

RHEUMATIC FEVER

Second Edition

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By

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**MAJOR PROBLEMS IN
CLINICAL PEDIATRICS**

ALEXANDER J. SCHAFER
Consulting Editor

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Foreword

We are pleased to be able to present this second edition of the second volume in the series of Major Problems in Clinical Pediatrics. Our pleasure derives in large part from our long association with the authors and from the high places they have attained in our esteem.

Dr. Markowitz obtained his M.D. from Syracuse University School of Medicine, interned, served throughout World War II as a medical officer in the U.S. Navy, then spent a year at Irvington House under Dr. Ann Kuttner. His lifelong preoccupation with rheumatic diseases originated then. After completing his residency training at The Johns Hopkins Harriet Lane Home he became my associate in the practice of pediatrics. During the fourteen years of our association not only did he become one of the best clinicians I have ever known but he assisted me mightily in my gropings for knowledge concerning the newborn infant. In addition, he still found time to perfect himself in the subspecialties of cardiology and rheumatology, and to carry out researches in these fields. When these burdens became too heavy for one man to carry he left practice to become Assistant Chief of the Department of Pediatrics of the Sinai Hospital of Baltimore and Director of the Subdepartment of Rheumatic Fever and Rheumatoid Arthritis at the Harriet Lane Home. He has since become Professor and Head of the Department of Pediatrics at the University of Connecticut School of Medicine.

Dr. Markowitz wrote the first edition of this book in close collaboration with Dr. Ann Kuttner, whose life has been warmly summarized in this volume by her colleague and intimate friend, Dr. Rebecca Lancefield. Dr. Kuttner's death necessitated the selection of another co-author, and Dr. Markowitz happily chose Dr. Leon Gordis to fill this breach. This was a natural choice inasmuch as Dr. Gordis had already written one section in the first edition, a chapter dealing with Community Health Services pertaining to the prevention and management of rheumatic fever.

Dr. Gordis was trained first as a pediatrician and then as an epidemiologist, and he has utilized his expertness in both these fields to the hilt. He is at present an Associate Professor in the Departments of Epidemiology and of Medical Care and Hospitals at The Johns Hopkins University School of Hygiene and Public Health, as well as an Associate Professor of Pediatrics at Johns Hopkins' School of Medicine. He also served for two years as an Associate Professor in the Department of Medical Ecology at the Hebrew University Hadassah Medical School in Jerusalem. He has written extensively on a variety of problems with the accent upon those concerning Community Health Care and Rheumatic Fever.

We believe that Drs. Markowitz and Gordis have maintained the original quality of excellence while bringing up to date the growing body of knowledge concerning this important topic.

ALEXANDER J. SCHAFFER

Preface

This monograph reviews the diagnosis, management and prevention of rheumatic fever and rheumatic heart disease in the light of new knowledge of the biologic and social aspects of these conditions.

In 1930 Glover wrote that "the incidence of acute rheumatism seems to show that it, like tuberculosis, is slowly but surely being conquered. . . . We seem to be seeing the same process of epidemiologic obsolescence in acute rheumatism that Creighton saw in smallpox." In our first edition we noted that Glover's prediction of obsolescence had not yet been fulfilled; and today, large pediatric services still see significant numbers of children with acute rheumatic fever, particularly in ghetto areas. Despite continuing advances in the study of the biology of the streptococcus, the pathogenic mechanisms remain unknown.

During the past decade, however, there has been increasing awareness of the need to consider the social determinants of the disease for planning preventive programs. Poor environmental conditions such as overcrowding, limited availability of medical care to high-risk groups, and poor patient compliance have now been recognized as major obstacles to the success of preventive efforts. Unfortunately, new advances which can be applied to rheumatic fever prevention have come very slowly in both the biologic and social areas, but this should not deter us from intensifying our efforts to apply currently available knowledge to the prevention of rheumatic fever and its sequelae.

We wish to thank Dr. Thomas Madden for his helpful suggestions regarding Chapter 5 and for kindly providing the accompanying photographs. We are also grateful to Dr. Lawrence Rothfield and Dr. Irwin Lepow, who reviewed Chapters 2 and 4. Dr. Angelo Taranta has been a constant source of stimulation and advice as well as a major contributor to the expanding body of knowledge in this area.

