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Rheumatic fever

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R H E U M A T I C F E V E R

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INTRODUCTION

My interest in rheumatic fever was aroused during my junior year in medical school at which time I first came into contact with it on ward rounds and in medicine clinics. It was the first time I'd ever realized the extent of its incidence, morbidity and mortality. And it is for these reasons that I chose to write on this subject taking it in general rather than any one specific phase or aspect. An attempt will, however, be made to lay special emphasis on the management and treatment and prophylaxis with inclusion of other information merely for a better understanding of the disease itself.

HISTORY

(47) Each year in the United States there are 170,000 new cases. In addition to this number there already exist 840,000 active and inactive cases per 100,000,000 population. Over the entire country Cohn estimates that 60-80% of all heart disease under forty years of age is of rheumatic in origin. To bring these figures down to more comprehensible terms, in New York City during the years of 1936, 1937, and 1938 rheumatic heart disease accounted for more deaths than tuberculosis, meningococcal meningitis, scarlet fever, measles, diphtheria, whooping cough, and poliomyelitis combined. It is interesting to note that rheumatic fever destroys seven times more children than poliomyelitis which causes far greater fear and apprehension by the laity, health authorities, and even many of the medical men. Headley found in Philadelphia that the rheumatic fever mortality, 25-30 per 100,000, was exceeded only by tuberculosis, lobar pneumonia, and syphilis.

(47) Polyarthritis, one of the cardinal symptoms of rheumatic fever, is older than history itself, the earliest known example of multiple arthritis being found in a fossil, the skeleton of a large swimming reptile (platecarpus), estimated to be 100,000,000 years old. This example was probably due to a type of hypertrophic arthritis which, while it is quite different from rheumatic fever in pathology, may be linked quite closely in at least one aspect, namely, its etiology. More will be brought out about this later.

Hippocrates (circa 400 B.C.) first described acute polyarthritis; "In those, in whom pains and swelling come and go around the joints, and these not after the manner of gout in the foot, one will find large viscera and in the urine a white sediment.... Now this disease occurs in those who in childhood and youth were wont to have nose-bleeding but have since lost it."

Celsus, the greatest of Latin medical writers, discussed rheumatic fever unwittingly when he wrote: "Children in whom there has been nosebleeding, which has ceased, are sure to be troubled by pains in the head, or they have some severe joint ulcerations, or they also become debilitated by disease." Aretaeus[33], the cappadocian, must have referred to rheumatic fever when he stated: "In many cases the gout has passed into dropsy and sometimes into asthma, and from this succession there is no escape." Avicenna[33], the Arabian physician, living in the latter 10th and early 11th century, in his Canon of Medicine, attributed pains in the joints to the "stagnation and subsequent imprisonment of the insoluble parts of the humours which summer brought into circulation."

Guillaume de Baillou[4](1538-1616) was first to use the term rheumatism (rheumatismos) as applied to a form of acute arthritis as distinguished from gout and to make rheumatism for the first time a clinical entity. He writes: "Now this affection, which is wrongly called catarrh--for the term catarrh signifies a downward flow from the head--is by others better termed rheumatismos, it

it appears.....the whole body hurts, in some the face is flushed; the pain is more severe around the joints, so that the slightest movement of the foot, hand or finger causes a cry of pain....one thing about the term rheuma, rheumatism, rheumatic tendency....this term must be understood not only as a downward flow from the head, but also as a discharge from the interior of the body into the outer parts and even into internal organs.

Thomas Sydenham, "Father of English Medicine", and appropriately called the "English Hippocrates" by his contemporaries, work the first accurate clinical description of acute rheumatism in his Observationes Medical: "The disease comes on at any time, but especially in the Autumn, and chiefly seizes those that are in the Flower of the Age.... It begins with shivering and shaking and presently heat, restlessness and thirst; and other symptoms which accompany a Fever. After a day or two, and sometimes sooner, the Patient is troubled with a violent Pain, sometimes in this, sometimes in that Joint, in the Wrists and Shoulders, but most commonly in the Knees. It now and then changes places and seizes elsewhere, leaving some redness and swelling in the Part lest possessed...." He attributed the cause of rheumatism to "morbific matter in the system." Writing in 1666 he advocates bleeding as the chief remedy in the cure, on the grounds that the disease is inflammatory "as indicated by the resemblance of the blood to that which is taken away in pleurisy," and from his fondness of the humoral doctrines.

Herman Boerhaave[69](1709), at Leiden, repeated in his Aphorism much that Sydenham had absented, and added that the disease invades "sometimes the Brain, Lung, and Bowels." His etiology for rheumatism was the "lentor of the fluids obstructing the vessels." Anton Storck[63], the Viennese pharmacologist, reported in 1761 to W. Watson the following interesting case: "Thomas C., aged 32 years, had the rickets in his infancy and continued weakly for several years after. In the winter of 1759, on taking cold, he was afflicted with peripneumonic and pleuritic symptoms; when he was seized in the summer of year 1760, after great exercise, with a fever, and a very violent rheumatism affecting his breast and all joints, especially the knees.... A palpitation of the heart, to which he had been subject for some years before, became now much stronger which struck Mr. Pulteney instantly, as it shook his body at every stroke.... The pulse went at the rate of 110 in the morning and in the evening 120 pulsations in a minute.... Mr. Pulteney thought from the great and uninterrupted palpitation and the feel of the pulse that there was something extroardinarily disordered in the heart itself.... As he was coughing on the night of April 20th (1761) an haemoptoe suffocated him instantly.... At post-mortem--the pericardium adhered almost everywhere so close to the heart as to form as it were the external coat of it. The heart itself was of enormous size, and of a very pale color, and loose and flaccid in its texture to a remarkable

degree. How very close this English pharmacist came to recognizing rheumatic heart disease.

In 1776, a Dutchman, van Swieten[69], wrote: "....sometimes when the pain of rheumatism in the limbs ceases, there arises an anxiety of the breast, a palpitation of the heart, and an intermitting pulse." In this same year William Cullen, the pharmacology professor at Edinburgh of William Withering--of Foxglove fame, pointed out that rheumatic joints never suppurate. Of treating acute rheumatism he advised that "the blood ought to be drawn in large quantity--in proportion to the frequency, fullness and hardness of the pulse, and violence of the pain." He taught that cold and damp caused "spasm affecting the extreme arteries" producing the local inflammation and fever.

J. C. Lettson[37], a famous Quaker physician, wrote, in 1773, of an eleven year old girl with "palpitation of the heart": "Upon laying the hand on the sternum, it gave a sensation to the touch--something like a fluid passing thru a cylinder, in the central substance of which a ball had been infixed, against which the impulse of the circulating fluid had been directed, and by it repelled with a vibratory motion along the cylinder." Had he diagnosed mitral stenosis?

David Pitcairn and Edward Jenner were the first to definitely associate rheumatic fever and heart disease. William Charles Wells[67] in his paper on "Rheumatism of the heart" in 1810 stated that "Dr. David Pitcairn, about the year 1788 began to remark that

persons subject to rheumatism were attached more frequently than others with symptoms of organic heart disease....he concluded that the two diseases depend upon a common cause and in such instances called the latter disease rheumatism of the heart.

In the second edition of Matthew Baille's Morbid Anatomy(3), which appeared in 1797, is found the earliest mention in print of rheumatism of the heart: "The causes which produce growth of the heart are probably not all of the ascertained. The chief cause is an ossification or thickening of some of its valves. On some occasions the heart will become enlarged from rheumatism attacking it: "Dr. Pitcairn observed this in several cases and is to be considered as the first person who made this important observation."

Original descriptions of rheumatic subcutaneous nodules were made by William Charles Wells(67)in 1812. Adam's observations are particularly interesting in that they are probably the earliest known mention of specific rheumatic myocardial involvement, and the more serious effect of rheumatic fever in children than in adults (1827). At this time William Prout(68), an English Chemist, was teaching than an accumulation of lactic acid in the blood was the essential cause of the rheumatic condition. Hence, the rationale for alkaline treatment.

At one time Napoleon's celebrated physician, Baron Covisant, attributed the rheumatic vegetations on the mitral cusps to venereal disease because of their resemblance to venereal wart. From

Laennec's discovery of the stethoscope in 1816 the study of heart disease received great impetus. But it was not until 1832 that the clinical signs of rheumatic endocarditis were first pointed out by Jean-Baptiste Bouillaud[8], who went so far as to state definitely that endocarditis was not just a rheumatic complication but one of the disease's most important manifestations. His Law of Coincidence was an important concept: "In the great majority of cases of acute articular rheumatism with fever, there exists in a variable degree a rheumatism of the sero-fibrinous tissue of the heart. The coincidence is the rule, and the non-coincidence the exception." He noted and described cardiac enlargement, change in shape of chest, a "bellows, file, or saw sound", and "different abnormal sounds, some arising from the rubbing of the opposite coats of the pericardium against each other, others from the complication of pericarditis with endocarditis. Bouillaud, in spite of his advanced knowledge, was the worst blood-letter of all. For treating acute rheumatic fever he recommended bleeding 4-5 bowls the first day, 3 bowls each on the 2nd and 3rd days, followed by later bleeding by leeching and venesection if the patient relapsed. He claimed to have treated 184 cases by this method, curing all but one; writing in 1832 he complained: "Truly we know not why so many daily say that they bleed the same as we do, and that nevertheless, they do not obtain the results which we announce. No, emphatically no; they do not bleed according to our method, whatever may be said to the contrary!"

Sir Thomas Watson[65], in 1835, stated: "I confidently believe the to and fro sound to always be indicative of inflammation of the external membrane. ....the blowing sound to be always indicative of inflammation of the internal membranes of the heart."

