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# University of Minnesota Hospitals
and
# Minnesota Medical Foundation




# The Pathogenesis of Rheumatic Fever

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UNIVERSITY OF MINNESOTA HOSPITALS
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MINNESOTA MEDICAL FOUNDATION

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# I. THE PATHOGENESIS OF RHEUMATIC FEVER*

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## Group A Streptococcal Infection and Rheumatic Fever

The causative agent in rheumatic fever is the group A hemolytic streptococcus. This can be said with the same degree of certainty as that lobar pneumonia is caused by the pneumococcus, and the statement can be supported by much the same kind of bacteriological and immunological evidence. There is, however, one important qualification to be appended. In pneumococcal pneumonia, the direct association of the infecting agent and the disease is clearly demonstrable, and therapeutic measures which destroy the microorganisms bring the disease abruptly to an end. In rheumatic fever, on the other hand, the actual presence of the infecting microorganism has not been proven to be a necessary part of the disease, and therapeutic steps which might be expected to destroy streptococci do not alter the course of the disease. All that is known is that a streptococcal infection must occur before rheumatic fever can occur, and the time gap, or so-called "latent phase", between the infection and the onset of the disease cannot yet be explained.

The evidence for the responsibility of group A streptococcal infection in the pathogenesis of rheumatic fever was first discovered by Coburn[1] in 1930, while this investigator was engaged in his residency training at the Presbyterian Hospital in New York. His observation that acute rheumatic fever was consistently associated with streptococcal infection has been abundantly confirmed and extended during the past two decades, and is now accepted by virtually all students of the disease. Other etiological agents have been tentatively proposed from time to time[2], such as green or indifferent streptococci, several varieties of viruses, and the pleuropneumonia-like group of organisms, but each proposal has failed of confirmation, while the case for group A streptococci has steadily strengthened year by year as new epidemiological information has been accumulated in all parts of the world.

There is now general agreement on this point. The majority of cases of acute rheumatic fever can be shown to have been preceded by an infection, usually of the nasopharyngeal mucosa, by group A hemolytic streptococci. In approximately 75 per cent of cases the microorganism can be demonstrated in nose or throat cultures at the time of occurrence of rheumatic fever. In almost all cases an elevated serum level of antibodies against antigenic components of the streptococcus is present, which can be taken as substantial evidence for a recent streptococcal infection. Epidemiological studies in the armed forces and civilian populations have established a precise correlation between the seasonal curves for group A streptococcal infection and rheumatic fever; such a correlation does not exist with non-streptococcal varieties of respiratory infection, such as influenza virus outbreaks.

Once an episode of rheumatic fever has occurred, the liability of an individual to new attacks of the disease is sharply increased. Numerous bacteriological studies by many groups of workers have shown conclusively that each new attack is associated with a new streptococcal infection. Moreover, recurrent attacks of rheumatic fever can be prevented by continual prophylactic therapy with sulfadiazine or penicillin, both of which have been shown to cause suppression of streptococcal infection.

* Certain experimental studies described in this paper were sponsored by the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, the National Institutes of Health, the American Heart Association, the Helen Hay Whitney Foundation and the Minnesota Heart Association.

## The "Latent Phase" in Rheumatic Fever

If one proposes the streptococcus as causative agent for rheumatic fever, there still remains the formidable problem of determining the mechanism by which the disease occurs. Because of the latent interval between the streptococcal infection and the actual disease, the problem is more complex than in other varieties of infectious disease. Indeed, this time gap is itself the center of the problem, and its existence has given rise to the various hypotheses which implicate hypersensitivity as a mechanism in the disease. There is a sound basis of logic for such hypotheses, if the sequence of events is thus: 1) an infection by streptococci occurs, 2) the infection subsides and the patient recovers, and finally, 3) after recovery, rheumatic fever occurs. But before going further into the problem of mechanism, it is necessary to consider whether this sequence of events really occurs, and whether a genuine latent phase actually exists.

