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The Biology of Group A Streptococcosis

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A. INTRODUCTION

1. Clinical Classification of Group-A Streptococcosis

Available information seems to justify the belief that group-A streptococci play a role in the pathogenesis of not only such illnesses as pharyngitis, scarlet fever, erysipelas, puerperal fever, lymphangitis, and their suppurative complications, but also a group of disorders, the late nonsuppurative sequelae, which include rheumatic fever and acute glomerular nephritis. The term "streptococcosis" has been suggested to include all these various clinical pictures resulting from group-A streptococcal infections[1]. The term "tuberculosis" is used in a similar manner to include the varied clinical disorders resulting from infection with *Mycobacterium tuberculosis*. It is the purpose of this report to review the current concepts of the mechanisms which allow group-A streptococci under natural conditions to induce this wide variety of disease pictures and to record the preliminary results of investigations relating to this problem now under way in our laboratory.

2. Consideration of Terms

An analysis of the mechanisms whereby group-A streptococci induce this wide variety of clinical disorders requires a study of all of the attributes that, under natural conditions, contribute to their pathogenicity and virulence. Watson and Brandly[2], in a recent review of the current concepts of virulence and pathogenicity as applied to various infectious agents, discuss the attributes of virulence and pathogenicity under the headings of communicability, infectivity, invasiveness, and toxigenicity. They point out that communicability is an essential attribute to virulence as a natural phenomenon, even though it is not involved in most experimental measurements of virulence. In an analysis of the mechanisms of virulence that are responsible for any particular clinical picture resulting from an infection, it must be clearly recognized that the host-parasite relationship makes essential careful consideration of the variable and complex properties of the host as well as those of the parasite. It must also

[1]This research was conducted under contract with the Office of Naval Research.

[2]The following students have participated in the experimental work: Perry Morgan, Margaret Whelan, Arthur Johnson, John Schwab, and James Prince. Various phases of this problem will be used toward the partial fulfillment of their graduate requirements for advanced degrees.

be remembered that under natural conditions herd structure, as defined by Topley and Wilson[3], influences this host-parasite relationship.

B. HERD STRUCTURE AS A FACTOR IN NATURAL PATHOGENICITY AND VIRULENCE

An inseparable determinant of natural virulence and pathogenicity of streptococcus is its ability to spread from one host and to establish itself in another. The individual host, its relationship to other hosts, and the environmental factors that permit a natural spread of the streptococcus to a variable extent in most areas of the world have been intensely investigated, especially during World War II[4,5]. However, it has been impossible to devise practicable methods for breaking this cycle in the environment, as is true of most infections transmitted by the respiratory route. It is beyond the scope of this communication to consider all the factors of herd infection and immunity that impinge on this problem. For the purpose of this discussion, it is important to point out that herd structure, by allowing individuals to have repeated infections with group-A streptococci, influences the type of host response induced by these organisms.

C. PROPERTIES THAT INFLUENCE THE INTERACTIONS OF THE PARASITE AND THE HOST

Group-A streptococcal cells have been fractionated into several component parts, and many soluble substances have been isolated from the media in which they were cultivated. These materials which were described recently and their properties reviewed[6] include a carbohydrate, designated as "C" substance, two proteins, "M" and "T", nucleoproteins or "P" substances, streptokinas, hemolysins "S" and "O", erythrogenic toxin, proteinase, hyaluronic acid and hyaluronidase. Observations on other bacteria indicate that the substances produced *in vitro* may be somewhat different from those produced *in vivo*[7,8]. This should be kept in mind in any attempt to evaluate the role of the substances isolated from streptococcal cultures in the various aspects of virulence and pathogenicity. This thesis will be elaborated below.

1. Mechanisms that Influence Communicability and Infectivity

M protein and hyaluronic acid seem to protect group-A streptococci from phagocytosis[9]. Since this protection is associated with continued multiplication of the bacteria, it is possible that M protein and hyaluronic acid play a role in the establishment of infections with these agents. The importance of M protein is indicated by the degree of type-specific immunity that is associated with anti-M antibodies; this is not true of the T-protein antibodies[10]. The demonstration by Todd[11] that streptolysin-O exerts a powerful lytic action on leukocytes suggests that this substance may also play a role in allowing the organisms to overcome host resistance. However, no correlation has been established between streptolysin-O production and virulence[11]. The fact that these organisms are highly communicable, but not prequently highly infective, is indicated by their presence in the upper respiratory tracts of 58 per cent of an apparently normal population[12]. Factors, such as trauma or virus diseases, which under some circumstances lower host resistance, are known to play a role in the establishment of infections. Nevertheless, the occurrence of many outbreaks of group-A streptococcal infections was without any apparent association with these factors[13]. As pointed out by Coburn[14], these latter outbreaks seem to result from the dissemination of a strain that combines communicability, properties of infectivity yet undefined, and the other atrributes of virulence. His epidemiological studies led him to believe that the host-parasite interactions resulting in subacute infections are associated with the development of organisms possessing these qualities, whereas the usual acute infection is not associated with the

development of such organisms. Coburn speculated concerning the nature of these changes and noted that organisms disseminated by "dangerous carriers" appear to have acquired the capacity to multiply rapidly in the presence of inhibitory substances of the normal mucous membranes. This property seems to be lost in a high percentage of new hosts during the process of the establishment of an acute infection. The acquisition of these new properties appears to involve an adaptive mechanism, the nature of which is not understood. If further investigations should reveal that this property of infectivity concerns some antigenic substance, a method for producing a general or non-type-specific immunity might become feasible. This aspect of the pathogenesis of infection is difficult to investigate by the usual laboratory methods; however, our understanding of group-A streptococcal infections will not be complete until this mechanism is elucidated.