We gratefully acknowledge the expert secretarial assistance of Miss Marsha Banasiewski and Miss Doris Spath and express our thanks to the Division of Biomedical Communication of the University of Connecticut School of Medicine and to Mr. Donald M. Yaeger of the Department of Photography of Sinai Hospital of Baltimore for charts and photographs. We are especially grateful to Mrs. Myra Roseman for her invaluable contributions to the preparation of this volume, in proofreading the manuscript, meticulously checking the bibliography, and preparing the index. Dr. Alexander J. Schaffer, who originally urged us to prepare this book, has continued as a valued friend and consultant. We also wish to express our gratitude to Dr. Rebecca Lancefield for having written the tribute to the late Dr. Ann G. Kuttner, who co-authored the first edition and who was our teacher.

Last but not least, our loving thanks to Selma, Hadassah and our children for their forbearance, encouragement and understanding during the preparation of this monograph.

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Ann Gayler Kuttner

Dr. Kuttner devoted the major part (1936-1968) of her research and professional life to the study of rheumatic fever. The other non-suppurative complication of group A streptococcal infections, acute glomerulonephritis, was also given a considerable share of her attention. During the period from 1922, when she received her Ph.D. degree in bacteriology from Columbia University in the department of Dr. Hans Zinsser, until 1936, when she became Chief Physician and Director of Research for the Study of Rheumatic Fever at Irvington House, she laid a very firm foundation for her life's work on this disease.

Her first scientific publication was her doctoral dissertation in 1923 on the newly emerging subject of bacteriophage. This was very logically followed, after a year in the laboratory of Dr. Ernest W. Goodpasture in Pittsburgh, by three years of research at the Rockefeller Institute Hospital. With Dr. Rufus Cole she investigated "nuclear inclusions," now known to be pathognomonic of viral infections. Using herpes simplex as a standard for comparison, they discovered the specific salivary gland virus of guinea pigs. This led to her elegant demonstration that inoculation of the virus by any parenteral route resulted in localization in the salivary glands as a necessary prelude to its appearance in the brain. The virus could not be passed directly from brain to brain, but only from brain to salivary gland to brain, or in series through the salivary gland.

One of her vacations was spent at this time in Boston improving her knowledge of pathology by enrolling in Tracy B. Mallory's famous summer course in human pathology. This was influential in her decision to proceed to medical school in 1927 in order to obtain her M.D. degree at Johns Hopkins, where she also served at the same time as bacteriologist to the Harriet Lane Home.

Her next three years (from 1933 to 1936) were occupied with a tour of duty at the Peking Union Medical School, a frequently chosen expedition for those in medical work at the time. With a group from China, she included a round-trip journey across Siberia on the Trans-Siberian Railroad to attend the 15th International Physiological Congress, which was meeting in Moscow in 1935.

Because of Dr. Kuttner's impressive background, Drs. Alfred E. Cohn and Homer F. Swift felt that she was eminently qualified to establish at Irvington House, New York, a new program of clinical and laboratory research on rheumatic fever. Immediately upon

her return from China to the United States in 1936, they invited her to initiate this program at Irvington House, which was then already operating as a rheumatic fever convalescent home. She set up excellent laboratories and made this a model research institution from which many important studies were published during her two terms as director, as well as afterwards by her successors.

Her influence in the field of rheumatic fever has been evident in these studies and in the young associates whom she trained. Her students were deeply influenced by her teaching and commitment to the proper care of children with rheumatic fever and by her fundamental investigations of this disease. Among her students were both authors of this second edition. The senior author was one of her fellows at Irvington House in 1946, and the junior, one of Dr. Kuttner's students in Baltimore 20 years later. Many of these trainees have gone out to other centers imbued with the fundamental clinical and scientific points of view to which they were exposed.

From her laboratory came innovative methods and findings of importance. For example, she adapted the bactericidal, or bacteriostatic, test to measure the immunity of patients with preceding streptococcal infections. This procedure was developed by Dr. E. W. Todd in the early 1920s from another point of view, and was later partially revived by Ward and Lyons to measure the "opsonic index" after streptococcal infections. Her work, however, brought it forward as a test that would measure the patient's specific response to the group A streptococcal M antigen, which was of prime importance in streptococcal infection and immunity. The method was further developed by Rothbard and remains the most reliable test for ascertaining type-specific immunity to human infections with group A streptococci.