First of all, there are good reasons to believe that an acute streptococcal infection is a more prolonged affair than casual observation of patients would suggest. It is true that in most cases of streptococcal pharyngitis or tonsillitis the fever, local discomfort and symptoms of systemic intoxication last for only a few days, and subside abruptly. As a matter of fact, clinical recovery from such infections occurs so rapidly and uniformly that it is difficult to prove any curative therapeutic effect for sulfadiazine or penicillin. But the disappearance of clinical symptoms by no means constitutes proof that an infectious disease is at an end, as is well illustrated by cases of brucellosis or typhoid fever. The only bacteriological evidence of a streptococcal respiratory infection is the presence of streptococci in cultures of the nose or throat, and when the course of the disease is evaluated by bacteriological methods, it is evident that the clinical impression is misleading. Most patients continue to show positive cultures for periods of weeks and even months after the onset of infection; if a positive culture can be taken as evidence for infection, these patients are still infected despite the absence of symptoms. This cannot be dismissed by invoking the term "carrier", or by suggesting that the positive cultures represent a saprophytic population of streptococci living only on the mucosal surface without causing tissue infection. For it has been demonstrated in the studies of the Streptococcal Disease Laboratory at Fort Warren, Wyoming[3], that the asymptomatic carrier state almost invariably represents a true streptococcal infection. The evidence for this is that persons with persistently positive throat cultures can be shown to possess elevated levels of anti-streptococcal antibody in their serum, and the presence of antibody can reasonably be assumed to indicate that infection has occurred.

On bacteriological grounds, then, there is reason to doubt the reality of the latent phase, since 75 per cent of patients still have the infection at the time when rheumatic fever begins. This figure would probably be higher if better methods were available for determining the presence of streptococci in respiratory mucosal tissue. As an illustration, Rantz, Jacobs and Kirby[4], cultured group A streptococci from the tonsillar tissues after tonsillectomy in 33 children, of whom only 18 had shown positive cultures in throat swabs made before operation.

There is evidence which indicates that rheumatic patients are not in normal state during the latent phase. In studies by Rothbard et al.[5], it was shown that some patients continue to have elevated erythrocyte sedimentation rates throughout the period between the apparent subsidence of streptococcal infection and the onset of rheumatic fever. Moreover, many of these patients actually seem to have a low-grade, vaguely defined sort of systemic illness during this period; although they no longer have the symptoms of acute throat infection, they do not feel altogether well[6].

## Streptococcal Infection as a Possible Mechanism

It is fair to ask whether the continuing presence of streptococci in throat cultures during the latent interval is a meaningful event, in terms of the mechanism of rheumatic fever. In other words, could rheumatic fever be a special manifestation of a continuing streptococcal infection, rather than, say, a hypersensitivity reaction for which living streptococci are no longer necessary? Although this cannot be answered one way or the other at the present time, it does not now seem as unreasonable a question as it might several years ago. Denny and co-workers[7] have shown that the early and energetic treatment of acute streptococcal infections with penicillin will reduce the incidence of subsequent rheumatic fever. One result of such treatment, of course, is to eradicate streptococci from throat cultures. It is not yet known whether similar therapy during the latent period has a similar preventive effect on subsequent rheumatic fever, but is is conceivable that it might. If so, this would greatly alter the conventional view of the mechanism of the disease.

The suggestion that rheumatic fever may be due to a continuing streptococcal infection, rather than a reaction to an infection which has disappeared, is contrary to almost all of the currently accepted views of the mechanism of the disease. There are very good reasons to disagree with the suggestion. For one thing, once rheumatic fever has begun no amount of treatment with penicillin can be shown to alter the natural course of the disease, and since streptococci are extremely susceptible to this antibiotic the point can be taken as evidence against the role of infection in the disease. For another thing, rheumatic fever has the aspects of a generalized systemic disease, involving all parts of the body, and if living streptococci were the cause one might expect to be able to demonstrate bacteremia. There is ample evidence that group A streptococcal bacteremia does not occur. On the other hand, these points do not exclude the possibility. If the streptococci were established in rheumatic fever as intracellular parasites, as is the case in brucellosis, it might be impossible to eradicate them with penicillin in spite of their innate susceptibility to this antibiotic. Moreover, as Eagle[8] has recently shown, the efficacy of penicillin is contingent upon the presence of microorganisms in active proliferation, and "resting" streptococci are not destroyed during treatment. As to the absence of demonstrable bacteremia, this does not really rule out the existence of living streptococci in tissues. The latter point is borne out by the results of the following experiments.