The story of the discovery of the benefit from salicylates is most interesting. Thomas Maclagan[43], believing rheumatic fever to be of low infectivity and observing that it was "apt to occur in low-lying, damp localities", believed it was like malaria "of miasmatic origin" and allied to, though distinct from, malaria. As the Jesuits, in about 1630, had found a remedy for malaria in the bark of the cinchona, growing on the Amazon's marshy banks where malaria was of high prevalence, so did Maclagan, in 1874, seek the remedy for rheumatic fever in damp, low-lying sites in the bark of the willow tree from which he extracted the principle--salicin. Within three years of its discovery salicin, salycylic acid or sodium salicylate were in general use wherever rheumatic fever prevailed.

Ludwig Aschoff[1](1904) described in microscopic detail the characteristic rheumatic lesion that today bears his name. The view that rheumatic fever is of microbic origin was first formulated in 1887, when Alfred Mantle of Durham reported the growth of a diplococcus from the blood and joint fluid of a child with acute rheumatism. Many others carried on this work--Poynton,

Payne strep. viridans; Berkhaug--a hemolytic strep.; Schlesinger, Coburn, Collis and others--beta-hemolytic strep. John Frederick Poynto of the Great Ormont Street Hospital in London, one of Britain's great rheumatologists, in 1913, stated: "In spite of all that has been written upon the treatment of acute rheumatism, there are thousands of young children who are so damaged by this disease that all known methods of "cure" are utterly useless to them. It is, therefore, to prevention that we must look for real advance."

DEFINITION AND ETIOLOGY

Most writers agree as to the definition of rheumatic fever, namely that it is a disease characterized by widespread inflammatory and proliferative changes in mesodermal structures.(32) It is very likely to be frequently recurrent. Among the several factors influencing and predisposing to this disease entity are age, season, heredity, geographic distribution and climate, economic and hygienic status, previous attacks, infection and general poor health. The specific etiology and its mechanism are, however, moot questions.

When the germ theory of disease first came out there was an enthusiastic search for a specific organism as the etiological agent for every disease which could be at all considered infectious. So unreasonable were some of the new etiological hypotheses that Koch then stated his famous postulates which lead to a more thorough proof of etiological relationship between a suspected invading pathogenic microorganism and the animal host. The past two decades have seen nearly the complete establishment of specific etiological infectious agents in infectious diseases, with the outstanding exception of rheumatic fever.

We are now becoming aware of the great number of virus diseases; of those caused by very small microorganisms, as the rickettsiae; and of certain disease conditions caused by organisms in a more indirect manner in addition to those that frankly destroy the host tissue.

The germ or virus which causes rheumatic fever has as yet not been demonstrated. Which ever it is does not seem to cause a specific infection but is rather polyvalent in action.(42) In recent years the beta-hemolytic streptococcus has become more and more implicated until now this aspect of etiology has become a little more than hypothesis. In fact this often forms a starting point for today's research in rheumatic fever. But that it is due to an actual blood stream invasion per se is becoming more doubted. It has been shown that penicillin(50) is effective against beta-hemolytic streptococci. But Watson, Rothband, and Swift(64) using penicillin in doses ranging from 1,975,000 to 3,470,000 Oxford units given over a two weeks period to eight young adults with acute rheumatic fever apparently failed to alter the course of their disease. Foster, McEachern, Miller, Ball, Higley, and Warren(25) in a similar study of the value of penicillin therapy in thirty-eight cases of acute rheumatic fever disclosed no evidence of benefit. In some cases it appeared clinically that the course of the disease was aggravated. Lichtman and Gross(39) site figures to support the hypothesis that rheumatic fever is not caused by the streptococcus per se. In the 5,233 consecutive blood cultures made with adequately sensitive methods in Mount Sinai Hospital, New York, they found non-hemolytic streptococci in over six per cent of cases in a group of diseases, including pernicious anemia, aplastic anemia, leukemia, colitis and pyelonephritis. In a group of rheumatic diseases (acute rheumatic,

chronic rheumatic cardiovascular disease and rheumatoid arthritis) they obtained the same percentage of transient positives as in the control group of non-rheumatic diseases.

Beta-hemolytic infections of the nasopharynx, especially sore throat and tonsillitis, frequently precedes exacerbations of rheumatic fever.(59) Early reports (1936) published abroad on the therapeutic value of sulfanilamide showed that smaller than therapeutic doses, administered before the streptococcus had had an opportunity to invade and multiply in the tissues, were effective in preventing beta-hemolytic streptococcal infections in mice. This lead to a prophylactic test in humans. A civilian series by Thomas(59) et al--150 in each of test and control groups--showed no recurrences of rheumatic fever with sulfonamides and ten per cent recurrences without the drug.

Allergy presents a big new field which too is becoming more precise and illuminating through modern immunological investigations. Perhaps it is well in the case of rheumatic fever that attention no longer is limited to the isolation of a specific organism to fulfill Koch's postulates, and also that it is not entirely regarded as a characteristic allergy. Some micro-organisms, classically exemplified by the diphtheria and tetanous organisms, destroy almost entirely through toxins liberated in the host; other organisms also have toxins causing damage in the host more insidiously. The work on scarlet fever has shown almost all of the serious destruction in the person harboring the infection

to be due to an erythrogenic toxin liberated by a type of beta-hemolytic streptococcus, although rare instances of the scarlet fever syndrome arising from staphylococcus producing an erythrogenic toxin have been recorded.

(52) Emphasis has been placed on the direct effects of a toxin, as in scarlet fever erythema, and more recently on remote effects, as the aseptic, postscarlatinal nephritis. A fundamental, broad biological type reaction in these cases is suggested, consisting of a combination of some foreign agent, most often a bacterial toxic substance with certain tissues of the host; then an incubation or latent period during which time the patient usually appears to be improving, and finally a rather abrupt occurence of such a "nachkrankheit" which often surprises the unsuspecting clinician. Many factors make it seem to be nonbacterial and similar to certain anaphylactic or allergic phenomena. This type of disease comes apparently from body tissues combining with a toxin to form an antigen, then a period during which antibodies against the tissue-plus-toxin complex are formed, and finally, when there is a sufficiently high titre, an autogenous antigen-antibody reaction occurs. Delayed serum sickness is an example of such a reaction.

Thomas(59) explains the resistance of rheumatic fever to sulfonamides and penicillin on the basis of an allergic state saying that if the drug is started during the latent period, after the streptococcal infection has occurred but before the

appearance of acute rheumatic fever, the acute rheumatic attack develops regardless of medication. On the other hand if the initial beta-hemolytic streptococcal infection is treated prophylactically, there is little chance for an allergic state to develop. Capt. T. J. Carter[14], U. S. N., Chief of the Division of Preventive Medicine, Bureau of Medicine and Surgery, recently stated that as a result of "the largest controlled experiment in the history of medicine" mass chemoprophylaxis against respiratory disease caused by streptococcal infections has been instituted at all naval training stations. Dr. Carter stated that in 1943 mass chemoprophylaxis involving a million men was undertaken in selected stations on a controlled basis; the result of which was very successful. "At one station the rate of admission for scarlet fever varied from 6.35/1000 to 171.6/1000 during the observation period before the use of sulfadiazine following the institution of the prophylaxis, the rate fell to zero within two weeks.... Tonsillitis at this same station fell from 426/1000 to 46/1000. Rheumatic fever, the most serious of the infections associated with the streptococcal organism because of the heart involvement, was reduced from 87/1000 to zero within four weeks." Dr. Carter estimated that the experiment alone saved over a million man-days for medical personnel and between fifty to one hundred million dollars.

[70]In addition to the specific etiology and its mechanism it is generally agreed that susceptibility is on an age and genetic basis and is supported by considerable evidence. For more than

fifty years there has been a wide spread clinical impression that heredity is a significant factor in the observed concentration of rheumatic fever in certain families. This belief was based in large measure on the observed familial incidence of the disease. Recent family studies have been in accord with this observation.

Since familial concentration is commonly observed in contagious, dietary, and parasitic disorders, a disease may not be considered hereditary on the basis of a high familial incidence alone. Nonhereditary factors must be excluded, and the operation of hereditary factors must be demonstrated by adequate genetic analysis. Genetic and epidemiologic studies have shown that the primary factor responsible for the familial concentration of rheumatic fever is hereditary susceptibility. In a series of rheumatic families studied it was found that the distribution of cases followed the general laws of inheritance. Furthermore, the frequency of cases was consistent with recessive mendelian inheritance.

These studies were limited to a clinic population in New York City. They indicated that, if environmental factors such as climate, living conditions, diet or bacterial agents were responsible for the onset of rheumatic fever in susceptible children, they were uniformly operative and available. It was found that the number of age-genetic susceptibles estimated in every calendar year over a twenty-year period of observation was in close agreement with the number of onsets observed. It was also demonstrated

that the intrafamilial pattern of spread of rheumatic fever did not exhibit the usual characteristics of a communicable disease. One case did not constitute an obvious risk for secondary cases in the family. Age susceptibility appeared to determine the time of occurence of cases in the family. It is important to emphasize that, although the number of genetic susceptibles estimated in these families was found to be in close agreement with the final number of cases observed, it cannot be concluded that every genetically susceptible child will necessarily develop rheumatic fever.

The implications of these observations are apparent. The responsibility of the family physician, pediatrician, cardiologist, and clinic is not limited to the medical supervision of the rheumatic patient. A complete family history and adequate physical examinations of every member of the family are advisable. When it is ascertained that one is dealing with a potential rheumatic family, instructions as to the nature of the disease and its protean manifestations should be given. Until specific preventive measures have been developed, potential susceptibles should be protected from all known predisposing factors which appear to play a role in the onset of the disease. Since the individual susceptible cannot be identified, all the children in a rheumatic family should be under medical supervision. In recessive inheritance eugenic principles are not applicable, unless perhaps in instances when both parents are rheumatic.

If susceptibility to rheumatic fever is transmitted as a recessive characteristic, the chance for each child (in a family group of families) to be susceptible may be expressed as follows: If both parents are rheumatic, nearly every child will be susceptible. If one parent is rheumatic and the other parent is nonrheumatic but a carrier, i. e., rheumatic fever is present among the immediate family, each child has a fifty per cent chance to be susceptible. If neither parent is rheumatic but both parents are carriers, each child has a twenty-five per cent chance to be susceptible. (If at least one child is rheumatic, it may be assumed that the negative parents are carriers.) If one or both parents are negative, i. e., definitely known to be nonrheumatic and noncarrier, susceptible children would be unlikely.