Its use in her laboratory and in others' contributed materially to establishing the concept that reinfection with the same specific type of group A streptococcus does not occur except when anti-M antibody formation is inhibited. Careful bacteriological studies were coincidental to this work. Studies of the epidemiology of streptococcal infections in this carefully-followed, closed population led Dr. Kuttner and her laboratory colleague, Elma Krumwiede, to the definition of several hitherto untyped group A streptococci into "new" serological M-types. With the introduction of chemotherapy and chemoprophylaxis in the late 1940s, it was obvious that Irvington House was of special value as a testing ground both of methods and results in this area and later in the effects of hormonal therapy. Because of her sound judgment and clinical skill, she was in great demand for evaluating trials such as the cooperative studies of the Combined Rheumatic Fever Study Groups of 1960 and 1965, which were carried out to assess the value of prednisone and acetylsalicylic acid therapy in rheumatic fever, especially as related to residual rheumatic heart disease. Her restraining influence was of importance in preventing

misuse of these therapeutic agents and in directing attention to their proper use in both prophylaxis and therapy.

Her continuing interest in acute glomerulonephritis was focused on the relation of skin infections to this disease during her renewed association with Dr. Markowitz at the Sinai Hospital of Baltimore in 1965. One of her last publications was a joint one with him on this subject.

Throughout all of her scientific life, beginning with her appearance at the Rockefeller Hospital in 1924, Ann Kuttner was a constant scientific colleague of mine, participating in discussions of streptococcal investigations and serving as a reminder of the value of tough critical judgments. She had a penetrating, completely honest outlook, which often resulted in a terse—sometimes “salty” but always direct—approach to her life and her work. She was so modest in her estimate of her own achievements that the impact of her contributions to the study of rheumatic fever was not widely known. I derived continual satisfaction and stimulation of scientific curiosity from my long and profitable association with her.

As a delightful friend, she joined in pleasant summer vacations with my family at Woods Hole on Cape Cod, enjoying the outdoor life with swimming, tennis, boating, and trips to the nearby islands. In New York she was a strenuous outdoor worker with her sister at the Ossining cabin which they shared on weekends. She made a swimming hole in their brook and was indefatigable in maintaining the wildlife in their woodland surroundings.

Hiking and camping with the Appalachian Mountain Club, as well as travels abroad and to meetings, were among her interests. Influenced by her family's background, she enjoyed the cultural and intellectual opportunities afforded to one living in New York, taking full advantage of the music, theatre, and museums.

She is greatly missed by her friends and associates.

REBECCA C. LANCEFIELD

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number of patients with the disease in a specified population at a point in time) In rheumatic fever, incidence describes the frequency of attacks of acute rheumatic fever, and prevalence, the rate of rheumatic heart disease existing in a community at a specific point in time. Another measure used in attempting to develop a picture of the size of the rheumatic fever problem is prevalence of history or immunologic evidence, which is the total number of people in a given population at a given time who give a history of ever having had rheumatic fever.

THE CHANGING PATTERN OF RHEUMATIC FEVER

Problems of Data Collection
No single source of data can give an accurate picture of the extent of rheumatic fever. It is therefore necessary to utilize different sources of data (Table 1) which share a number of important methodologic limitations.

Incomplete Ascertainment. Sources which depend on a physician or medical institution reporting each case generally miss a significant proportion of the true cases in a community. The degree of underascertainment depends in some measure on the incentive for reporting. Of course, even the best of ascertainment will miss cases.

During the past 40 years, the epidemiology of rheumatic fever has undergone significant changes in economically developed countries such as the United States. Rheumatic heart disease appears less prevalent among school children and young adults than it was a few decades ago. This decline may be due to changes in either the incidence or severity of rheumatic fever or both. Most American and British observers believe that acute rheumatic fever is less frequent than before in their countries, but the data reviewed in this chapter question how much the incidence of first attacks has declined. There is little doubt, however, that the severity of rheumatic fever and the frequency of recurrences have both diminished.