A group of 20 rabbits were infected by an intravenous injection of living streptococci, and blood cultures were made at intervals thereafter. In most instances there was bacteremia which lasted for several days, after which the cultures were consistently negative. When the blood cultures had been negative for 4 days or longer, the animals were sacrificed, and cultures of whole pieces of heart, kidney and liver tissue were made in nutrient broth. In 5 of the animals, or 25 per cent of the group, group A streptococci were recovered from one or more of the organs. It should be added that cultures of the heart's blood were also made at the time of death, and were negative in each instance. The results indicated that a streptococcal infection could persist in internal tissues without being accompanied by septicemia.

Further evidence on the same point, but indicating a much more prolonged persistence of streptococci in tissues, was obtained in an experiment in which streptococcal bacteremia was reactivated by treatment with cortisone. Four rabbits were infected by an intravenous injection of type 24 group A streptococci on June 5, 1952. Transitorily positive blood cultures occurred in each, but all were negative when tested several weeks later. On July 23, approximately 6 weeks after infection, each animal was given cortisone in a dosage of 25 mg. intramuscularly, each day for a week. On the third and fourth days of cortisone, two of the animals developed positive blood cultures for hemolytic streptococci. One was shown to be group A,

type 24; the other strain was lost before it could be typed. Cortisone was discontinued, and the blood cultures again became negative. In the latter part of September, three and a half months after infection, cortisone was again given to the rabbits, and streptococcal bacteremia occurred 4 days later in two of the animals. One of these was the same rabbit in which type 24 streptococci had been demonstrated in the first course of cortisone, and on this occasion the streptococcus could not be typed. The other rabbit was one in which cultures had been negative during the first course, and in this animal the streptococcus was shown to be group A, type 24.

These experiments furnish evidence that the hemolytic streptococcus may remain dormant in the tissues of rabbits for long periods of time after a systemic infection.

There is an exceedingly strong piece of evidence for a similar state of affairs in the streptococcal infection of human beings with rheumatic fever, which has been overlooked or disregarded for many years. It is the demonstration in Edinburgh by Green[9], in 1939, of living group A streptococci in the heart valves of patients with fatal rheumatic fever. Green performed detailed postmortem bacteriological studies in nine cases of fulminating rheumatic fever. In five of the patients streptococci had been cultured from the throat before death, and each strain was typed serologically. At autopsy, the blood cultures were negative in all nine. But cultures of the mitral or aortic valves in eight of the patients were positive for group A streptococci, and in the five with positive throat cultures the microorganisms in the valves were found to be of the same serological type as those in the throat.

Regardless of how one feels about rheumatic fever, it is necessary to pay attention to this piece of work. Taken at its face value, it suggests that rheumatic fever is associated with an actual streptococcal infection of the heart tissue. The only alternative explanations are that the observations were due to a contamination or error, or that the streptococci made their way from the throat to the heart as an agonal infection. Neither seems plausible. It is difficult to see how contamination with different serological types of streptococci could have occurred in eight out of nine instances, or involved valve cultures without also involving cultures of the blood or other tissues. It is equally difficult to see how an agonal infection could have occurred only in this restricted tissue site without involving the blood. The work of Green was confirmed in the following year by Collis[10], at the Rotunda Hospital in Dublin, who cultured 42 valves from 17 fatal cases of rheumatic fever and grew hemolytic streptococci from 22 of the valves. The latter work is less conclusive than that of Green, since the streptococci were not grouped or typed.

At the present time it would be technically difficult to repeat these observations, in view of the fact that few patients die with rheumatic fever without having received penicillin therapy before death. Nevertheless, such attempts should be made whenever possible.