The preceding data may be used to estimate the number of genetic susceptibles present in a family when the genetic constitution of the parents with respect to rheumatic fever is known. If at least one child is known to be rheumatic, the number of genetic susceptibles present in a series of such families may be estimated. Genetic factors have been established which facilitate computation of the number of susceptibles present. It is merely necessary to tabulate the series of families according to family size and multiply each group of families of given size by the appropriate genetic factor. These estimates may then be compared with the actual number of cases of rheumatic fever present in the series.

It is generally believed that the incidence of rheumatic fever is lower in certain sections of the country and infrequently among children of the more favorable economic groups in all sections. Estimation of the role of certain environmental factors may best be made by using the family as the unit for genetic study. For example, if the mortality rates published by the Bureau of Census reflect the relative prevalence of rheumatic fever in various localities, it would be expected that in family studies in certain mountain states where the mortality rate is high there would be close agreement between the number of susceptibles estimated and the number of cases of rheumatic fever actually observed. Similarly, in the South Atlantic States, where the mortality rate is reported low, it might be expected that there would be a disparity between the number of susceptibles and the number of cases observed. Such comparisons, made on data accumulated from different geographic locations and diverse economic groups, should yield significant information as to the role of climate and environment in this disease.

Of practical importance is the opportunity afforded for evaluating preventive and therapeutic procedure by making a careful genetic selection of families. Since nearly all the children in families where both parents are rheumatic are probably susceptible to rheumatic fever, even a small series of such families would provide a critical experimental group for study. Recognition and observation of the potential rheumatic family offer a promising field for future research in rheumatic fever.

In a recent report by Peete[48] observations are summarized on patients seen in clinic and private practice over a four-year period who showed any signs of rheumatic fever or rheumatic heart disease. The patients were given a list of foods with instructions to check after each meal all the foods eaten and to write in any additional ones taken which did not appear on the list. The survey included a comparison of the dietetic habits of fifty patients, some with acute and some in the chronic state of rheumatic fever, as compared with twenty-five normal school children. A comparative study showed that the average diet of the rheumatic patient was low in those foods which supply vitamins A and D and minerals, especially calcium, phosphorus, and iron. Some deficiency in proteins and an excessive intake in starchy foods and refined sugars also were apparent. The diets of both groups showed a restricted use of eggs. It was significant, Peete believed, that the average number in families of seventy-five rheumatic patients was 7.5 members per family, whereas the average in the control group of better economic status was 4.5. Among the conclusions of this study were that the incidence of acute rheumatic fever and rheumatic heart disease increases as exposure to the sun decreases; few recurrences of active infection developed when families cooperated satisfactorily in the correction of the deficient diet and in addition of cod liver oil to these diets; poor dietary habits were found among those even with adequate financial means. Finally, this investigator felt that the deficiency leading to

the development of rheumatic infection closely follows the incidence of clinical rickets and that it alters immunity to the infective organism that produces the clinical picture of acute rheumatic fever. He emphasizes the importance of adequate amounts of vitamin A and D, milk, protein, and sunlight in the prophylaxis and prevention of recurrences of this disease. The conclusions expressed should be accepted with reserve. The genesis of rheumatic fever has not yet been explained: most features of the disease would appear to label it as due to a comparatively specific agent not yet identified, although numerous precipitating or predisposing factors presumably occur, among which diet may be included.

PATHOLOGY

Our conception of the essential pathology[9] of rheumatic fever has undergone an interesting evolution. For centuries the acute arthritis flitting from joint to joint has been well recognized. About a hundred years ago the relationship of valvular lesions to acute rheumatism was established, but these lesions were thought to be sequelae of the acute disease, and not a primary manifestation as we now know them to be. Of late years the truth has begun to dawn that rheumatic fever is an inflammatory condition of the fibrous tissues involving first and foremost the heart, and, as a rule, the joints, the subcutaneous tissue, occasionally the brain, and probably certain other organs. Regarding the relative importance of the cardiac and the arthritic lesions, it has been wittily said that rheumatism is a disease "which licks the joints, but bites the heart."

The disease pursues a somewhat different course in children from what it does in the adult. In children the joint pains may never appear. The child suffers from tonsillitis and a sore throat, these are replaced by chorea, and one day a heart murmur is discovered. In the adult the intensely painful swelling of the joints is much more characteristic, fever is higher, and skin lesions are much rarer. It must be emphasized, however, that rheumatic fever is principally a disease of childhood; about seventy-five per cent of the cases occur before the age

of twenty years. Conversely, about ninety-five per cent of heart disease in children is rheumatic.

In respect to the heart itself, a similar evolution of thought may be noted. Interest was at first focused upon the characteristic vegetations along the line of contact of the valves and the accompanying pericarditis. The lesions in the myocardium were then discovered, and their effect upon the heart's action studied by means of the electrocardiogram. Finally it was recognized that the essential valvular lesion was an inflammation of the entire valve, a valvulitis, and that the vegetations were to be regarded as merely incidental.

In considering the pathology of rheumatic heart disease one is apt to pay undue attention to the particular lesions in the pericardium, the myocardium or the valves. It is more important to realize that, as in tuberculosis, so in rheumatism, there is one fundamental basic lesion whose characters may vary with the anatomical site in which it occurs, just as the phenomena to which it gives rise may vary in like manner, but which nevertheless represents the essential reaction of the tissues to the rheumatic cause. This lesion is the submiliary nodule, so-called because it is smaller than the miliary nodule of tuberculosis, being barely visible or invisible to the naked eye. It is found in the valves and muscle of the heart, in the pericardium, in the synovial membrane and periarticular tissue of joints, in the subcutaneous tissue, and even in the meninges and brain.

There are four main components of the rheumatic nodule:

1. The center is composed of a small amount of necrotic material. This consists for the most part of swollen and fragmented collagen.

2. Around this center are grouped the Aschoff cells, peculiar large endothelioid cells with one or several vesicular nuclei, and a basophilic cytoplasm with characteristically ragged edges. Naked masses of cytoplasm may be present. The cytoplasm of the Aschoff cells stain a brilliant red with Poppenheim's pyroninmethyl green, but the tissue must be specially fixed in alcohol. These cells constitute the most characteristic feature of the lesion. They are probably derived from the histiocytes or resting wandering cells, members of the reticuloendothelial system. The giant cells resemble those of Hodgkin's disease rather than the multinucleated giant cells of tuberculosis.

3. Lymphocytes and plasma cells are to be seen in varying numbers, together with an occasional polymorphonuclear leukocyte. Occasionally the polymorphonuclears are so numerous that the lesion is practically an abscess.

4. A fibroblastic proliferation more or less marked in degree is always present.

This collection of proliferated cells is known as the Aschoff body. It varies greatly in size; there may be only a few cells, or it may be visible to the naked eye. It may be round, but frequently in the myocardium it is elongated or lemon-shaped. It

bears a definite relation to the adventitia of the small branches of the coronary arteries, not perivascular in the sense that the cuff of inflammatory cells in syphilis or encephalitis lethargica is perivascular, but nevertheless lying alongside the wall of a vessel as it runs in the interstitial tissue between the bundles of muscle fibers. The cells of the Aschoff body are mainly the result of local proliferation, but it cannot be denied that probably some of the small round cells and certainly the polymorphonuclear leucocytes are to be regarded as evidence of the exudative type of reaction. Edema, frequently seen in the valves, is another manifestation of this reaction. It is, however, in the joints and in the pericardium that exudation is seen to the best advantage.

The subcutaneous nodule provides another fairly typical example of the pure lesion, although under the microscope a certain diffuseness is often to be observed, as well as some edema. The nodules occur in the deep fascia, particularly over bony prominences, such as the malleoli, the crest of the ilium and the vertebral spines; perhaps one should rather say that they are more readily observed in these situations. These nodules are painless and do not inconvenience the patient in any way, but they are of extreme interest to the observer as an indication of what is going on in the heart and in the brain, for in rheumatic fever alone are they found. As in the case of tuberculous masses, the larger nodules, those recognizable clinically, are composed of an aggregation

of submiliary nodules. The nodules appear quickly and may disappear with equal celerity, or they may persist for months.

SYMPTOMS, SIGNS, AND DIAGNOSIS

Jones[36] has outlined some strict diagnostic criteria for the diagnosis of rheumatic fever. He divides these into the major and minor manifestations.

The major manifestations offer the least likelihood of an improper diagnosis. Disagreement would seem to exist largely in the relative importance of the individual manifestations. Few clinicians would disagree as to the diagnosis in an acutely ill person presenting a combination of these major manifestations. In only three clinical syndromes is there often any confusion with such a combination of findings. Two of these are relatively rare, while the third is common. They are Still's disease (in children), disemated lupus erythematosus, and the acute form of rheumatoid arthritis. Occasionally long observation is necessary to differentiate these from rheumatic fever, and one must constantly bear them in mind when seeing an acutely ill patient. Since active carditis is found in all fatal rheumatic fever cases it may be listed as the first major manifestation. Numerous evidences may be found of definite structural or functional cardiac change during acute rheumatic fever. Knowledge of the heart findings prior to the onset is often of prime importance. Incontrovertible evidence of active carditis may be accepted if the patient develops definite cardiac enlargement, significant cardiac murmurs, pericarditis (friction rub), or congestive failure. This would

seem to hold at any age if other major manifestations exist. They are at times overlooked in the older patient. In the young patient these findings are usually indicative of rheumatic fever despite the absence of polyarthritis, and, indeed, in children such a clinical picture is not unusual. Doubt will certainly be raised concerning what comprises a significant murmur. A loud, long, blowy, apical systolic murmur, widely heard and not varying with position may be considered significant, as well as any type of diastolic murmur.