2. Mechanisms that Influence Invasiveness

The invasive character of group-A streptococci is well recognized. Their ability to spread along mucous membranes and to invade the adjacent tissues is well established by histological and bacteriological studies. Invasion of lymphatics and entrance into the bloodstream with localization in joints, on heart valves and elsewhere, is also a fairly common occurrence in this infection[15]. The mechanisms responsible for this character of virulence are not clearly understood. M protein, hyaluronic acid and streptolysin-O, by protecting the organisms from phagocytosis and allowing them to multiply in the tissues may play a role in invasiveness. As indicated in several reviews[16,17], a great deal of investigation has been carried out in an attempt to implicate the enzyme hyaluronidase as a major factor in determining the invasive quality of these organisms. However, experimental studies suggest that hyaluronic acid, although not as important as M substance, plays a role in protecting these organisms from phagocytosis[9]. Since this substance is the substrate for hyaluronidase, this presents a paradox difficult to evaluate. It was once believed that the production of a hyaluronic acid capsule and of hyaluronidase were mutually exclusive phenomena. However, the demonstration by Pike[18] that cultures of some encapsulated strains of group-A streptococci, as they grew older, exhibited decreasing amounts of hyaluronic acid is interpreted to indicate a weak and variable hyaluronidase activity. He was unable to relate this property to any aspect of virulence. Sallman and Birkeland[19] demonstrated hyaluronidase to be an important factor in the pathogenicity of group-A streptococci for ten-day-old chick embyros and suggested that this indicated a relationship between hyaluronidase production by streptococcal strains and their virulence for humans. Russell and Sherwood[20], using thirteen-day-old embryos, observed no correlation between hyaluronidase production and the capacity of streptococcal strains to kill, or to spread in this host. McClean's[21] studies suggest that the role of hyaluronidase in virulence may vary depending on the route by which the organisms are introduced. Although specific antibodies[22] and non-specific inhibitors[23,24] are produced which neutralize the activity of this enzyme in vitro, it has not been established, to the reviewers' knowledge, that such substances play a role in immunity to this infection. If this enzyme is an essential factor in invasiveness, such substances might be expected to afford protection from this attribute of virulence. Further investigation along this line will possibly help to evaluate the importance of hyaluronidase in this infection.

Proteinase, another enzyme produced by group-A streptococci[25], conceivably plays a role in the invasiveness of these organisms. Like hyaluronidase, however, it destroys a surface component, the M protein, which has been established to be more important than hyaluronic acid in protecting these organisms from phagocytosis[9], thereby creating another paradox paralleling

that of the hyaluronic acid-hyaluronidase system. Since proteinase is antigenic, further evaluation of the role of this enzyme in the virulence of streptococci might be attempted along the lines suggested above for hyaluronidase.

Streptokinase, a substance produced by most of the strains of group-A streptococci, has been extensively investigated since it was first demonstrated by Tillett and Garner[26]. The current concepts of its actions are reviewed by Rammelkamp and Dingle[6]. The activity of streptokinase depends upon its ability to activate the formation of plasmin from a proenzyme present in human sera. This enzyme is capable of digesting fibrin and other proteins. These properties suggest that this substance has an important function in the quality of invasiveness exhibited by these organisms. Tillett[27], after studying 1,300 strains of streptococci, concluded that the streptococci associated with suppurative and invasive types of infection are with few exceptions possessed of fibrinolytic properties and are usually the most potent in causing lysis of fibrin. However, some strains of group-A streptococci which do not produce this substance have been found to induce characteristic lesions[28]. Menkin[29] states that streptococci tend to spread from a local site more readily than, for example staphylococci, because they induce less tissue damage and fail to initiate the process of lymphatic blockage to the degree found in lesions induced by staphylococci. According to this concept, the invasive quality of streptococci is attributed to the fact that they are able to multiply in tissue without producing a severe necrotizing effect which would cause lymphatic blockage. Streptokinase would not be important in this explanation because fibrin formation is not believed to take place to any important extent in streptococcal infections. Further studies will be necessary before the mechanisms that enable these organisms to invade tissues are completely elucidated.

3. Mechanisms that Influence Toxigenicity

Another attribute of virulence, toxigenicity, includes the mechanism of host-parasite interactions which result in tissue damage, the various associated functional changes and, in some instances, death of the host.

Topley[30] pointed out that the mere presence of the parasite within the tissue does not explain its harmful effect. When one considers the toxic properties of the substances produced *in vitro* by group-A streptococci, the C carbohydrate, M and T proteins, hyaluronic acid, and nucleo-proteins or P substances, they are found to exhibit no primary tissue damaging abilities. The possibility that altered host reactivity may permit these substances to play a role in tissue damage will be discussed below. The recent review by Bernheimer[31] indicates that the streptolysins have been investigated extensively as to their toxicity. Although these substances alone will not stimulate the production of lesions similar to those associated with acute streptococcal disease, it seems that the leukocidin effect of streptolysin O might play a role in producing the cellular picture observed in these lesions. The work of Todd[32] and Bernheimer[29] demonstrating the lethal properties of these substances for laboratory animals suggests a possible role for streptolysins S and O in the pathogenesis of streptococcosis. The lethal property of the serum extracts of group-A streptococcal cultures described by Weld[33] has been shown to be due to streptolysin S. Since high antistreptolysin titers do not appear to be associated with increased resistance to this infection, it is unlikely that the streptolysins by acting as primary toxins play a central role in the pathogenesis of these infections.

The direct action of erythrogenic toxin[34] explains only the toxic phe-

nomena peculiar to scarlet fever. Therefore, most of the toxic reactions associated with these infections cannot be ascribed to a primary effect of this substance.