Table 1. Sources of Data on Rheumatic Fever and Rheumatic Heart Disease

SOURCES OF DATA

- 1. General
- Mortality Reports
- Statistics from States with Mandatory Reporting
- Selective Service
- Insurance Companies
- School Health Records

Incidence and Prevalence as Indices

The extent of an illness such as acute rheumatic fever is better measured in terms of morbidity than mortality because the case-fatality rate (the number of people dying from rheumatic fever among those people who have the disease) is very low. The most frequently used morbidity indices are *incidence* (the number of new cases in a population during a specified time period) and *prevalence* (the

number of patients with the disease in a specified population at a point in time). In rheumatic fever, incidence is generally used to describe the frequency of attacks of acute rheumatic fever, and prevalence, the rate of rheumatic heart disease existing in a community at a specific point in time. Another measure used in attempting to develop a picture of the size of the rheumatic fever problem is *prevalence of history or cumulative prevalence*, which is the total number of people in a given population at a given time who give a history of ever having had rheumatic fever.

Problems of Data Collection

No single source of data can provide an accurate picture of the extent of rheumatic fever. It is therefore necessary to utilize different sources of data (Table 1) which share a number of important methodologic limitations.

Incomplete Ascertainment. Sources which depend on a physician or medical institution reporting each case generally miss a significant proportion of the true cases in a community. The degree of underascertainment depends in some measure on the incentive for reporting. Of course, even the best of ascertainment will miss cases which do not come to medical attention and this is particularly significant in a disease such as rheumatic fever in which the case-fatality rate is low, the clinical picture variable with many mild cases, and the frequency of the disease highest among the poor whose medical services are often extremely limited in availability and accessibility.

Inclusion of Diseases Other Than Rheumatic Fever. Many of the sources listed accept the diagnosis of rheumatic fever as given and do not have any mechanism for verifying the diagnosis. This leads to a

**Table 1. Sources of Data on Rheumatic Fever
and Rheumatic Heart Disease**

I. General

- Mortality Reports
- Statistics from States with Mandatory Reporting
- Selective Service
- Insurance Companies
- School Health Records
- Hospital Admissions and Discharges
- Clinic Records
- Private Physicians' Records

II. Specific

- Rheumatic Fever Surveys
- Heart Sound Screening in Children
- Rheumatic Fever Registries

serious problem, particularly since the diagnosis is by criteria and physicians vary in their use of the criteria. The fact that the criteria do not include all cases further contributes to this problem.

Population Selection. The population from which cases come is often highly selected or not precisely defined. If, for example, one looks at the number of cases of rheumatic fever admitted to a single hospital, it is frequently not clear whether the hospital serves a defined population and, if so, whether cases arising in this group might not have been admitted to other hospitals. Populations of insured individuals or of college students are highly selected on the basis of medical, ethnic, socioeconomic and other factors, and therefore may be unrepresentative of the population at risk for rheumatic fever.

INCIDENCE OF RHEUMATIC FEVER

Surveys Specific for Rheumatic Fever

In order to overcome the above problems, several studies have been carried out in the United States in recent years with the specific objective of estimating rheumatic fever incidence. In general, they attempt to define a specific population at risk and to ascertain all cases of rheumatic fever occurring in this population during a specified time period, whether hospitalized or treated at home. These studies also attempt to verify the accuracy of diagnosis so that cases which were erroneously diagnosed are not included in the rheumatic fever incidence rates obtained.

Quinn et al. (1967) studied the incidence of rheumatic fever in Nashville, Tennessee, from 1963 to 1965 using intensive case-findings methods and reported an incidence of 12.6 per 100,000 population (all ages). This rate was three times as high as that reported by the local health department. Black rates were almost twice as high as white rates.

Gordis et al. (1969a) estimated the incidence of rheumatic fever in Baltimore from 1960 to 1964 by reviewing all discharges for rheumatic fever from Baltimore hospitals over the 5-year period. For the age group 5-19, the annual rates were 13.3 per 100,000 for initial attacks, 2.3 for recurrences, and 15.6 for all attacks. In order to correct for nonhospitalized cases, 700 practicing physicians were surveyed to estimate the proportion of rheumatic fever patients who were treated at home. When corrected for these nonhospitalized cases, the total annual incidence of acute rheumatic fever was estimated at 24 per 100,000 population, age 5-19 years. The black-to-white ratio was 2.5:1 for first attacks and 4:1 for recurrences.

Even with adequate validation of cases to ensure that those diag-