Arthralgia is the second of the major manifestations. Migrating polyarthritis is generally considered the classic feature of rheumatic fever. While it is common, especially in the young adult patients, no one symptom offers greater diagnostic difficulty, whether the joint changes are objective or mere subjective complaints. One must remain skeptical where this is the only real clinical finding aside from fever. It is advisable to search frequently for some evidence of carditis and other major and minor rheumatic fever manifestations before accepting arthralgia as being proof of the existence of rheumatic fever. Usually transient mild polyarthritis, without other diagnostic features suggestive of rheumatic fever or some other medical condition, rarely proves to be a problem of serious import. Of course, one must take exception to this if, for instance, the patient has been exposed to a known beta-hemolytic streptococcus or scarlet fever epidemic. If the patient has had tonsillitis, pharyngitis, or even a cold

in the past two or three weeks, and serologic tests indicate a recent hemolytic streptococcus infection, the burden of proof rests with the physician who would not interpret such a syndrome as rheumatic fever, since this represents the usual epidemiologic pattern of the disease. However, in the absence of such findings and other rheumatic fever manifestations, arthritic symptoms should not be considered certain proof of the existence of the disease.

While chorea, the third major manifestation, is a symptom complex, it is closely related to rheumatic fever. In the experience of Jones and Bland(35) about one half of all rheumatic fever patients (young patients) have chorea at some time, Conversely, approximately three fourths of their young chorea patients in time develop other major manifestations of rheumatic fever. This would seem closely to associate the two, and it is a rather satisfying relationship from a diagnostic point of view. Since chorea is rarely seen after adolescence, it is not usually helpful with the diagnosis in adults. However, an occasional adult with questionable rheumatic fever findings give a history of childhood chorea. The presence of definite chorea, associated with questionable signs and symptoms, helps establish a definite diagnosis of rheumatic fever.

While subcutaneous nodules are characteristic, they rarely occur in the early stage of the acute illness, and in a large percentage of instances abundant evidence of carditis exists. Hence, only in rare patients are they helpful from a diagnostic

point of view, but more often in the determination of the presence of active rheumatic fever in a person with known previous rheumatic fever or rheumatic heart disease.

Recurrences of Rheumatic Fever. Perhaps no feature of rheumatic fever is more striking or more important than the tendency of the disease to recur. Perhaps also no more serious aspect as to prognosis exists. A history of previous definite rheumatic fever or rheumatic heart disease is strong evidence of the existence of the active rheumatic fever in the presence of even mild signs and symptoms.

Since the histologic changes are generalized, it is not surprising that the signs and symptoms are varied. Almost any complaint may be a part of the disease pattern; however, a limited number occur often enough and of such apparent significance as to warrant diagnostic consideration. These are the minor manifestations.

Fever. A definite elevation of the body temperature is one of the most common and most variable findings in rheumatic fever. Fever alone, even in the presence of laboratory abnormalities, is insufficient to make a diagnosis of initial rheumatic fever. At the present time fever alone (or often in the presence of an extracardiac or so-called functional murmur) is a common erroneous basis for a diagnosis of rheumatic fever. While fever is helpful, it may be misleading, and other features are usually more important.

A frequent occurence is abdominal pain, the exact cause of which is yet undetermined. Many explanations have been offered. Its occurrence is frequent during evident active rheumatic fever. Of particular interest is the frequency with which it is the initial symptom. This is usually clinically indistinguishable from acute appendicitis. This may pose a difficult diagnostic problem in known rheumatic individuals. It may be well to state that, since actual acute appendicitis may occur in rheumatic fever patients, decisions as to the need for operation are not easy.

While precordial pain is a common symptom, evidence of carditis is usually found when it is significant. At times precordial pain may suggest coronary involvement. One must remember, however, that mild or transient precordial pain is one of the commonest symptoms of neurocirculatory asthenia, even in the presence of definite heart disease.

While many rashes have been described in rheumatic fever, it has been Jones' experience that erythema marginatum is by far the most significant cutaneous manifestation. The evidence at hand rather suggests that it might be more properly classified as a major manifestation of rheumatic fever. Further study is needed on this score. Various purpuric manifestations do occur, but they are apparently less frequent than in the past.

Nontraumatic nosebleeds are common in rheumatic fever. They appear to be less severe and less frequent than a decade ago.

Their relationship to rheumatic fever is on a clinical basis as yet. In association with other findings they may be useful in the diagnosis.

During acute rheumatic fever various pulmonary changes are not unusual (even consolidation). The clinical and histologic patterns vary considerably. Without other evidence of rheumatic fever, pulmonary changes are rarely diagnostic.

Since at the present time all laboratory abnormalities found in rheumatic fever are nonspecific in character, they are best listed as being of minor significance. Among these are the E.K.G. These may be demonstrated in many patients especially if repeated tracings are made. Prolongation of auriculoventicular conduction time is the most frequent finding, but numerous other changes may be encountered (such as inversion of T waves, transient changes in electrical axis during failure, and so on). The development of a microcytic anemia (severe in only a small percentage of patients), an elevated white blood count, and an increase in the sedimentation rate of red blood cells are the most common abnormalities. The latter is perhaps the most useful. These tests are of more pertinence in evaluating the presence of active rheumatic fever (in a known rheumatic individual) than is a diagnostic aid. Occasionally rheumatic fever may be active without these laboratory abnormalities. Of especial interest is the frequent normal sedimentation rate in the presence of heart failure.

In summary, it may be stated that even a combination of these minor manifestations may not be sufficient to make a certain diagnosis of rheumatic, although they may be suggestive. It is further suggested that any single major manifestation with at least two of the minor manifestations would seem to place the diagnosis on reasonably safe grounds. The most common basis for a mistaken diagnosis with acceptance of this criterion would be the occurrence of some degree of arthralgia in the presence of fever and some laboratory abnormality. Here the history of a previous respiratory infection, exposure to a hemolytic streptococcus epidemic and/or the development of hemolytic streptococcus immune bodies would be a helpful and probably conclusive positive aid.

CLASSIFICATION OF THE PATIENT

(53)Reflecting upon the natural history of rheumatic fever, namely; as its acute fulminant episodes appear in early childhood; as its recurrent flares affect the child of school age; as it hampers development and interferes with adaptation to life's demands on the part of adolescents and young adults during their most important, their formative years; and, finally, as it imposes the hardships of circulatory breakdown upon those who have survived to middle age; reflecting upon this chain of events in the natural history of a single disease, one is impelled to stand at respectful attention and plan with reservation from time to time. From this chain of successive events it becomes apparent, also, that the treatment, or better termed, the management of the rheumatic cardiac must be individualized and should be a continuous and uninterrupted process for years. Adequate management, in turn, implies that the physician-in-charge be alert, resourceful, and adaptable.

By assembling several components of a diagnostic pattern(53), we arrive at a comprehensible clinical diagnostic pattern which may then serve as a basis for rational therapy and rational adjustment. Such a diagnostic pattern tells us: A, about the status of the etiological factor; B, about the type of anatomical involvement; C, about the physiological abberations; and D, about the degree of circulatory embarrassment. It informs us also that

certain accompanying extracardiac factors have complicated the clinical picture. For example:--

Case I

A--Rheumatic

B--Mitral insufficiency; enlarged heart

C--Sinus tachycardia

D--Functional capacity very low

Accompanying condition: Recurrent rheumatic fever with pericarditis

Case II

A--Undetermined (rheumatic)

B--Mitral stenosis and insufficiency

C--Sinus tachycardia

D--Functional capacity low

Accompanying conditions: Anemia and malnutrition. Smoldering rheumatic fever.

It is probably more important to classify a case for management from a clinical standpoint of view, i.e., with special emphasis on the activity of the inflammatory process and how "sick" is the patient.

Taran[57] has compiled a practical but simple classification of management with the clinical aspects in mind. He places a rheumatic case in either acute, protracted, subacute, quiescent or chronic decompensatory phases.

In the acute phase the patient is quite sick, suffering from, perhaps acute arthritis, acute chorea, acute carditis with heart failure. Hospitalization until over this phase is best. Since specific diagnostic tests are lacking, the decision as to the time of discharge rests with the physician in charge. There are several non-specific tests which are helpful in this regard about which more will be said later. The beginning of the acute phase precedes admission to hospital by weeks; its duration is much longer than is apparent from clinical observation. Most acute episodes begin with mild symptoms and signs (unrecognized in the majority) and roll up slowly and insidiously until the obvious explosion occurs. Then the patient is hospitalized. The explosion subsides in a few weeks, but in all patients a slow subclinical active disease continues for months after the explosion. Although the preexplosive and postexplosive stages are not easily recognized, it is agreed by most students of rheumatic disease that treatment in these stages is a paramount importance if cardiac damage is to be prevented. Under the present set-up, the patient is admitted too late and discharged too early.

The protracted phase begins after several weeks have passed and the patient still has sings of active disease. These children are discharged home to remain in bed and report to the doctor from time to time. In some instances the child is sent to a convalescent home. In this group of cases are found children with rheumatic fever, carditis without heart failure, and chronic chorea. It is

obvious that this phase of the disease does not differ in any important respect from the acute phase except in the matter of degree of activity. Thus the continuity of treatment is broken in a continuous disease process.

From the point of view of total management of this disease, this phase of rheumatic disease is of even greater importance. The signs and symptoms and laboratory tests are evasive. It requires considerable judgement and close observation over a period of many months to determine when the acute phase is definitely at an end. The degree of cardiac damage is proportional to the degree of medical neglect during this phase.

After the patient remains in bed at home for several weeks, he is reclassified to the subacute phase. He may not present any obvious signs of carditis or chorea but continues to show some laboratory evidence of active rheumatic disease. During this phase the child complains of mild rheumatic symptoms. Rapid examination and judgement formulated will fail to detect mild rheumatic activity and often such a child is returned to normal childhood activity in such a condition. This child who returns two years later with unequivocal signs of mitral stenosis and enlarged heart and from five to ten years later has marked depletion of cardiac reserve and at or immediately past adolescence becomes a cardiac invalid.