## Hypersensitivity as a Possible Mechanism

The currently popular view that rheumatic fever is a manifestation of hypersensitivity is based on several pieces of evidence. In the first place, the disease often looks like a reaction involving sensitization. There is first an infection and then a period of apparent recovery, and then a florid exhibition of symptoms resembling those encountered in serum sickness, including pain and swelling in the joints, erythematous skin eruptions, and fever. Moreover, the rheumatic individual develops higher levels of antibody against components of the streptococcus than are seen in normal people after streptococcal infection, and this has been interpreted as evidence to support the hypersensitivity concept. Finally, the prompt remission of clinical symptoms which usually occurs after treatment with cortisone or ACTH has been taken to indicate an allergic basis for the symptoms.

Additional support for the concept has been derived from experimental studies of serum sickness in animals. Klinge[11], Rich and Gregory[12] and others have shown that injections of foreign serum in rabbits may cause the appearance of inflammatory arterial lesions similar to periarteritis nodosa. The interpretation of these experiments is open to question. The amount of foreign serum required to produce the lesions is so extremely large (20-40 cc. of horse serum per rabbit, intravenously) that something more than pure hypersensitivity seems to be involved; the possibility that toxic properties of the foreign protein may be concerned has not been ruled out. Furthermore, as has been pointed out by More and his co-workers[13], these experiments do not provide a true analogy for the mechanism of rheumatic fever, since Aschoff bodies are not demonstrable in the heart tissue. Inflammatory lesions of arteries resembling periarteritis nodosa are occasionally seen in human rheumatic fever, but they are neither a common nor characteristic feature of the disease.

The demonstration that rheumatic patients develop higher levels of anti-streptococcal antibody than non-rheumatic individuals is open to an alternative interpretation which does not involve hypersensitivity. Anderson and co-workers[14], in a study of comparative levels of several varieties of anti-streptococcal antibodies following scarlet fever, found that early treatment of the disease with penicillin resulted in much lower antibody responses than when the disease was allowed to run its full course. Similar observations in patients with streptococcal pharyngitis were made by the Fort Warren group of workers[7]. On the basis of these findings, it is reasonable to suggest that a high level of antibody may simply indicate that a more severe or extensive streptococcal infection has occurred, and, as has already been suggested, this may be the case in rheumatic fever. There is no evidence that rheumatic individuals differ from normal people in their capacity to form antibody against antigens other than streptococci, and no basis exists for the frequently stated assumption that rheumatic subjects are immunologically abnormal.

A variant of the hypersensitivity concept, suggested by Cavelti[15], has received much attention in recent years. This is the theory that a streptococcal infection causes an alteration in the host tissues which renders them antigenic, with the result that auto-antibodies directed against heart or kidney tissues appear in the blood. Cavelti stated that cardiac and renal lesions could be produced by immunization of animals with mixtures of streptococci and homologous tissue extracts and reported the demonstration of anti-heart antibody in rheumatic fever patients by a technique involving sensitized collodion particles. Other workers have attempted to reproduce these findings without success[16,17,18].

In short, the concept that a mechanism involving hypersensitivity is at work in rheumatic fever, although undeniably attractive, has not yet been established by any kind of experimental data.

## Attempts to Produce Experimental Rheumatic Fever in Animals

The most urgent present need in research in rheumatic fever is an experimental model with which the disease can be observed and manipulated in experimental animals. This is of crucial importance, not only for obtaining an understanding of the mechanism of the disease, but also for the development of therapeutic measures which cannot be studied in human subjects. For these reasons, a great deal of work by numerous investigators has been devoted to attempts to reproduce the disease in animals. The production of hypersensitivity to foreign proteins, mentioned earlier, has been widely employed as an approach to the problem. Another approach has involved the use of streptococci and their products as antigens, in attempts to cause bacterial hypersensitivity. The most notable example of this method is the work of Murphy and Swift[19], who found that a few rabbits developed carditis following a series of intradermal injec-

tions of different serological types of streptococci. The cardiac lesions consisted chiefly of focal necrosis of cardiac muscle fibers, with inflammatory reactions incident to the necrosis. In a comparative histological study, the authors showed that similar cardiac lesions were present in human beings with fatal rheumatic fever.