The importance of the enzymes proteinase and hyaluronidase and the proenzyme streptokinase in the production of lesions associated with tissue invasion by these organisms is not clearly established. Hyaluronidase is the only one of these known to be able to break down a constituent of normal tissue. The changes induced when hyaluronidase breaks down the hyaluronic acid of tissue ground substance are not sufficient to explain the lesions induced by the invasion of group-A streptococci[35]. It is possible that this action contributes to the lesions observed[36,37]. It seems unlikely that these enzymes are directly responsible for the striking tissue changes or for the associated signs and symptoms occurring in the phase of group-A streptococcal infections associated with the presence of viable organisms in the lesions.

One may postulate, as is done in the case of pneumococcal infections[38], that group-A streptococci multiplying in tissues produce damage either by the mechanism of competitive-inhibition or through the production of local or general acute deficiencies in one or more metabolites essential to the host cells. There are no studies to support this theory. However, in view of the failure to isolate toxic products from group-A streptococci which are capable of bringing about all of the observed damage to the host, experiments designed to detect such metabolic disturbances might be worthwhile.

Another possible mechanism of tissue damage postulates the formation of poisonous substances from the host tissues. Menkin[29] believes that most of the observed inflammatory reactions result from the action of substances liberated from injured host cells. This concept does not explain the nature of the primary damage but may explain some of the secondary reactions observed in an individual infected with these organisms. Some observations relating to this problem will be recorded below.

A great deal of information has been accumulated which indicates that any attempt to analyze the toxigenic properties of group-A streptococci must take into consideration the changing reactivity of the host to the various products of these organisms. This changing reactivity of the host seems to be brought about by previous infection with group-A streptococci. Powers and Boisvert[39] emphasized the role of changing host reactivity to group-A streptococci in the production of the different clinical pictures exhibited by patients of various age groups.

Changing host reactivity, hypersensitivity, or allergy has been put forward as an essential part of the mechanims by which group-A streptococci produce the late nonsuppurative sequelae which include rheumatic fever and acute glomerular nephritis. In this theory it is postulated that the invasion of the tissues of certain individuals by these organisms induces a state of hypersensitivity which subsequently leads to a hypersensitive reaction resulting in the anatomical and the functional changes associated with these disorders.

Rheumatic fever and acute glomerular nephritis are not associated with the presence of group-A streptococci in their characteristic lesions as is true in case of group-A streptococcal pharyngitis and the other acute diseases. No toxic substance has been identified, which might account for the lesions associated with the late sequelae as has been accomplished in case of the reaction characteristis of scarlet fever. The temporal relationship of the sequelae to the primary infections makes it appear unlikely that they result from the action of a bacterial toxin of the usual type. Fischel[40], in his recent review, credits Menzer with first advancing the concept of hypersensitivity as it relates to rheumatic fever, and points out the many different types of observations

that support this theory. This disease has features in common with serum sickness--a disorder known to result from a hypersensitive reaction. The latent period between scarlet fever and the late sequelae led Escherich and Shick[41] to observe that it was similar to the period required to develop active sensitization. Herry[42], in 1914, produced lesions with features similar to Aschoff nodules by a process which he believed sensitized rabbits to an "endotoxin of diplococci" isolated from cases of rheumatic fever. Following this study, many investigators, using procedures involving hypersensitive reactions chiefly of the immediate reacting type, induced in experimental animals lesions with some features of rheumatic fever and acture glomerular nephritis. These observations have been interpreted to mean that hypersensitive reactions play an essential role in the production of the late nonsuppurative sequelae of group-A streptococcal infections[43].

Rantz, Boisvert, and Spink[44], after extensive studies of rheumatic fever during the last war, suggested that this disease is invariably induced by group-A hemolytic streptococci, that the clinical manifestations are the result of altered sensitivity of the tissues to products of the hemolytic streptococcus and that repeated infection with different types of these organisms might be necessary for the development of these disorders. These observations were followed by the production in rabbits of a disorder resembling rheumatic fever by Murphy and Swift[45]. These investigators accomplished this by the use of serial dermal infection with different types of group-A streptococci. These findings are compatible with the concept that altered host reactivity plays an important role in the late nonsuppurative sequelae. The influence of ACTH and cortisone on the course of rheumatic fever also emphasizes the important of the host reactivity in the production of this condition[46]. The studies of Good and Campbell[47] of changes in the bone marrow plasmocytes and serum gamma globulin during acute streptococcal infections and rheumatic fever are strong evidence in support of a host response to antigenic stimulation during streptococcosis.

There are certain weaknesses in the concept which involves hypersensitivity as the major cause of the late nonsuppurative sequelae. For instance, many infestigators have failed to demonstrate consistently immunological reactions that differentiate patients experiencing an uncomplicated recovery from this infection and those developing the late nonsuppurative sequelae[48]. Immunological investigations of patients exhibiting the late nonsuppurative sequelae of group-A streptococcal infections have served to substantiate the occurrence of a preceding streptococcal infection by demonstrating circulating antibodies to various streptococcal products or the presence of skin sensitivity to various antigens isolated from these organisms. However, these reactions to not appear to differ significantly from those occurring in individuals who appear to have recovered from the preceding infection without complications. Nevertheless, the evidence that a hypersensitive type of reaction is involved in the mechanism whereby group-A streptococci cause these late sequelae is of such a nature as to warrant further intensive investigations along these lines. More fundamental information concerning the mechanism whereby antigenic materials, especially those of streptococcal origin, are disposed of by the infected host, the relation of these mechanisms to antibody production, and the development of hypersensitive reactions might suggest immunological methods that would allow specific diagnosis of the late nonsuppurative sequelae. Most of the previous studies have been directed toward detection of antibodies to various streptococcal products. If the current concept of serum sickness is correct, it is only the individual with residual antigen in their tissues at the time of appearance of antibodies who exhibit symptoms of this disorder. It is possible that the individuals who develop the late nonsuppurative sequelae are those who retain streptococcal antigens at

certain sites in their tissues until antibodies appear; on the other hand, those who are able to rid their tissues completely of antigen before antibodies appear escape the late complications. Preliminary studies relating to the fate of antigenic material in the tissues of animals have been undertaken and will be mentioned below.