When the quiescent phase begins or ends is unknown. Its diagnosis is based upon a lack of evidence of activity. A patient

who presents a history of rheumatic fever and at the time of examination does not present physical or laboratory evidence of active infection is said to be in the quiescent phase. An interruption of the quiescent period by obvious signs of rheumatic infection is said to be a recurrence. A close observation of a quiescent group of children shows that there is no clear-cut distinction between quiescence and activity. Repeated careful examinations and laboratory studies show that quiescence is punctuated by short periods of mild activity.

The last and most discouraging group in this classification is the chronic decompensator. An attitude of hopelessness denominates the management and treatment of this group of children. These hearts are beyond repair and therefore cannot possibly be restored to communal usefulness. In our experience, there is cogent evidence to show that chronic decompensation in childhood is another expression of protracted rheumatic activity. We are encouraged by the fact that a large proportion of these "hopeless cripples" may yet be restored to usefulness and their life cycle prolonged if they are not discarded too early in the management of the rheumatic fever case.

MANAGEMENT AND TREATMENT

In the management of the acute attack rest is most important. In order to minimize valvular damage, therefore, every effort should be made to reduce the work of the heart and the pressure existing within its chambers[10]. It is obviously impossible to give the heart absolute rest but its work can be materially diminished by putting the patient at bed rest. On the average the pulse rate is reduced ten beats per minute by putting the patient at bed rest and this during the course of a day will reduce the number of heart beats by approximately 10,000--a significant economy. The period of bed rest should be maintained so long as any signs, clinical or laboratory, or persistent infection are present. This may be a matter of months or even a year or two and demands great patience on the part of all concerned. It[49] is important that the parents and the patient, if he is old enough, be carefully and fully informed as to the gravity of the situation. The nature of the disease should be described in full with its complications and its tendency to smolder subclinically and recur. They must be willing to cooperate completely through long periods of treatment. They must be informed as to the limited therapeutic means available so that they may not become too impatient after protracted weeks of bed rest.

Diet is an important item in this disease. Because the patient is sick he probably won't feel much like eating. And

because of the chronicity of rheumatic fever it is important to keep the patient well nourished. For these reasons the food must be appetizing. It should[44] not be forced, of light character, easily digested, liquid or semi-liquid. [5]A high carbohydrate, low fat diet best fits these requirements. Protein should be given in basic amounts, i.e., approximately 2 to 2.5 grams per kilogram body weight. It goes without saying that the diet must contain minimum requirements, at least, of vitamins, minerals, etc. Rinehart emphasized vitamin C deficiency as of etiological significance but Pitt[49] maintains that vitamin C exerts no specific therapeutic effect on this disease. Whether it does or doesn't, orange joice, which contains appreciable amounts of vitamin C, is a pleasant means of boosting the carbohydrate intake and the vitamin C requirement will be satisfied.

Probably the most important part in treatment of rheumatic fever, and the same might be said of any disease or injury suffered by an individual, is relief from his symptoms. They are what brings the patient to the doctor and they are what the patient expects the doctor to allay. A high percentage of rheumatic patients complain of polyarthritis, fever, and discomforts of chest and abdomen. Relief[10] from these can usually be obtained by the use of salicylates. With reduction of fever and remembering the rule of thumb that the heart rate is increased by ten beats per every degree temperature, this is another means

of augmenting the decrease of work performed by the heart. It is doubtful[10] that the salicylates have any other useful function in the treatment of rheumatic fever, consequently the dosage employed should be no larger than necessary to accomplish these ends. Although it may, at times, be necessary to give toxic amounts of salicylates to produce these results there seems to be no advantage in the routine administration of salicylates to the point of intoxication. The desired therapeutic effect may be obtained with as little as 0.60 grams (gr X) of aspirin every four hours or the total dose may need to be doubled or even trebled. On the whole aspirin is better tolerated than sodium salicylate but both should be accompanied by equivalent doses of sodium bicarbonate provided there is no heart failure. Bauer[5] dogmatically says that "the use of aspirin is like sending a small boy on a large man's errand" and for this reason advocates the use of sodium salicylate grams five to ten every twenty-four hours in divided doses with equal amounts of sodium bicarbonate. As for sodium salicylate being more efficacious than aspirin Goodman and Gillman[28] says the acetylsalicylic acid is effective in a somewhat lower total dosage than sodium salicylate. In regards to the administration of sodium bicarbonate with salicylate therapy it has been shown by Smull, Wegria, and Leland[54] that when a serum salicylate level has been established and is being maintained by the oral administration of salicylate,

the simultaneous administration of approximately equal amounts of sodium bicarbonate results in a definite fall of serum salicylate level. Also the simultaneous administration of equal amounts of sodium bicarbonate and sodium salicylate prevents the establishment of as high a serum salicylate level as would be obtained with sodium salicylate alone.

Recently Coburn[19] advocated the administration of large doses of salicylates in acute rheumatic fever. He recommended the intravenous administration of ten grams of socium salicylate in 1,000 cc. of 0.9 per cent sodium chloride every day for four days. Intravenous medication was given slowly over a period of four to six hours, so that sufficiently high concentrations of the drug in the body could be reached and maintained. Plasma salicylate values of four hundred micrograms per cc. could be attained by this method. In fact, Coburn believed that values of one hundred fifty to two hundred micrograms, easily attained by oral administration of salicylates, while providing relief from the acute symptoms of rheumatic fever, failed to halt the progress of the disease. He contended that serum salicylate values of three hundred fifty micrograms per cubic centimeter or more must be maintained if the "rheumatic reaction was to be held in check". Protocols of his small series of cases furnished some remarkable results, especially the rapid resolution of the acute phases of the disease, as judged by the quick return of sedimentation rates to normal and the sudden disappearance of

clinical signs. (Lichty and Hooker[40] have conducted experiments apropo to the effect of acetylsalicylic acid on sedimentation rate of erythrocytes in rheumatic fever. Their findings will be brought out in the criteria for convalescence.) Many are not in accord, however, with this thesis of the early curtailment of the damage inflicted by the "rheumatic reaction". It has been pointed out that sufficient time has not elapsed to judge fairly the results of Coburn's treatment. This is particularly true in regard to the incidence of mitral heart disease, pericarditis and pancarditis, common aftermaths of acute rheumatic fever.

Large amounts of salicylates cannot be given without careful clinical observation of the patient. Deaths and severe complications from salicylates have been recorded[2]. Patients should be questioned concerning any sensitivity to salicylates before the drug is given. The appearance of tinnitus, vertigo, deafness, nausea or other symptoms should indicate the cessation of further administration of the drug until the symptoms disappear and then continuation with a lower dosage. Hypoprothrombinemia has been reported[41] to follow salicylate therapy; some[46] have found that adequate amounts of vitamin K will protect against this contingency.

The whole problem of salicylate intoxication was recently studied by Fashena and Walker[22] after their attention has been drawn to the subject by the observation of a patient with salicylate

poisoning. They studied six children, to whom they gave large amounts of sodium salicylate by mouth every four hours. Blood salicylate levels of three hundred fifty micrograms per cubic centimeter were maintained throughout the study. Prolongation of prothrombin time was found in every instance.

Rheumatic fever often is accompanied by a widespread vascular damage, thus increasing the hazards of hemorrhagic complications after salicylate administration. When adequate amounts of vitamin K are given with salicylates, much of the danger of these complications may be prevented. Possible hazards in the administration of salicylates should be remembered, so that unnecessary dangers may be avoided.

Cardiac pain, like pleuritis, is often due to the inflammation and irritation of the parietal pericardium and pleura. An ice-bag[44] may give some relief but if not enough, codeine is helpful. It will not be necessary to continue this medication since an effusion usually occurs within a day or two separating the two roughened surfaces. [34]Howard says that x-ray therapy often exerts favorable effect on precordial pain. This may be due to the effusion just referred to. The amount of effusion must be watched by physical means and perhaps x-ray so that any cardiac embarrassment by tamponade might be prevented.

Occasionally[34] so-called attacks of epilepsy may occur in an individual suffering from acute rheumatic fever, especially

in those individuals of a more mature age. Epilepsy may be tentatively ruled out with the electrocardiogram which shows a third degree or complete block. Actually the manifestation was that of syncope. The heart block is due to a lesion of rheumatic fever, Aschoff body, directly involving one of the larger trunks of the bundle of his preventing the excitatory impulse from reaching the heart muscle. First degree heart block is very common in rheumatic fever manifesting itself only on the E. K. G. with prolongation of the PR interval. The treatment(34) for the former is rest and taking it easy until the body adjusts itself to and the heart compensates for its decreased rate. Cerebral symptoms relative to cerebral ischemia are relieved somewhat by adrenalin to increase the blood pressure although one would hesitate in its use during the acute phase.

Since the advent of penicillin which has proved so effective in the treatment of several diseases which have, heretofore, proved absolutely or comparatively refractory to previous forms of chemotherapy, one would naturally wonder about its effect upon acute rheumatic fever. In a small series run by Watson, Rothbard, and Swift(64) in which doses of penicillin ranging from 1,975,000 to 3,470,000 Oxford units were given over a two week period, there was apparently no alteration in the course of the disease. In a somewhat larger series of thirty-eight cases of acute rheumatic fever Foster, McEachern, Miller, Ball, Higley, and Warren(25) found no evidence of benefit. In some

cases it appeared clinically that the course of the disease was aggravated. Penicillin does, however, have a very definite role in the treatment of one of the complications of rheumatic fever about which more will be said later.

The handling of the subacute and chronic phases of rheumatic fever resolves itself more to management than to actual treatment. For this and other reasons, especially economic, it is usually permissable for the patient to go home. Among the "other reasons" mentioned above is consideration for the child's feeling of being confined in a hospital. Hospitalization[58] is a traumatic experience too often not so considered by those of us conditioned by hospital routine. The child feels he has been snatched from the security of home life when he finds himself alone with strangers in a situation of which he has never dreamed. His home may be crowded, the economic situation uncertain, his parents harassed and lacking in understanding, but home it is and to him spells security. Dr. Richard Cabot[66] also found that many children remaining for a long time in hospital wards become institutionalized and retarded in their physical and mental convalescence.