Although the incidence of carditis in the experiments of Murphy and Swift was very low, and many months of observation were usually required before lesions occurred, their work represented a significant advance in research on rheumatic fever. It provided the first real clue to suggest that the rabbit might be a satisfactory model for the study of experimental pathology in this disease and stimulated the activities of investigators in many other laboratories.

Numerous experiments dealing with the effects of repeated streptococcal infection in this laboratory have failed to provide a workable model in which cardiac lesions could be produced in a satisfactory percentage of animals. The same was true when attempts were made to combine the effects of streptococcal infection with hypersensitivity reactions to various foreign proteins. But when the effect of the generalized Shwartzman reaction[20,21,22,23] in streptococcus-infected animals was investigated it became possible to produce extensive cardiac lesions, to be described below, in a majority of rabbits within a period of two or three days. The present status of this approach to the problem of experimental "rheumatic fever" may be summarized as follows:

It is known that an infection of the skin of rabbits by group A streptococci brings about a state of preparation for the local Shwartzman reaction. Thus, when an animal with skin infection is given an intravenous injection of endotoxin from a variety of gram negative microorganisms, hemorrhagic necrosis occurs in the infected skin site within a few hours. On the basis of this observation, it was postulated that if group A streptococci are capable of producing a special effect on the heart in the course of systemic infection, it might be possible to reveal this effect by injecting gram negative bacterial endotoxin.

Accordingly, rabbits were infected by intravenous injections of a type 1 strain of streptococci, and two days later they were given an intravenous injection of meningococcal endotoxin. The results are illustrated by a series of photomicrographs which accompany this presentation. Briefly, two distinct types of cardiac lesion were encountered, and the incidence of each type depended on the size of the doses of streptococci and toxin. With large doses, myofiber necrosis occurred in over 80 per cent of the animals within two or three days after the injection of toxin. These lesions were strikingly similar to those described by Murphy and Swift in rabbits subjected to repeated streptococcal infection. They were not, however, in any way specific for streptococcus-infected rabbits, since myofiber necrosis also occurred when the conventional generalized Shwartzman reaction was produced by two intravenous injections of meningococcal toxin, without streptococci.

When the doses of streptococci and toxin were reduced, however, a new cardiac lesion was encountered in which the streptococcus appears to be more specifically involved. This lesion consisted of infiltration of the walls of the coronary arteries by homogeneous eosinophilic material resembling fibrinoid, accompanied by varying degrees of necrosis of the arterial walls. Under optimal conditions of dosage, fibrinoid necrosis of the coronary arteries occurred in approximately 50 per cent of animals. It developed within 24-48 hours after the injection of toxin, and usually caused death of the animals during this time. It appeared to be a selective lesion of the coronary arteries, since the vessels of the lungs, liver, spleen and kidneys were not involved. It did not occur in control animals given streptococci alone, or meningococcal toxin alone, nor in rabbits injected with toxin before instead of after streptococci.

Valvulitis involving the mitral and aortic valves, with fibrinoid vegetations in the valve surfaces, were encountered in some of the rabbits with coronary artery lesions.

The significance of these cardiac lesions, in terms of the rheumatic fever problem, remains to be determined. Similar lesions of fibrinoid necrosis are characteristically seen in disseminated lupus erythematosis, periarteritis nodosa, thrombotic thrombocytopenia, and, as was shown by von Glahn and Pappenheimer[24], in certain cases of acute rheumatic fever. The results of the present study suggest that this group of diseases may involve a disturbance which is analogous to the generalized Shwartzman reaction. This would not necessarily implicate gram negative microorganisms or their toxins. Although the Shwartzman phenomenon itself does not involve an immunological mechanism, it appears to represent a sort of prototype for many different varieties of hypersensitivity reactions involving tissue damage. For example, Stetson[25] has shown that the basic histological changes in the local Shwartzman reaction are indistinguishable from those of the Arthus reaction, and others have demonstrated that the local Shwartzman reaction can be provoked by an injection of foreign protein in sensitized animals[26]. Thus far, we have been unable to produce fibrinoid necrosis of the coronary arteries in streptococcus-infected animals with materials other than gram negative bacterial toxin, but further studies along this avenue are necessary.