The concept advanced to explain the absence of viable streptococci in the lesions of rheumatic fever patients by those who believe that the disease results from a specific type of streptococcus is of interest. These workers postulate that, although the organisms are rapidly killed, they stimulate the tissue changes observed[49]. The experimental studies of Clawson[50] support the concept that rheumatic endocarditis and bacterial endocarditis occur as a response to a direct valvular infection and that they differ in the manner of host response to the presence of the organisms in the tissues. The studies of Mallory and Keefer[51] also suggest that the sequelae of events leading to the late nonsuppurative lesions of streptococcal infections is initiated by the presence of organisms at the sites that show the characteristic late lesions.

It should be kept in mind that the concepts of direct infection and hypersensitivity are not mutually exclusive. Elucidation of the precise toxigenic mechanisms leading to the late sequelae will require many new facts.

D. EXPERIMENTAL

The brief review indicates the gaps in the available knowledge of the mechanisms which allow group-A streptococci to produce the host changes that constitute the many clinical pictures of streptococcosis. The information relating to properties of both parasite and host concerned in these interactions is far from complete. Work done with Bacillus anthracis[7,8,52,53] suggests one possible reason why the various in vitro studies of group-A streptococci have not allowed the isolation of substances that account for all the properties it exhibits in vivo. Studies of B. anthracis made it known that the multiplication of this organism in the skin of rabbits results in the production of a capsular material that differs markedly in biological properties from the capsular material produced in vitro. Under these conditions B. anthracis also produces immunizing antigen that is not produced in ordinary culture media. For this reason, experiments were designed which would permit the study of group-A streptococci in an in vivo environment. This was accomplished by extending the methods that had been applied in the earlier studies of anthrax. The steps in this procedure are illustrated in Figure 1. This procedure has allowed the separation of intact group-A streptococcal cells, and of certain soluble and insoluble products, from extracts of lesions which had been produced in the skin of rabbits by the injection of these organisms.

The observed properties of the group-A streptococcal cells removed directly from lesions may be briefly summarized as follows: (1) Strains have been found to show enhanced virulence as measured by intravenous injection into rabbits. This is illustrated in Figure 2. (2) It is possible to induce variation in colonial form and the associated changes in cellular structure. By a single passage in the skin of rabbits, strains of streptococci in the glossy or rough phase, have been converted to the matt or, more commonly, the mucoid phase. It is believed that this will prove to be a useful procedure in studying these organisms because conversion from the glossy phase to the mucoid phase has been most difficult to accomplish by previously described methods. Table 1 summarizes some of these observations[3]. The lesions induced in rabbits by a single intravenous injection of organisms removed directly from lesions of the skin of rabbits are similar to those previously described as resulting from the same type of experiments using organisms

R A B B I T (Approximately 2.5 Kilo.)

35 ml. (9.2 x 10^7 organism/ml.) of T28 (glossy) B-streptococci injected intracutaneously at 70 sites over the entire shaved abdomen and thorax.

↓

Killed after 24 hrs. (usually moribund)

↓

Lesions excised (385 gm.) and frozen --70°C.

↓

Thawed, macerated in a meat grinder and added 770 ml. cold 0.85% NaCl (2 ml./gm.)

↓

Extracted by continuous stirring at 2°C. for 14-18 hrs.

↓

Filtered through 4 layers of gauze.

↓

Centrifuged at 30,000 R.P.M. (30 min.) Spinco 40

Sediment

↓

Dispersed in 10 ml. supernatant (1)

↓

Frozen -70°C. (2 ml./vial)

↓

Contains sedimentable toxin plus mucoid organisms 4.7×10^7 to 2.3×10^9 ml.

Supernatant (1)

↓

Filtered - Selas bacterial filters (bacteria-free)

↓

Dialyzed against distilled H_2O - 24 hrs.

↓

Centrifuged - 2500 R.P.M.

Precipitate

↓

Dissolved in NaCl and phosphate buffer pH 7.4 - 0.3, ionic strength

Soluble toxin

Supernatant (2)

(non-toxic)