Rest is still the main item. A good, wholesome, appetizing, high carbohydrate, low fat diet is also essential. Anemia is almost a constant feature of the rheumatic diseases for which ferrous sulfate grains three to five t.i.d.p.c. usually is helpful.

Probably the most important phase in the management and prognosis of the rheumatic is his rehabilitation. The first concern is whether there is any evidence of active rheumatic infection or not. There should be[63] (1) Absence of symptoms--arthritis, arthralgia, abdominal and precordial pains, and nosebleeds; (2) Absence of fever--a persisting low-grade fever indicates a search for infection in the throat and more rarely the onset of infective endocarditis; (3) Absence of upper respiratory infection--careful examination of throat, ears, and sinuses is important. The presence of hemolytic streptococcus in the nose and throat is a portent of forthcoming trouble; (4) A stable pulse rate--the sleeping pulse should be definitely lower than the waking pulse; (5) Absence of chorea as described in the diagnosis; (6) Absence of nodules--must be looked for with elbows and knees flexed. Palpate for on the occiput. These are most common with pericarditis, coming out, often in crops, three to four weeks after the acute onset; (7) Gain in weight--a valuable index of progress; (8) Sedimentation rate--it must be remembered that during cardiac failure the sedimentation rate will often drop to normal or below, and this drop may be one of the early signs of impending failure, conversely, its increase after failure is evidence of recovery. Lichty and Hooker[40] stumbled onto a fact important in the interpretation of the sedimentation rate of the erythrocytes where salicylate therapy is being used. Prior to 1940, salicylate therapy was

often continued for several weeks after the sedimentation rate became normal, but recently the drug has been discontinued as soon as a normal rate was obtained, assuming that the rheumatic activity had then ceased. To their surprise the sedimentation rate in several cases became appreciably elevated during the first week after stopping medication. This was occasionally associated with an elevation of temperature, the return of symptoms, or both. In a few of the cases receiving second or third courses of the drug, the same phenomenon was observed.

The hospital course of seven patients showing this type of reaction is considered. Each child had acute rheumatic fever, and all except one showed definite cardiac involvement. The rates were determined at approximately weekly intervals using the Rourke-Ernestene technic. This method has been used for several years and has always given apparently consistent and reliable results in the rheumatic patients. Salicyl was administered by mouth in the form of acetylsalicyl acid combined with sodium bicarbonate. The celerity with which the "rise" occurred after discontinuing the drug suggests that this salicyl compound may have the ability to lower the sedimentation rate as well as the temperature and the leukocyte count in this disease.

In seeking an explanation of this reaction, the studies of Bendien, Newburg, and Snapper appeared to be pertinent. These authors noted that when sodium salicylate is added to human blood in vitro, the erythrocytic sedimentation rate is greatly reduced.

In a few preliminary experiments, they (Lichty and Hooker) have been able to confirm their findings, but the minimal effective concentration of sodium salicylate, using this method is 90-120 mg.%. This represents three times the value given as an average blood level obtainable in rheumatic patients. And finally (9) the clinical examination of the heart. This is more important in estimating the heart's functional capacity. In regards to the cardiac reserve(63) we find far too many children are submitted to unnecessary restrictions because of a history of past rheumatism and the presence of a murmur. The most useful clinical guide in estimating the heart's functional capabilities is its size, and in the absence of clinical enlargement, the presence of murmurs per se does not call for restriction in activities, once the patient has been proved to be free of infection and has been regraded to normal exercise. Cardiac breakdown in a child is not due to over-exertion but to reinfection, a fact which must be constantly kept in mind in the supervision of these cases. Two main causes of cardiac enlargement after rheumatic involvement are an old pericarditis and aortic regurgitation; the former is much the commoner. When the apex beat is found outside the nipple line and is due to cardiac hypertrophy, often associated with some precordial bulging, then the child should have his activities restricted but even so may be allowed to take exercise within his capacity. In broad terms it may be said that subject to the overriding point of cardiac enlargement a patient

with an apical systolic murmur attributable to rheumatic infection should be managed as a normal child so far as cardiac function is concerned, but the presence of diastolic murmurs, which so often mean an ultimate mitral stenosis, are more difficult to assess; even in this event, however, judgement must be based on other factors, such as the size of the heart and the child's reaction, rather than on the murmurs themselves.

When the physician decides that it is safe for the patient to get up this must be done gradually, starting with a short time each day out of bed in a chair and later, at gradually increased intervals, walking about the room or taking mild exercise. All the while the patients sedimentation rate, pulse differential between day and night, and temperature must be kept closely checked. On the first evidence of any change for the worse, the patient should be immediately put to complete bed rest again. There is far too much unnecessary invalidism mixed up with this problem of the child with rheumatic heart disease, and one of the most important functions of the physician is to release children from the bondage so often needlessly imposed by the practitioner and school medical officer.

Before taking up the management of the inactive rheumatic patient we shall mention a few of the complications seen in conjunction with this disease. Occasionally acute auricular fibrillation occurs. If the arrhythmia is of only two or three months duration,[34] an attempt can be made to restore normal

sinus rhythm by the use of quinidine grains one every hour for thirty-six hours. With failure to achieve satisfactory results, digitalis must be used to control the ventricular rate.

The problem of complete block and its management was mentioned earlier.

While the problem of bacterial endocarditis is not directly a complication of rheumatic fever, the latter sets a nice stage for such an infection. So often in rheumatic fever the lips of the valve cusps become roughened with a verrucous nodular pattern of fibrin which may or may not ulcerate. As was previously mentioned an occasional organism gains entrance into the blood stream and if all conditions were optimum for this organism, particularly the streptococcus viridans, and it (or they) implanted in one of the ulcers a bona fide bacterial endocarditis will result. Before penicillin was introduced bacterial endocarditis was considered to be sure death sooner or later. Recently Dawson and Hunter[21] reported twenty patients with subacute bacterial endocarditis treated with penicillin. The infecting organism was a streptococcus in all instances. While it is recognized that a long follow-up will be necessary before the ultimate outcome is established, therapy was apparently successful in fifteen of the twenty. All fifteen patients are now clinically and bacteriologically free from infection. While it is still too early to be dogmatic about penicillin in endocarditis, it looks promising.

As a complication of rheumatic fever, congestive failure usually occurs.some years after the initial infection, i.e. if the heart was damaged in such a way so as to interfere with its mechanical efficiency. Of course absolute bed rest(61), barring the necessity of having to use the bed pan, and restriction of fluids to 1,200 cc. or less per day. No salt is added to the diet except that used in cooking. The use of diuretics will depend upon the individual case as to whether he is excessively edematous or not. (In respect to the use of diuretics one point is quite important. In event that digitalis has been used and not proved effective it must be remembered that the digitalis will be stored in the edema fluid and sudden mobilization of this fluid may result in digitalis poisoning.) Of the xanthine derivatives theobromine calcium salicylate can be recommended on the basis of its ease of administration (orally), its low cost and good results (65%). It rarely causes a gastrointestinal upset. The optimal daily dose is three to five grams in three doses. The mercurial diuretics are more effective than the xanthines but have several contraindications among which is kidney damage. These are given in doses of one cc. intravenously preceded by three to four grams of ammonium chloride in the previous twenty-four hours.

The use of digitalis is quite controversial. In its use one must consider three factors which influence the muscular

action of digitalis in congestive heart failure[24]. (1) The etiologic type of disease, (2) the extent of the disease, and (3) the presence or absence of active infection. Hypertensive and the coronary types of heart failure (with normal rhythm) are more amenable to digitalis therapy than those with a rheumatic or luetic etiology. The extent of the disease and the question of active infection do enter into any survey of rheumatic heart failure with normal rhythm, which is considered much less responsive to digitalis than those with auricular fibrillation. Heart failure with normal rhythm is said to be far less frequent than auricular fibrillation and to have a less favorable prognosis than in a corresponding degree of this arrhythmia. For many years the superiority of digitalis has rested on its particular value in rheumatic heart failure with auricular fibrillation, largely but not entirely due to the high ventricular rate. Evans[24], however, found that the actual heart rate is an unreliable index of successful digitalization, and Wood[24] stated that although a fall in pulse rate is usually associated with improvement from digitalis therapy it is not essential. Toxicity[61] may manifest itself by auricular fibrillation. Also occasionally bigeminal rhythm due to ventricular premature beats. Also a 2:1 heart block. For these an electrocardiogram should be run every two to three days during digitalization and shortly thereafter.

PROPHYLAXIS

Prophylaxis is the best treatment for any disease and this is especially true in rheumatic fever since once the individual has the disease there is no specific treatment. And too often the heart is permanently damaged in invalidating the victim to a greater or lesser degree.

Since much of the evidence on the etiology of rheumatic fever seems to point towards an allergic state resulting from a bodily reaction to a focus of infection of streptococcus it might be well to start from this angle. The tonsil recieve the brunt of this attack. In a group of two hundred forty-five treated (tonsillectomy and adenoidectomy) and one hundred sixty-five untreated children Wilson(69) has attempted to learn what the likelihood is of recurrence at each age for children in both groups. If the analysis of the data is correct, it may be an explanation of the contradictory results obtained by various observers concerning the effect of tonsillectomy in rheumatic children. If the majority of the children reported on in any series have reached an age of ten years or more at the time of operation, the results of the operation might appear to be favorable as judged by recurrent activity. If, on the other hand, the sample is overloaded with cases that were operated on at earlier ages, a high incidence would be the probable result and the benefit of tonsillectomy would very likely be questioned.

