1944

Etiology of rheumatic fever

Peyton Thomas Pratt
University of Nebraska Medical Center

ETIOLOGY OF RHEUMATIC FEVER

Peyton T. Pratt

Senior thesis presented to
the College of Medicine,
University of Nebraska,
Omaha, 1944.

INTRODUCTION

This thesis is a review of the literature and a personal analysis concerning the etiology of rheumatic fever. The factors involved will be divided into two groups: the predisposing factors and the basic factors. The former will be presented mainly as a review with a short summary at the end of each topic. The basic factors, heredity, streptococcus hemolyticus, and a state of allergy, first will be presented historically. This will be followed by a personal analysis concerning the part each plays in the etiology of rheumatic fever.

In discussing any disease, it is necessary to have definite criteria for recognizing the disease. There will be no detailed discussion concerning rheumatic fever, but a basis for a clinical and pathological diagnosis will be mentioned.

There is some question about the relationship between rheumatic fever, rheumatic heart disease, and Sydenham's chorea, but the concensus of opinion is that they are all related. Jones includes all these factors in his diagnostic criteria. He divides them into major and minor manifestations. Any two major, or one major and two minor findings are sufficient for a diagnosis.

Major manifestations

1. Carditis
   (a) Increased heart size
   (b) Significant murmur(s)
   (c) Pericarditis
   (d) Heart failure
   (e) Electrocardiograph - prolonged PR interval
2. Arthralgia
3. Sydenham's chorea
4. Subcutaneous nodules (late)
5. Reliable record or history of rheumatic fever

Minor manifestations

1. Variable low-grade fever
2. Abdominal and/or precordial pain
3. Erythema marginalis
4. Epistaxis
5. Weight loss or failure to gain
6. Pulmonary changes
7. Laboratory
   (a) Microcytic anemia
   (b) Leukocytosis
   (c) Rapid sedimentation rate

A pathological diagnosis of rheumatic fever must of necessity be based on the end results of rheumatic fever, thus laying emphasis on the heart. The criteria are summarized from Boyd.[8] The heart is the primary site of infection, and grossly it exhibits mitral involvement (100 percent), aortic stenosis (forty to fifty percent), tricuspid (thirty percent) and pulmonary (rarely) valvular involvement. Microscopically, valvulitis is the most important, with evidence of rheumatic nodules (Aschoff bodies) in the vessel walls of the valves. This progresses to fibrosis and scarring which results in thickening and shortening of the valve cusps. In a similar manner it also produces shortening of the chordae tendinae. Aschoff's bodies and fibrosis will also be found in the interstitial tissue of the myocardium, intima of the coronary and other arteries, and fascia, particularly over boney prominences (subcutaneous nodules). Serous surfaces are consistently involved. Pleuritis is most common with fibrinoid pericarditis next in frequency. In an autopsy of an acute case, one will find characteristic inflammatory changes in the joint structures.

PREDISPOSING FACTORS

The predisposing factors concerning the etiology of rheumatic fever will be presented first, as in some instances they are relatively unimportant or inconclusive. In other cases, they combine to form a background for the basic factors which will be discussed later.

CLIMATIC AND GEOGRAPHICAL DISTRIBUTION

These two will be discussed together as no adequately controlled experiments have been presented to warrant separate discussion. With the change in geographic location, there also occurs a similar change in climate.

In 1924, Harrison and Levine[40] demonstrated the distribution of rheumatic fever and rheumatic heart disease in the United States. They used the number of hospital admissions of rheumatic fever and mitral stenosis at autopsy as their criteria. They were able to demonstrate that this disease is most common in Boston, followed by St. Louis and Baltimore. It was least common in Oklahoma City, Galveston, and New Orleans.[69] This was substantiated by Nichols. He states that from 1931-36 there had been one-tenth the

number of hospital admissions with rheumatic fever, rheumatic heart disease, and chorea in Miami as there were in Boston for the same period.[14] Christie finds that in northern California the general incidence of rheumatic fever is low.[6] Bilderback, in reviewing eighty-seven cases of rheumatic fever, states that the incidence in Oregon is comparable to the northern half of the United States. This fact holds true for Nebraska also.[101]

In Australia there is a greater incidence of rheumatic fever in the southern temperate part, although the occurrence in the tropical north is quite high.[21] In New South Wales, Maddox[64] finds a lower incidence with little variation in occurrence with geographical changes.

In studies of hospital admissions throughout the United States, England, and elsewhere, the incidence of rheumatic fever was found to increase as one progressed toward the more temperate zones; the occurrence is rare in the tropics.[30,90,91]

The latter view is refuted by Carruther[12] in Miraj, India, where he finds rheumatic heart disease in forty-seven percent of his heart patients. He also states that Kutumbrah,[56] in Vizagapotam, and Baneyea,[5] in Cal-

cutta, India, reported numerous cases of rheumatic fever and rheumatic heart disease. This also occurs in Ceylon where twenty-three percent of the cardiovascular disease is rheumatic.[31]

Lewis,[59] from 1876-1890, attempted to show correlation between storm centers and rheumatic fever "epidemic". He has never been substantiated. Any specific climatic factor cannot be studied, as it would be impossible to control adequately all the factors.