FIGURE 1: Preparation and Fractionation of Rabbit Lesion Extract

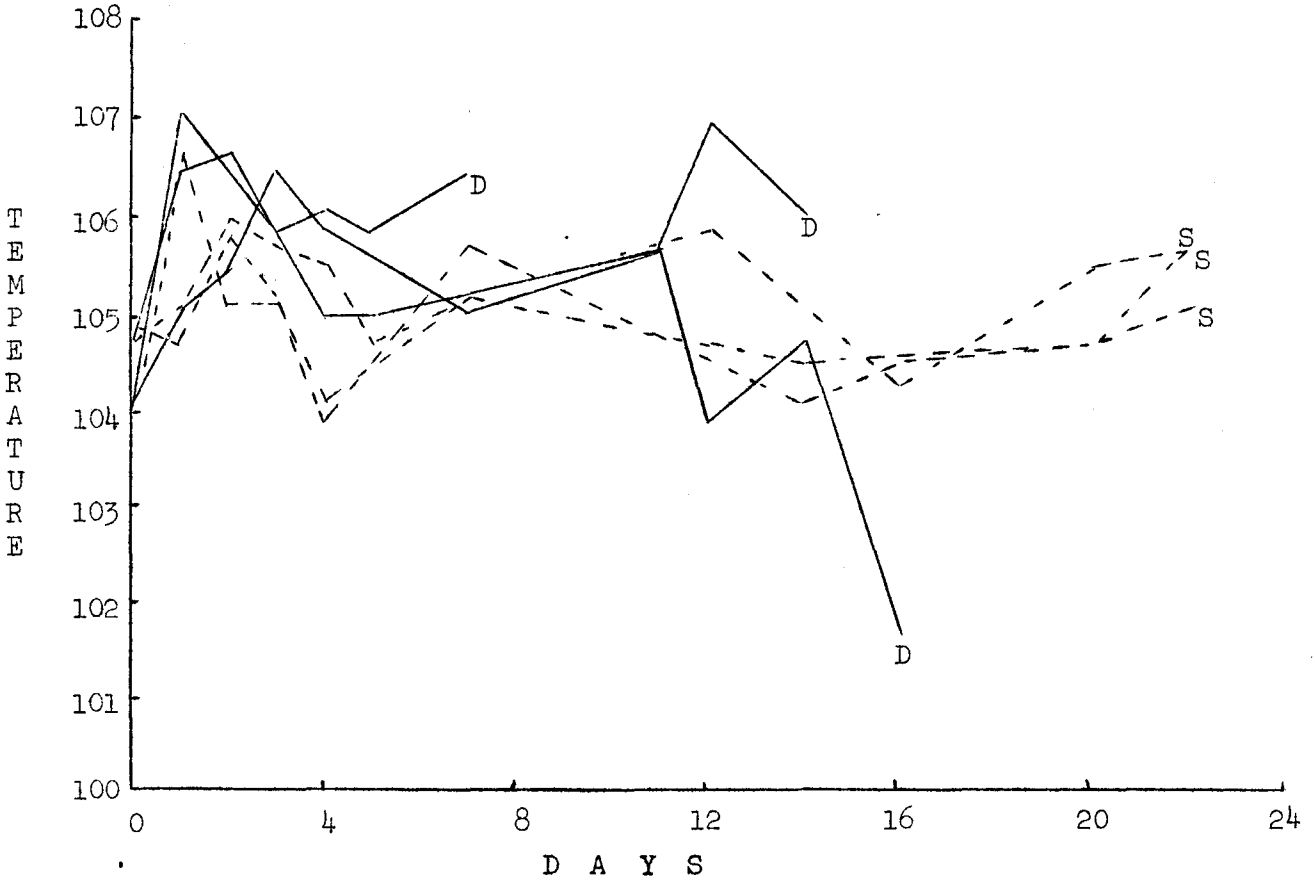

FIGURE 2: The Relative Virulence of Group A, Type 28 Streptococcus

Solid line = organisms from skin lesion extract - 4.0×10^7/ml.
Broken line = organisms from culture medium - 7.5×10^7/ml.

produced in vitro. The most striking lesions were those resulting from localization of the organisms in the lungs, joints, and on, or in, the heart valves with the production of pneumonia, suppurative arthritis and actue ulcerative bacterial endocarditis. The incidence of acute bacterial endocarditis somewhat higher than that previously reported as being produced by the intravenous injection or organisms grown in vitro[54]. Rabbits which survived a single injection were given one or more injections at two-week intervals. The incidence of mitral valve involvement in this group was higher than in the group dying after a single injection. These results are given in Table 2.

It was noted that the rapid injection of the sediment, containing the streptococci, into the veins of rabbits caused immediate death when more than 0.1 ml. was injected. This observation led to a series of studies as to the nature of this toxic property.

This toxin is not a product of the streptococci but is associated with a sedimentable tissue component of the host. Similar toxic sediments prepared from brain, lung, and other tissues have been described by Thomas[55,56]. These toxic particles, which are sedimentable at speeds of 12,000-14,000 r.p.m., exhibit marked thromboplastic activity. Heparinized animals are protected against this toxic substance. Normal rabbit serum appears to inhibit the action of this toxin. Injection of sublethal amounts of this material increases the toler-

TABLE 1: THE CONVERSION BY INTRADERMAL PASSAGE IN RABBITS OF GROUP A STREPTOCOCCI TO MUCOID PHASE

TYPE	STRAIN	COLONY FORM		
		Before Passage	After 1st Passage	After 2nd Passage
18	P18	glossy	mucoid	
22	AT22	"	"	--
3	D 58	"	"	--
17	SD592	matt	"	--
17	CO	glossy	glossy and matt	glossy and matt
4	T4-AT4R65	glossy	mucoid	--
28	AT28	"	"	--
19	2848F	"	matt	mucoid
11	Blackmore	"	mucoid	--
24	AT	"	"	--
43	V1620	"	"	--
5	1930	"	"	--
"	NY5	"	"	--
23	AT23	"	"	--

TABLE 2: THE INCIDENCE OF MAJOR MACROSCOPIC LESIONS INDUCED BY INTRAVENOUS INJECTIONS OF GROUP A STREPTOCOCCI GROWN IN VIVO

Number of Injections, 0.1 ml.*	Total No. Rabbits	SITE AND INCIDENCE OF LESIONS				
		Joints, One or More	Pulmonary	Heart Valve		
				Mitral	Tricuspid	Pulmonary
1	33	11	31	6	11	1
2, or more	9	.6	7	6	2	1

*Inoculum: 1:16 dilution of sediment from skin lesion extract

- - -

ance of animals to doses that would be lethal to normal animals. The toxicity of this sediment for rabbits and mice is given in Table 3.