The evidence which is available does not lend support to the view that rheumatic fever per se is an indication for the removal of the tonsils. Furthermore, it would not seem advisable to perform a tonsillectomy during rheumatic activity. Thomas[59] is of the same opinion as Wilson stating that beta-hemolytic streptococcal infections of the throat continue whether the tonsils and adenoids are present or not. However, it seems obvious that if an individual had some chronically infected tonsillar tissue which continued to flare up acutely periodically, the only thing proper to be done would be excision of the tissue during one of its relatively quiescent stages. In other words the question of tonsillectomy is an individual problem.

Chemoprophylaxis has seemingly proved very hopeful in preventing rheumatic fever. This includes salicylates and the sulfonamides. Coburn and Moore[18] had a series of forty-five cases treated with four to six grams salicylate daily at the onset of pharyngitis or when throat culture showed the presence of hemolytic streptococcus and a control group of one hundred thirty-nine patients. All were exposed to prevalent upper respiratory infections. Only one of the forty-five treated cases developed the disease. It is possible that this amount of salicylate would prevent the symptoms of rheumatic fever from being appreciated by the patient who, without the salicylate, may have some fleeting joint pains, fever, etc.--just enough to label it as a recurrence. However, with such conclusive results it is

quite probable that the therapy was effective.

The feature to be appreciated by Coburn's and Moore's prophylaxis with salicylates is that it isn't a mass treatment without regard for anything. But it is a treatment used only in event of sore throat and/or when hemolytic streptococci were found in the pharynx.

The literature contains many prophylactic studies with the use of some sulfonamide. This started early in 1936 when reports published abroad on the therapeutic value of sulfanilamide showed that smaller than therapeutic doses, administered before the streptococcus had had an opportunity to invade and multiply in the tissues, were effective in preventing beta-hemolytic streptococcal infections in mice. This lead to a prophylaxis test in humans. A civilian series by Thomas et al[59] with one hundred fifty in each of the test and control groups showed no recurrences with a sulfonamide and ten per cent recurrences without a sulfonamide. Cecil[15] in 1940 found sulfanilamide in chronic recurring rheumatic fever was no good. But using sulfanilamide prophylactically, i. e. between actual attacks, he had only one recurrence out of twenty-six highly susceptible rheumatic children. In 1942 Hansen, Platou, and Dwan[30] reported a small series which had been watched for a period of four years. The treated cases numbered fifty-three and the control group numbered thirty-two . The drugs used were sulfanilamide, sulfathiazole, and sulfadiazine given one to three grams daily in divided doses. Of the

fifty-three only two had flare-ups and one was within six days of institution of the drug. The control group had twenty-one relapses in seventeen of the children. Toxic reactions were seldom encountered. The degree of cardiac involvement, size of heart and functional classification seemed to be favorably influenced by the treatment. Feldt[23] reported a series from the angle of patient-seasons and found the same as all the others.

In the latter part of 1944 Captain Carter and Commodore Coburn reported a series large enough that conditions could not alter the conclusion to be drawn from the experiment. They tried sulfadiazine prophylactically in a group of 250,000 navy men. The control group was of equal size. Of the rheumatic fever cases in these groups there was less than one per cent recurrence in the treated group and fourteen times as many in the control group. Severe respiratory disease was reduced eighty to ninety per cent. Streptococcal infections were reduced in eighty-five per cent.

Since rheumatic fever[59] is an allergic state analogous to the beta-hemolytic streptococcus--if the drug is started during the latent period, after the streptococcal infection has occurred but before the appearance of acute rheumatic fever, the acute rheumatic attack develops regardless of the medication.

As soon as a patient has reached a satisfactory convalescent stage following acute rheumatic fever, i. e., when he is free from arthritis, fever, and other symptoms in the absence of salicylates, prophylactic sulfonamide should be started. It is not necessary

to wait until the sedimentation rate is entirely normal. It is important to start prophylaxis before the patient returns to his home environment from hospital or convalescent home, to avoid immediate reinvasion of the nasopharynx by the beta-hemolytic streptococcus. In an effort to avoid toxic reactions, Thomas[59] suggests starting most patients on 0.5 grams a day for three weeks, during which time the patient should be protected from close contact with crowds, after which the dose should be increased to one gram a day. This treatment goes on day in and day out, summer and winter, year in and year out, for at least five years, and probably longer in younger children, if the patient is to be safely steered through the period when recrudescences are most frequent.

The danger of toxic reactions, statistically, is very small as has been convincingly shown by the U. S. N. program. Mild reactions such as transient skin eruptions, which were annoying but not dangerous, developed in from three to six men out of one thousand, while serious reactions, such as agranulocytosis and exfoliative dermatitis, were exceedingly rare among the five hundred thousand men who have received prophylactic sulfadiazine at one time or another during the last six months. Since the risk of serious toxicity during treatment is much less than the chance of untreated rheumatic subjects developing recrudescences leading to serious rheumatic heart disease, we should certainly treat the rheumatic patient to the best of our present therapeutic

knowledge with prophylactic sulfonamide therapy.

Several precuations should be taken to safeguard a patient to whom sulfonamide prophylaxis is given[59]. (1) The patient should be in best possible physical condition, with adequate diet, and without unusual factors affecting his health or environment during the early weeks of his treatment. It was noted in the navy that the number of mild toxic dermal reactions was nearly four times as great among new recruits who recieved prophylactic sulfadiazine while they were being immunized to typhoid, tetanus, etc. as among seasoned personnel. (2) Dosage should be started at 0.5 grams per day, increased to one gram per day after three weeks. (3) The patient is instructed to report any rash or sore throat immediately, without further dosage with sulfonamides by themselves or by any other physician. (4) And last, a total leukocyte count should be made frequently during the early weeks of treatment. Agranulocytosis usually starts somewhere between the second and fourth weeks.

In a recent report (January, 1945) Captain T. J. Carter[10] stated that as a result of "the largest controlled experiment in the history of medicine" mass chemoprophylaxis against respiratory disease caused by streptococcal infections has been instituted at all naval training stations. In 1943 mass chemoprophylaxis involving a million men was undertaken in selected stations on a controlled basis, the result of which was very successful. "At one station the rate of admission for scarlet fever varied from

63.5 to 171.6 per one thousand during the observation period before the use of sulfadiazine. Following the institution of the prophylaxis, the rate fell to zero within two weeks. Tonsillitis at this same station fell from four hundred twenty-six to forty-six per one thousand. Rheumatic fever, the most serious of the infections associated with the streptococcal organism because of the heart involvement, was reduced from eighty-seven per one thousand to zero within four weeks.". Speaking in terms of labor this experiment alone was estimated to have saved over a million man days for medical personnel and between fifty to one hundred million dollars.

The remarkable results of the U. S. Navy experiments and the almost rare toxic manifestations from the sulfonamides as compared to the incidence of recurrence of rheumatic fever are practically sufficient in themselves to justify this method of treatment. Perhaps with a study of Wilson's[70] work on the hereditary susceptibility in rheumatic fever and a conscientious attempt to find and evaluate a rheumatic medical history in all patients in combination with Coburn's and Moore's[18] work on the prophylactic use of salicylates, it might be possible to cut down on the primary incidence of rheumatic fever very appreciably. Considering the relative toxicities of salicylates and sulfonamides, though small in the prophylactic doses used, it might be more prudent to reserve the sulfonamide treatment for the prevention of recurrences.

Some work has been attempted along the lines of immunization against rheumatic fever; and, although published comparatively recently, most of this work was started several years back. Wasson and Brown[62] ran such a series which, while it was favorable for immunization, the results were not at all as conclusive as those reported for salicylates and sulfonamides, nor were they conclusive enough to be out of the realm of chance. In lieu of the recent evidence that rheumatic fever is an allergic manifestation, it seems that immunization per se is not the key to the solution. But perhaps, along this line, some method of desensitization might be worked out. Of course, more will have to be understood about the antigens, allergens, allergic mechanisms, etc., before much can be attempted in this direction.

RHEUMATIC FEVER AND PREGNANCY

Chronic rheumatic heart disease complicated by pregnancy is, on a percentage bases, relatively uncommon, averaging[29] between one and one and five tenths per cent. But on a numerical basis it is common enough to warrant quite reasonable consideration. On the other hand acute rheumatic fever complicated by advanced pregnancy[31] is of such rare occurrence as to warrant individual case reports. The reason advanced for the rarity of this situation is that, statistically, rheumatic fever is a disease of childhood and adolescence rather than that of maturity. Hence, recurrences are less likely to take place. It has been pointed out previously that the average age at the time of the first attack of rheumatic fever is thirteen and five tenths years, whereas the average age of pregnant cardiac patients is twenty-seven to twenty-eight years.

The initial phase in the management of the pregnant rheumatic heart patient is classification of that patient in an attempt to determine beforehand whether or not she can carry a pregnancy to term and if and when she will require absolute bed rest during any part or all of the pregnant state. Using the criteria of the New York Heart Association and based on a history prior to pregnancy, there are four functional classes.

Class I--Asymptomatic organic heart disease

Class II--Organic heart disease with evidence of distress on moderate exertion

Class III--Organic heart disease with evidence of distress on slight exertion

Class IV--Failure at bed rest

Gorenberg and McGeary[29] reported a series of three hundred forty-five cases in regards to cardiac failure in relation to this functional classification. The following table shows their results.

Class	Total	Failed
I	143	4 (2.8%)
II	116	9 (7.7%)
III	81	59 (72.8%)
IV	5	5 (100%)
	345	77 (22.3%)

Age is also a factor to be considered in prognosticating for the group. Their table shows:

Age (yrs.)	Total	Failed
20	32	4 (12.5%)
21-25	135	13 (9.6%)
26-30	100	26 (26%)
31-35	49	16 (32.6%)
36-40	25	14 (56%)
40	4	4 (100%)
	345	

A combined study of these two tables and the individual patient should give one some indication as to the type of treatment. The successful management[45] of pregnancy complicating serious rheumatic heart disease requires a program of medical and surgical obstetrics of the highest order. This includes good antepartum care, careful functional evaluation, adequate digitalization and shortening of the second stage. The pulse and respiratory rates intrapartum provide a valuable guide to the cardiac status. When indicated, vaginal therapeutic abortion

is a relatively safe procedure for interruption of early pregnancy. Barring other obstetrical complications, the vast majority of cases can be successfully delivered by the vaginal route but, while it has been performed with decreasing frequency, abdominal delivery still has its place in those patients who fail to improve in spite of treatment, especially in the latter months of pregnancy.

