 out of 104 cases yielded positive blood cultures for St. viridans, and 4 out of 54 yielded positive joint cultures. He further showed that complement-fixation tests on the patients serum with various antigens prepared from the culture of St. viridans were positive. He also took cultures from the teeth, tonsils and nasal cavities, and showed that St. viridans was present in the majority of cases. Harding (66) followed up by showing

that 89% of 300 cases of arthritis at Camp Lewis in Washington revealed focal infections.

Cecil and Archer (25) confirmed this evidence by reporting focal infections in the great majority of 200 cases studied with the most common site being the teeth and tonsils.

Monro (93), who had previously failed to get positive cultures, finally succeeded in obtaining gram positive cocci from both the joints and blood in 1922.

In 1928, Forkner, Shands and Poston (56) cultured St. viridans from joints in 11 of 63 cases, and from the draining lymph nodes in 9 out of 21 cases.

Cecil, Nicholls, and Stainsby (26), in 1929, reported that they had isolated a specific organism. Out of 78 cases, 61.5% gave a positive streptococcus blood culture as compared to a control series of 4% positives. Of these streptococci, 83% were culturally and biologically identical and appeared to be attenuated hemolytic streptococci. They called this the "typical strain," and they also isolated streptococci from 5 out of 7 joint effusions. Animal inoculation resulted in a chronic non-suppurative polyarthritis in the majority of experiments.

Two years later, Nicholls and Stainsby (96) re-

ported that out of 110 cases, 103 (93.6%) showed a definite agglutination with the "typical strain" of St. hemolyticus. This was not shown by controls. But they also showed that there existed a close antigenic relation between their strain and the streptococci from scarlet fever and erysipelas.

Gray and Gowen (63), in a study of 37 cases and 32 controls, have reported finding St. viridans type in 25 cases.

All these observations tend to confirm the theory that chronic infectious arthritis is a streptococcal infection. But I do not intend to infer that other organisms cannot cause this condition.

Fibrositis.

Fibrositis is rather a vague clinical term, defined by Wyatt (139), "as a low grade inflammation of the white fibrous tissues which enter into the makeup of those bodily structures that are concerned with locomotion."

There are very few reported studies of this entity, for opportunities for direct study are rare. Both metabolic and bacterial causes have been advanced. I shall only attempt to present but a few evidences pointing to the bacterial cause.

As early as 1913, Rosenow (114) reported that streptococci from both rheumatic and non-rheumatic myositis tended to localize and produce non-suppurative lesions in the muscles of animals following intravenous injection. This localization occurred with strains isolated from both the focus of infection and the involved muscles. Thus, he was convinced of the infectious theory of myositis.

Eight years later, Rosenow and Ashby (116) reported their study of 28 cases. They found localized infections around the teeth and tonsils in nearly all of the 28 cases. Following removal of these foci, a very striking improvement was observed in all but one of the patients.

Streptococci are found in the great majority of cases to be the offenders in the various foci of infection involving the oral structures. Therefore it seems very probable that streptococci play an important role in fibrositis.

Wyatt (139) is of the opinion that although various strains of St. viridans are the most frequent bacterial causes, a number of other strains may also produce fibrositis.

Bacterial Endocarditis.

Bacterial endocarditis may be divided into two types, acute and subacute, based upon clinical duration. Libman (82), the first to use this classification, grouped the acute as those having a duration up to 6 weeks and the subacute--those having a duration from 6 weeks to years. There is also a bacteriological difference. The acute are caused by St. hemolyticus, staphylococcus, and other organisms. The subacute are caused by the St. viridans.

Schottmuller was the first to call attention to the fact non-hemolytic streptococci could be isolated from the blood of cases of subacute infectious endocarditis (138).

Horder (1), in 1906, reported that he had found streptococci in the blood in nearly 90% of his cases. Libman and Celler (84) also found the same organism in 35 out of 36 cases. A few years later, Libman (81) reported positive blood cultures from 73 out of 75 cases. A characteristic cocci (St. viridans) was found in 71 of the cases. He also went further to show that the blood of these patients contained agglutinins and complement-fixing bodies for the strains isolated from the blood.

Rosenow (109), in 1912, observed that endocarditis caused by streptococci in the course of a severe infection ran a rapidly fatal course. Endocarditis following streptococcus tonsillitis ran a chronic course. Therefore he concluded that the first was caused by a highly virulent streptococcus and the latter by a less virulent coccus.

Oille, Graham, and Delweiler (1915) found anhemolytic streptococci in all of their 23 cases (83).

Kinsella (76) in 1917 found St. viridans in a high percentage of cases, and further proved the existence of specific antibodies in the blood of such patients.

Kastner (1918) was able to isolate a streptococcus from the blood in all of 16 cases (138).

Salus of Prague (1920) isolated St. viridans in 18 cases at repeated intervals (82). At the same time Lampe of Germany reported positive cultures in only 6 of 19 cases (138). Murray also obtained a rather low percentage of St. viridans cultures (30).

Clawson (30) in an analysis of 220 cases found St. viridans in only approximately 30%.

Lehman (80), in a study of 22 cases from 1922 to 1925, obtained positive cultures of St. viridans in 20. Wright (138) followed up by reporting 12 positive cul-

tures in 19 cases.

Horder (71), who in his early series had found organisms in nearly 90% of his cases, reported his second series in 1926 in which the percentage dropped to 47%. In the same year, Kreidler (78) isolated streptococci in a high percentage of 15 cases from both the blood and cardiac vegetation. All but one proved to be St. viridans.

Morrison in 1927 (94) reported his studies of 145 cases, 84 or which gave positive St. viridans cultures and 42 no growths.

Schlesinger (119) went as far as to say that in children suffering from the disease, positive cultures for streptococci are almost the rule.

In conclusion, I wish to emphasize that subacute endocarditis is constantly associated with St. viridans, and acute endocarditis is frequently associated with St. hemolyticus (pyogenes).

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