## Summary

The role of the group A hemolytic streptococcus as the causative agent of rheumatic fever has been reviewed, and the possibility that rheumatic fever may be a special manifestation of a continuing systemic infection by streptococci has been discussed. The currently popular concept that hypersensitivity, in the immunological sense, is responsible for rheumatic fever has been criticized; it is suggested that there is actually little evidence to support this concept.

A new experimental model involving a modification of the Shwartzman reaction in rabbits with systemic streptococcal infections has been described. Employing this model, cardiac lesions consisting of myofiber necrosis, fibrinoid necrosis of the coronary arteries and valvulitis can be produced in a majority of animals within a short period of time. It is suggested that necrotizing arteritis in the heart may represent a special property of the streptococcus in this experimental circumstance.

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## II. MEDICAL SCHOOL NEWS

### Coming Events

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|---|---|
| February 12-14 | Continuation Course in Cardiovascular Diseases for General Physicians |
| February 16-18 | Continuation Course in Recent Advances in Diagnosis for Internists |
| February 17 | Phi Delta Epsilon Lecture; "Iron Metabolism and Iron Deficiency Anemia"; Dr. Carl V. Moore, Professor, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; Owre Amphitheater; 8:00 p.m. |
| March 2-4 | Continuation Course in Clinical Dietetics |
| March 26 | Special Lecture; "Trace Elements in Biochemistry and Medicine"; Dr. Burt L. Vallee; Peter Bent Brigham Hospital, Boston, Massachusetts; Owre Amphitheater; 4:00 p.m. |

* * *

### Continuation Course

The University of Minnesota will present a continuation course in Recent Advances in Diagnosis for Internists at the Center for Continuation Study on February 16 to 18, 1953. Although intended primarily for specialists in internal medicine, the program will be of interest to many pediatricians and general physicians. Emphasis will be placed on those techniques which have been introduced or developed within the past five to ten years which have increased our knowledge of basic physiology and which are becoming or give promise of becoming standard diagnostic procedures. Recent developments in the fields of cardiology, respiratory disease, renal disease, hematology, and gastro-enterology will be included.

Under the direction of Dr. C. J. Watson, Professor and Director of the Department of Medicine, an outstanding guest faculty has been assembled: Dr. Carl V. Moore, Professor, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; Dr. Thomas E. Machella, Associate Professor of Medicine, Associate in Physiology, and Chief, Gastro-Intestinal Clinic, University of Pennsylvania School of Medicine, Philadelphia; Dr. Robert P. Grant, Head, Section on Cardiodynamics, National Heart Institute, U. S. Public Health Service Hospital, Baltimore; and Dr. William W. Engstrom, Associate Professor, Department of Medicine, Marquette University School of Medicine, and Director, Metabolism Section, Milwaukee County Hospital. The remainder of the faculty will include clinical and full-time members of the staff of the University of Minnesota Medical School and Mayo Foundation.

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### Faculty News

Dr. Ancel Keys, Director of the Laboratory of Physiological Hygiene, addressed the breakfast meeting of the Hennepin County Committee of the Minnesota State Association of Life Underwriters on January 27, opening the annual Heart Fund campaign. He discussed factors which influence the death rate in this country.

Dr. Wesley W. Spink, Professor of Medicine, departs shortly for a brief lecture tour of some of the Atlantic coastal states. On February 9 he will discuss, "Investigations on Brucellosis" at the University of Virginia at Charlottesville, Virginia. On February 12 he will talk on "Clinical Problems Relating to the Management of Infections with Antibiotics" at the Tenth Annual Medical and Surgical Symposium at Watts Hospital, Durham, North Carolina. The following day he will present a paper entitled, "Investigations on the Problem of Staphylococci Resistant to Antibiotics" at Duke University School of Medicine, Durham, North Carolina.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

February 9 - 14, 1953

Monday, February 9

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; W-612, U. H.