From the few figures given above it is shown that pregnancy is definitely deleterious to a rheumatic heart.

Boyer and Nadas[11] made a study on the "ultimate effect" of pregnancy on rheumatic heart disease. They found that the average age at death from congestive heart failure is significantly older for women who have borne children than for those who have had no pregnancies when all cases eighteen years of age or older are considered. This is accounted for by the fact that the nulliparous control group is not comparable to the parous group because of death early in the reproductive period of a large number of those who had not been pregnant.

When only those patients are considered who lived to approximately the end of the reproductive period, i. e., forty years of age, there is no significant difference in the average age at death of the nulliparous or parous women. Furthermore, multiple pregnancies (four or more) cannot be shown to reduce the average age of death.

There is no significant difference in the average age at death for males and females with rheumatic heart disease whether the groups are considered as a whole or are subdivided according to the valves affected (exclusive of affection of the aortic valve alone) and the presence of auricular fibrillation. Accordingly, males can be used as a control group for parous women, thus obviating certain objections to the use of nulliparous women as controls.

Consideration of postmortem data did not reveal that the increased load of pregnancies and motherhood produced any appreciable increase in cardiac hypertrophy.

It is concluded, therefore, that pregnancy has no delayed deleterious effect on the course of rheumatic heart disease.

This article by Boyer and Nadas includes the statement that they "felt that inclusion of patients dying of congestive failure precipitated by, or during the course of pregnancy was not consistent with the purpose of the study." It seems to me that exclusion of such cases makes the purpose of the study consistent with nothing. It is obvious with anyone giving the study some thought that the women with more serious lesions die in the attempt to have a baby and, therefore, are left out of the study entirely. As will be brought out in the next section on prognosis, an appreciable percentage of people having one or more attacks of rheumatic fever come out with no sign of cardiac damage. And these will be included in the study. A study of this kind classifying

the patient as to functional capacity of the heart will, as was shown before, force one to draw an entirely different conclusion.

This conclusion was drawn by Sodeman and King[55] who report that the increasing load of pregnancy, as it progresses, adds strain to both the normal and the damaged heart, and, with reduction of cardiac reserve by heart disease to an unknown degree short of that producing insufficiency, this added burden may be expected to exceed the reserve in certain patients and precipitate cardiac failure.

Since most heart disease, usually ninety per cent or more, in pregnancy is rheumatic, such a factor as auricular fibrillation can be evaluated very well in this more or less homogenous group.

The age at which the patient becomes pregnant has a direct bearing upon the possible development of congestive heart failure. It was found, for example, that in two hundred sixty-seven patients, less than thirty years of age, only forty-three, or sixteen and one-tenth per cent showed signs of heart failure, whereas in thos over thirty years the figures were thirty-four of seventy-eight or forty-three and six tenths per cent.

Auricular fibrillation adds an increased hazard to pregnancy. "So important is this disorder that extremely high mortality rates have been reported.... Auricular fibrillation may be considered as an adequate contraindication to pregnancy. If the patient is seen in the first few months of pregnancy, termination by therapeutic abortion is justified." However, if the woman knows the

risk involved and has a real desire for a child, adequate control of the heart rate by digitalization and a rigid program of rest may make possible continuation of pregnancy.

"Marked enlargement of the heart reflects severe cardiac strain. Addition of the strain of pregnancy increases the insult to a condition in which the prognosis is already a grave one. Such patients should not become pregnant."

PROGNOSIS

More often than is generally realized, death occurs before adolescence is attained. For this reason it is necessary to consider the prognosis of rheumatic fever from two standpoints[27]: First, the period of active infection, which is most marked during childhood, though by no means limited to this age group; and Second, the permanent damage which remains after the rheumatic activity has subsided.

It may be well to inquire first of all as to the likelihood of the heart's involvement in any child who has suffered a rheumatic episode. It is well known that a good many children suffer repeated attacks of chorea or polyarthritis without demonstrable injury to the heart. Yet this favorable turn of events is seen less often than is generally believed. Of the entire group of 1,487 patients, there were 864 (58%) who have shown signs of heart disease. Remembering that many of these patients have had their rheumatic infection for a relatively short time, it is inevitable that some of those who at present show no evidence of cardiac involvement will exhibit signs of cardiac damage as time goes on. On the other hand out of a series of five hundred eighty cases in which thirty-seven manifested signs of mitral distress after the first attack, signs disappeared within one year in nineteen and over a number of years in a total of eighteen. This will eventually lead to approximately the same figure that Brown and Wolff got in their series of one hundred seventy-five cases in which

fifty per cent of the group showed no evidence of heart disease after a follow-up period averaging seven years.

Of the eight hundred sixty-four patients who showed signs of heart disease, one hundred forty-six (nine and eight tenths per cent of total rheumatic patients) are known to have died. The peak of death is between seven and twelve years. Only two of this group survived beyond the fifteenth year of life. Further inspection of the case histories[27] reveals the fact that in a surprising number the total duration of the rheumatic infection from onset to death was measured in weeks or months, and that the patient succumbed to the initial rheumatic assault. In this group of one hundred forty-six fatal cases, five died within less than one month of the onset of the first symptom of rheumatic fever, nineteen others within less than four months, and twenty others in less than a year. In other words, a fatal outcome occurred within a year of onset in forty-four cases (30%). This thirty per cent is a misleading figure in that it is based on the total number of deaths. On the basis of the entire total who had the disease, the percentage is considerably lower--three plus per cent. While death in acute and very severe cases may not be rare as stated by Sir Thomas Lewis[38], it is at least not common.

It is worthy of emphasis that heart failure in children is brought on by activity of the rheumatic processes rather than by cardiac strain due to valvular injury[27]. This fact has been established by postmortem studies, both gross and microscopic,

of the hearts of one hundred sixty-five patients who had had rheumatic heart disease. Evidence of active rheumatic infection was found in one hundred six instances. The age distribution was significant. Of twenty-two children who succumbed within the first decade of life, every one showed signs of active infection. In forty-four individuals who died between the ages of ten and twenty years, forty-one revealed signs of rheumatic activity. Of the three who failed to show such signs, only one died of myocardial failure. The other two died of causes unrelated to their heart disease. Even in the age group between twenty and thirty years, seventy-eight per cent, and in the age group between thirty and forty, seventy per cent showed postmortem evidence of active rheumatic mischief. The above figures are illuminating in that they emphasize the role of rheumatic activity, not only in childhood but well into adult life in bringing about a fatal issue. Perhaps this is the basis of the controversial issue on the use of digitalis in rheumatic heart disease and why it has an adverse effect on some patients and not on others. Also this information may help supply further basis for extended prophylaxis as prescribed previously.

It is believed that the mode of onset or the presence of various rheumatic phenomena influence the prognosis. At least these factors are associated with the outcome. Taran[57] emphasizes the following: (1) the younger the child at the age of onset, the more severe the initial attack; (2) the more severe

the initial attack, the longer the duration of the active infection; (3) the more severe the initial attack, the more frequent the recurrences; (4) the younger the child at age of onset, the more protracted the active rheumatic episodes; and (5) the more severe the onset and the younger the child, the greater the cardiac damage at the end of six years.

Cohn and Lingg[20] summarized the prognosis nicely from an analysis of 3,129 cases of rheumatic cardiac disease. They found that recurrent manifestations are most common during childhood. They are most prevalent before puberty rather than during the first five years after onset. Also they found that when the disease begins in childhood, carditis is the most frequent but rarely the only type of infection. At all ages, polyarthritis is the most frequent single manifestation. It is the only manifestation exhibited by forty per cent of patients between the ages of fifteen and thirty. After thirty years of age there is no manifest infection in about half of all patients.

The earlier the age at onset, the greater is the chance that infection will be "severe" during the next few years. When the infection is "severe" in the early years of the disease expectancy is shorter than when the infection is "mild". Of children with "severe" infection, less than one-half survive childhood, about one-tenth survive adolescence and less than two per cent survive the third decade. Even when the infection is "mild" in childhood, only a third survive to the age of thirty, and only one tenth to

the age of forty-five.

Prognosis is less favorable with "mild" signs of infection in childhood than in older persons with the same degree of infection.

When the first manifestation of rheumatic fever is carditis, the chances are three to one that infection during childhood will be "severe". When the onset is characterized by joint symptoms or chorea or by a cardiac murmur alone, the chances are three to two that infection will be "mild". In adult life infection is "mild" or absent in nine out of ten cases, whatever the onset.

CONCULSIONS

About the only conclusion one can make concerning rheumatic fever is that it is a problem. This is evidenced by the vast amount of literature published and the varying opinions on each aspect. However, I have tried to choose from the most recent literature that which appeared to be the trend in several aspects of the disease, and from these I have concluded:

1. That rheumatic fever in so far as its etiology is concerned, is much like a delayed serum sickness. The streptococcal toxin combining with body tissues to form an antigen against which antibodies are built up and when a sufficiently high titre is reached a reaction occurs.
2. That the course of rheumatic fever is long and the pathological processes may be smoldering long after any subjective symptoms are present.
3. That the conventional treatment with salicylates allays the objective signs as well as the subjective symptoms such as temperature, leukocytosis, and erythrocytic sedimentation rate.
4. That the most useful clinical guide in estimating the heart's functional capabilities after the inflammatory phase and irrespective of any other signs is its size.
5. That many rheumatic heart patients die as result of an

acute recurrence regardless of age and for this reason--

6. Prophylaxis is the most important means of treating rheumatic fever. This can be applied to primary infections using Wilson's work on hereditary susceptibility and on recurrences using either sulfonamides or salicylates.

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