An additional toxic component with action similar to tht toxic sediment was observed in the bacterial-free supernatant fluid (Figure 1). This soluble

feasibility of applying this method to a study of the distribution of antigenic material in the tissues of the host and to their rate of disappearance from different tissues.

E. DISCUSSION

In the brief review presented, an attempt has been made to emphasize the fact that the clinical disorders included under the term "streptococcosis" result from an expression of the natural virulence and pathogenicity of group-A streptococci. The consideration of the various attributes of virulence and pathogenicity under the headings of communicability, infectivity, invasiveness and toxigenicity should not be interpreted to imply that these attributes are distinct and unrelated properties[2]. A single property of the parasite may play a role in allowing the organism to establish itself at the portal of entry, to invade the adjacent and distant tissues and to produce structural and functional alterations of the host, thereby contributing to infectivity, invasiveness, and toxigenicity; however, for discussion it is convenient to consider sepatately these various attributes of virulence. An attempt has been made to emphasize the importance of considering the environmental, host, and parasite factors in any analysis of the sequence of events leading to the clinical pictures classified as streptococcosis. This should prevent overemphasis of the importance of any single factor. An exact understanding of the mechanisms involved in any of these areas might allow the development of methods to interrupt this cycle of events. However, it is obvious that our knowledge of the virulence and pathogenicity of group-A streptococci as they act in nature is deficient in all of these critical areas.

Our experimental approach to certain of these problems varies from previous work in that it is concerned with the study of group-A streptococci and their products in an in vivo environment, whereas the previous laboratory experiments have, to a great extent, related to in vitro studies. We believe the preliminary studies, as recorded, establish the feasibility of such an approach. The isolation of large numbers of these organisms directly from lesions has been accomplished. It has been demonstrated that these organisms on removal from lesions exhibit an enhanced virulence when injected intravenously into rabbits. Moreover, conversion of colonial form to the mucoid phase indicates a complete organism which is made up of all of the recognized antigenic constituents, inclusive of M protein and hyaluronic acid. The anatomical changes induced in rabbits infected by the intravenous route with bacteria taken directly from lesions are not markedly different from those previously reported; however, these alterations were brought about by a relatively small inoculum. The incidence of acute ulcerative bacterial endocarditis was somewhat higher than that previously reported as occurring after the intravenous injection into normal rabbits of streptococci from culture media. A sublethal infection of this type followed by a lethal infection seems to increase the incidence of involvement of the mitral valves. The significance of this observation is not clear from these studies. However, it suggests that the altered host reactivity induced by the previous contact with the organism may be playing a role in these results.

Since this experimental approach involves the extraction of lesions, it is possible to look for substances from the host's tissues that might play a role in the manifestations of this infection. Toxic substances derived from the host were demonstrated to be present in extracts of these skin lesions in a particulate and soluble form. Compared with extracts of normal skin, these extracts seem to contain more of the toxic materials in the soluble form. Any analysis of the virulence and pathogenicity of group-A streptococci should take such substances into consideration.

The increased resistance induced by injection of sublethal doses of these

TABLE 3: TOXIC PROPERTIES OF A SEDIMENTABLE SUSPENSION FROM RABBIT SKIN LESION PRODUCED BY TYPE 28 GROUP A STREPTOCOCCUS

RABBITS		MICE (Rockland Swiss)	
Volume of Suspension (ml.)	Death / Total	Dilution of Suspension (0.5 ml.)	Death / Total
0.4	2/2	1-2	6/6
0.2	2/2	1-4	6/6
0.15	1/2	1-8	6/6
0.1	0/2	1-16	6/6
		1-32	3/6
		1-64	0/6

toxin, lethal for mice, was concentrated by dialyzing the supernate against distilled water. Employing this technique, it was possible to remove the toxin in what appears to be a euglobulin fraction. Concentration was obtained by dissolving this precipitate in a small volume of 0.85% NaCl buffered at pH 7.4 with phosphate at a total ionic strength of 0.3. This soluble, non-sedimentable fraction was toxic for mice and exhibited marked thromboplastic activity.

Although small quantities of soluble toxin were obtained from macerated normal skin, comparative determinations indicate that a larger yield resulted following the extraction of streptococcal lesions. It is possible, therefore, that the interaction of the parasite and the host results in the liberation of the toxin in a soluble form.

In some respects, this soluble toxin has properties in common with necrosin[57]. The importance of these host factors on the various manifestations of streptococcal infections is being evaluated.

As previously pointed out, an understanding of the mechanisms whereby hypersensitivity plays a role in the late sequelae will require further clarification. Although many workers have stressed the importance of the production of antibodies and their relationship to these diseases following a streptococcal assault, little emphasis has been placed on the possible retention of streptococcal antigens in the various tissues of the host. The work of Felton[58] on pneumococcal polysaccharides and their ability to persist in the various tissues of the host for periods of months, or years, and at the same time block the antibody-forming mechanism demonstrates the possibility of antigen persisting in tissues for long periods of time.