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

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

11:30 - 12:30 Physical Medicine Staff Seminar; Functional Results of Intramedullary Fixation of Fractures; R. S. Blanchard; Heart Hospital Auditorium.

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

12:30 - 1:30 Physiology Seminar; The Inter-Action of Calcium and Magnesium with Proteins; Charles W. Carr; 214 Millard Hall.

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

4:00 - Pediatric Seminar; Some Aspects of Epidemiology of Rheumatic Fever and Acute Glomerulonephritis; Floyd Denny; Sixth Floor West, U. H.

4:00 - 5:30 Seminar on Fluid and Electrolyte Balance; Gerald T. Evans; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

4:30 - Public Health Seminar; 15 Owre Hall.

4:30 - 6:00 Physiology 114A and Cancer Biology 140 -- Research Conference on Cancer, Nutrition, and Endocrinology; Drs. Visscher, Bittner, and King; 129 Millard Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Erling Platou; Station K.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Monday, February 9 (Cont.)

Ancker Hospital

8:30 - 10:00 Chest Disease Conference.

1:00 - 2:00 Medical Grand Rounds.

Veterans Administration Hospital

8:00 - 9:00 Neuroradiology Conference; J. Jorgens, R. C. Gray; 2nd Floor Annex.

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

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

2:00 - Psychosomatic Rounds; Bldg. 5.

Tuesday, February 10

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; 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.

12:30 - 1:30 Physiology 114D -- Current Literature Seminar; 129 Millard Hall.

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

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Veterans Hospital Staff; Eustis Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Medical-Roentgenology Conference; Auditorium.

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

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

10:00 - Cardiac Rounds; Paul F. Dwan; Station I, Classroom.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

12:30 - Grand Rounds; Fractures; Sta. A; Willard White, et al.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Cal, and Lipschultz.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Tuesday, February 10 (Cont.)

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

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

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

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

10:30 - Surgery Tumor Conference; L. J. Hay, J. Jorgens; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

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, February 11

Medical School and University Hospitals

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

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

12:30 - 1:30 Radioisotope Seminar; Survival of Erythrocytes Tagged with $CR^{51}$; Robert G. Goldish; 12 Owre Hall.

1:30 - 3:00 Physiology 114B -- Circulatory and Renal System Problems Seminar; Dr. M. B. Visscher, et al; 214 Millard Hall.

4:00 - 5:30 Physiology 114C -- Permeability and Metabolism Seminar; Nathan Lifson; 214 Millard Hall.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

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

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

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

2:00 - 4:00 Medical Ward Rounds;

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

Wednesday, February 11 (Cont.)

Minneapolis General Hospital

8:30 - 9:30 Grand Rounds; William P. Sadler and Staff; Sta. C.

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Platou; Station K.

12:15 - Pediatrics Staff Meeting; Classroom, Station I.

1:30 - Visiting Pediatric Staff Case Presentation; Station I, Classroom.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.

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

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I.

4:00 - Combined Medical-Surgical Conference; Conference Room, Bldg. I.

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

Thursday, February 12 (HOLIDAY)

Friday, February 13

Medical School and University Hospitals

8:00 - 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.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, 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; Neurosurgical Procedures for Pain Relief; Carrel M. Caudill and Lyle A. French; Powell Hall Amphitheater.

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

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

4:00 - 5:00 Physiology 124 -- Seminar in Neurophysiology; Ernst Gelhorn; 113 Owre Hall

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

## Friday, February 13 (Cont.)

Ancker Hospital

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

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Pediatric Surgery Conference; Oswald Wyatt, Tague Chisholm; Station I, Classroom.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

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

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

## Saturday, February 14

Medical School and University Hospitals

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

9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Station 54.

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

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

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

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

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

11:30 - Anatomy Seminar; The Ultra-Structure of the Myofibril; Richard G. Hibbs; 226 Institute of Anatomy.

Ancker Hospital

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

Minneapolis General Hospital

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

Veterans Administration Hospital

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

8:30 - 11:15 Hematology Rounds; Drs. Hagen, Goldish, and Aufderheide.
11:15 - 12:00 Morphology . . . . . Dr. Aufderheide.