The application of the precipitin tehcnique to the quantitative determination of minute amounts of antigen in the presence of complex tissue components and fluids of the body has permitted an investigation in our laboratory on the fate of two purified antigens when injected into laboratory animals. Preliminary results with type-II pneumococcal polysaccharides have confirmed the work of Felton[58]. The maintenance of a high level of purified bovine albumin in the circulation of a rabbit prevents the development of hypersensitivity to this antigen. These preliminary observations indicate the

toxic substances suggest that the host is capable of rapidly activating some mechanism that tends to neutralize the effect of these materials. Thomas[54,55] demonstrated that this protective mechanism was associated with an increased blood coagulation time. The determination of the nature of this host reaction will be of interest. It is possible that it may be related to certain of the nonspecific reactions of the host to injury, recently reviewed[59]. Hamilton and Syverton[60] demonstrated in the hearts of individuals with rheumatic fever an increase in tissue mast cells and postulated the derivation therefrom of Anitschkow cells with an associated production of mucopolysaccharide substances that include heparin-like materials. It was suggested that mast cells may play a role in the production of the characteristic tissue changes associated with this disorder. Studies of the effect of these toxic compounds on heparin liberation are being investigated. Glick and Sylven[61] have demonstrated a relationship between nonspecific hyaluronidase inhibitor and heparin-like substances. It will be of interest to determine whether these toxic materials from the host tissue are capable of stimulating the formation of nonspecific hyaluronidase inhibitor.

It is believed that the immunological techniques applied to the quantitative determination of small amounts of antigens in tissues, as presented above, may allow a new approach to the problems of why one individual develops late sequelae, while many others do not exhibit these changes. The distinction may relate to a difference in the rate of antigen elimination. The method described by Murphy and Swift[45] which involved the use of multiple serial dermal infections of the rabbit by different strains of group-A streptococci to produce, in a small per cent of their animals, a disorder which resembles rheumatic fever offers an approach by which this theory might be tested. It would be of interest to determine whether the animals which develop the reaction eliminate antigenic material from their tissues at a different rate from those which failed to exhibit the changes resembling rheumatic fever. It is quite possible that the mechanism whereby the host deals with antigenic materials is genetically controlled. Quantitative variations in such a mechanism might explain the well-established congenital predisposition as a factor in susceptibility to rheumatic fever as emphasized by Wilson[62].

Since the results of Murphy and Swift[44] were not accomplished by the use of products of organisms grown in vitro but involved the multiplication of group-A streptococci within the tissues of the host, they are compatible with the belief, emphasized in this report, that an in vivo environment may stimulate the production of essential substances that are not formed in available culture media.

F. SUMMARY

1. A brief review is presented of available information that concerns herd structure, host factors and parasite properties as they relate to the phenomenon termed "streptococcosis", which is considered to be an expression of the natural virulence and pathogenicity of group-A streptococci.

2. Experimental studies by the authors now under way, or completed, are based on the thesis that an in vivo environment can modify the characteristics of group-A streptococci. These studies have made known the practicability of studying the properties of these organisms as they occur in the tissues of an infected host, and certain of these properties are compared with those of organisms grown in vitro.

3. The readily demonstrable toxic properties of extracts derived from streptococcal lesions are considered in their relation to similar materials from other tissues and in their role in the toxigenic mechanisms of streptococcosis.

4. Experimental methods are described which permit an assay of antigenic material in various tissues of an infected, or previously infected, host, and the possible influence of the rate of antigen removal on the development of late nonsuppurative sequelae is considered.

5. An effort was made to emphasize the complex interactions of environmental, parasite, and host factors that must be elucidated before a complete understanding of the biology of group-A streptococcosis is feasible.

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II. MEDICAL SCHOOL NEWS

Coming Events

January 18	George Chase Christian Lecture; "On Research in Human Cancer. Problems and Results." Johannes Clemmesen; 15 Medical Sciences.
January 22 - 26	Continuation Course in Ophthalmology for Specialists
Jan. 29 - Feb. 10	Continuation Course in Clinical Neurology for General Physicians, Neurologists, and Psychiatrists.
January 30	J. B. Johnston Lecture; "Wakefulness and Sleep." Horace W. Magoun; Auditorium, Museum of Natural History.
February 15	E. Starr Judd Lecture; "The Surgical Treatment of Constrictive Pericarditis." Emil Holman; Medical Science Amphitheater.
February 15 - 17	Continuation Course in Cardiovascular Diseases for General Physicians.

George Chase Christian Lecture

The annual George Chase Christian Lecture in cancer will be given by Dr. Johannes Clemmesen on Thursday, January 18 at 8:00 p.m. in Room 15, Medical Science Building.

Dr. Clemmesen is Chief of the Danish Cancer Registry, and is well-known for his contributions to scientific literature in cancer. The subject for Dr. Clemmesen's lecture is "On Research in Human Cancer. Problems and Results." All who are interested are cordially invited to attend.

* * *

Faculty News

Dr. Owen H. Wangensteen will be honored at a special dinner meeting of the St. Paul Surgical Society on Wednesday, January 17. The guest speaker on this occasion will be Dr. Alfred Blalock, Department of Surgery, Johns Hopkins University Medical School, whose contributions to the field of cardiovascular surgery have won him world-wide recognition.

Dr. Clarence Dennis was the speaker at the January 8 meeting of the Hennepin County Medical Society. Dr. Dennis's subject was "Surgery in the Older Patient."

Dr. David Glick, of the Department of Physiological Chemistry, was recently in San Francisco where he was a guest speaker at a joint meeting of The College of American Pathologists and The California Pathological Society. The subject of Dr. Glick's address was "Recent Trends in Histochemistry."

Regional Seminar Started in Moorhead

Doctors George N. Aagaard and Richard L. Varco journeyed to Moorhead, Minnesota, on January 3 to open another regional postgraduate seminar in Cardiovascular Disease, Cancer, and Psychosomatic Medicine.

Physicians of the western Minnesota area surrounding Moorhead, together with physician guests from Fargo, North Dakota, attended the opening presentations on hypertension and carcinoma of the lung. This is the third such seminar series to be started during this present academic year, earlier ones having already been completed in Crookston and Virginia. Another similar series will be opened Thursday, January 11, when Doctors Aagaard and Varco will speak on the same subjects to physicians in the Willmar area. The seminars are sponsored by the Minnesota Department of Health, the Minnesota State Medical Association, the Minnesota Heart Association, and the Minnesota Cancer Society.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

January 14 - 20, 1951

Sunday, January 14

University Hospitals

9:00 - 10:00 Surgery Grand Rounds; Station 22.

10:30 - Surgical Conference; Todd Amphitheater.

Monday, January 15

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109 U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Seminar; Examination and X-ray Studies of Scoliosis; E-101, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 12:50 Physiology Seminar; The Evaluation of Obesity; Josef M. Brozek; 214 Millard Hall.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jenson, A. B. Baker and Staff; U. H.

4:00 - Public Health Seminar; 113 Medical Sciences.

4:30 - 5:30 Dermatological Seminar; M-436, U. H.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staffs; Powell Hall Amphitheater,

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Tobin; 5th Floor Annex.

10:00 - 11:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

1:00 - 2:00 Staff Meeting; Classroom; 4th Floor.

Monday, January 15 (Cont.)

Minneapolis General Hospital (Cont.)

2:00 - 3:00 Journal Club; Classroom, Station I.

Veterans Administration Hospital

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; Conference Room; Bldg. I.

1:00 - Metabolic Disease Rounds; N. E. Jacobson and G. V. Loomis; Bldg. I.

4:00 - Research Conference; Conference Room, Bldg. I.

Tuesday, January 16

Medical School and University Hospitals

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:00 Physiology-Surgery Conference; Intra-arterial Dissection for Atherosclerosis; Albert Sullivan and Davitt Felder; Todd Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by General Hospital Staff; Drs. Lipschultz and Stansbury; Eustis Amphitheater, U. H.

*800 p.m. Minnesota Pathological Society Meeting; Experimental Nutritional Megaloblastic Anemia; C. B. May, Elsa Proehl, C. U. Lowe, and C. P. Barnum; Medical Science Amphitheater.

Ancker Hospital

1:00 - 2:30 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

8:30 - Pediatric Allergy Rounds; Dr. Nelson; 4th Floor Annex.

Veterans Administration Hospital

8:45 - Surgery Journal Club; Conference Room; Bldg. I.

Tuesday, January 16 (Cont.)

Veterans Administration Hospital (Cont.)

8:30 - 10:20 Surgery Conference; Seminar Conference Room, Bldg. I.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell.

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Chest Surgery Conference; J. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

1:30 - Liver Rounds; Samuel Nesbitt.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, January 17

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:00 - 1:00 Radio-Isotope Seminar; 113 Medical Sciences.

4:00 - 6:00 Ophthalmology Seminar; Todd Room, 5th Floor, U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

8:00 p.m. Dermatological Pathology Conference; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Robin; 5th Floor Annex.

11:00 - 12:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

Wednesday, January 17 (Cont.)

Minneapolis General Hospital (Cont.)

12:15 - Staff Meeting; Effect of Sulfonamides and Antibiotics on Infectious Diseases; Franklin Top; Fourth Floor Annex.

1:30 - Pediatric Rounds; E. J. Huenekens; 4th Floor Annex.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans and Bernard O'Loughlin; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, January 18

Medical School and University Hospitals

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

12:00 - Physiological Chemistry Seminar; Critique of Alkaline Phosphatase Staining by the Gomorie; Morton Alpert; 214 Millard Hall.

4:00 - 5:00 Physiology Seminar on Cardiac Metabolism; 129 Millard Hall.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - Bacteriology Seminar; The Differentiation Between Aerobacter Aerogenes and Klebsiella Pneumoniae; Carroll Kucera; 214 Millard Hall.

5:00 - 6:00 X-ray Seminar; Report of Meeting of Radiological Society of North America; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatrics Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

*8:00 p.m. George Chase Christian Lecture; Research in Human Cancer--Problems and Results; Johannes Clemmesen; 15 Medical Sciences.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

11:30 - Pathology Conference; Main Classroom.

1:00 - 2:00 EKG and X-ray Conference; Classroom, 4th Floor Annex.

Thursday, January 18 (Cont.)

Minneapolis General Hospital (Cont.)

2:00 - 4:00 Infectious Disease Rounds; Large Classroom.

4:00 - 5:00 Infectious Disease Conference; Large Classroom.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; Conference Room, Bldg. I.

1:00 - Chest Rounds; William Stead.

Friday, January 19

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Functions of the Vertebral Venus Circulation; Harry Z. Mellins; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

2:00 - 4:00 Physiology Conference; 214 Millard Hall.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U. H.

4:15 - 5:15 Electrocardiographic Conference; 106 Temp. Bldg., Hospital Court, U. H.

5:00 - 6:00 Urology Seminar; Histologic Diagnosis of Prostatic Cancer, Especially by Frozen Section; Robert Hebbel; Eustis Amphitheater, U. H.

Friday, January 19 (Cont.)

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Tobin; 5th Floor Annex.

9:30 - Surgery-Pediatric Conference; O. S. Wyatt and T. C. Chisholm; 4th Floor Annex.

11:00 - 12:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

1:30 - Chest Conference; Wm. Tucker and J. A. Myers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I

Saturday, January 20

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; Wallace H. Cole and Staff; M-109, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - Anatomy Seminar; Genetic Susceptibility of Mice to Glomerulonephritis, Arthur Kirschbaum; Methods for Histologic Localization of Radio-Isotopes; Samuel O. Cornwell; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Saturday, January 20 (Cont.)

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

11:00 - 12:00 Pediatric Clinic; Charles May; Classroom, 4th Floor Annex.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.

* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.