Coburn,[18] believes that the geographical distribution is merely a reflection of the change in climate with increase in streptococcus in certain localities. White[107] corroborated this finding by stating that streptococcic infections are less frequent in the tropics and subtropics.

In summarizing, it appears evident that the incidence of rheumatic fever increases as one goes from the warmer to the colder temperate climates.

SEASONAL DISTRIBUTION

The seasonal distribution is fairly consistent. It seems to be associated with months which are colder or in which there is more precipitation.

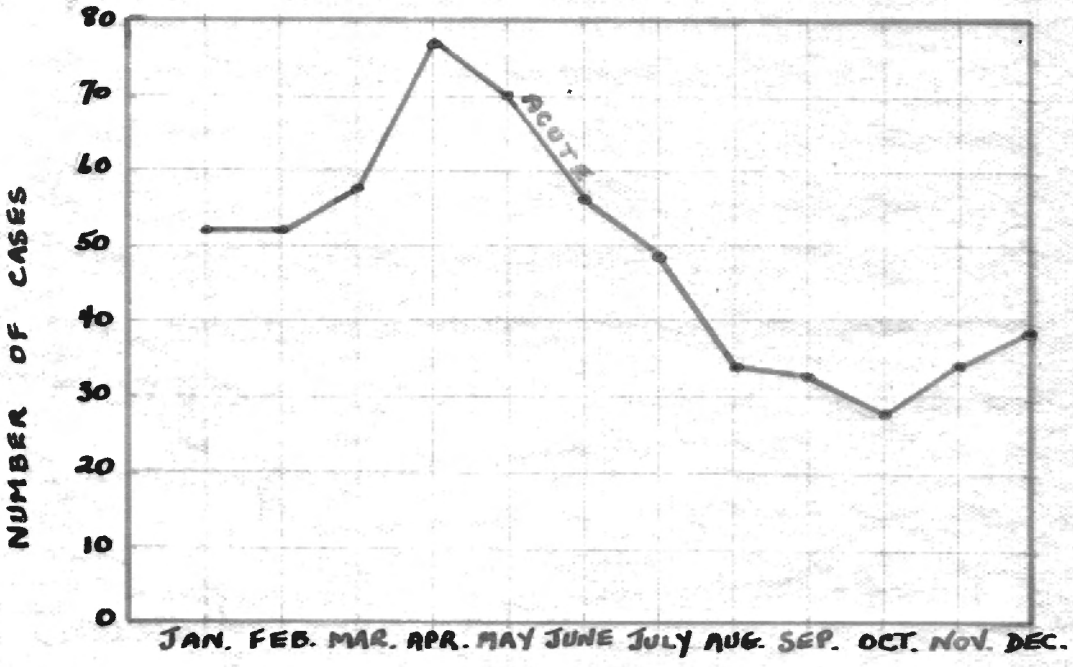

Figure I. Seasonal incidence of rheumatic fever in 584 cases. From Sutton.[98]

In New York there is a definite peak in the spring. Sutton[98] finds it most marked in April and May. See Figure I. Coburn and Pauli[18] find it highest from November to April. Wilson[108] finds the peak of incidence in the spring.

These results are corroborated throughout the United States by Boas,[7] in New York City, Bilderback and Overstreet,[6] in Oregon, Christie,[14] in Northern California, McCullough and Irvine-Jones,[61] in St. Louis with increase in winter months also, Kaiser,[51] in Rochester, New York, and Pounders and Gay[78] in Oklahoma City. Shapiro,[94] of Minneapolis, Minnesota, in his review finds a peak in March andApril and another one in November and December.

Hedley[41] reports that in Philadelphia, the greatest incidence is in April and the lowest in October. He has made studies over periods of years and has found that the general trend is the same with slight variation from year to year. He also states that in Great Britain the incidence is greatest in the fall and December. This was also found by Glover[36] in Cambridge, in studying a group of adolescent boys under barrack conditions.

In summarizing, one can state that the vast

majority of rheumatic fever cases occur during the late winter and early spring months, particularly in April. In Philadelphia forty-six percent of 816 cases of rheumatic fever occurred during February, March, April, and May.[97] In Great Britain the peak months are in the fall.

SEXUAL DISTRIBUTION

There is a slight increase in the incidence of rheumatic fever in girls as illustrated by Figure II.

Author	No. of Cases	Male %	Male No.	Female %	Female No.
Sutton (98) New York City	584	48.0	280	56.0	304
Maddox (64) New South Wales	382	49.5	189	50.5	193
Christie (14) Northern California	116	48.3	56	51.7	60
Wilson (108) New York City	696	44.3	309	55.7	387
Hedley (42) Philadelphia	2541	45.8	1162	54.2	1379
Stroud (97) Philadelphia	685	48.7	334	51.3	351
Kaiser (51) Rochester, N. Y.	1126	46.0	518	54.0	608
Ash (3) Philadelphia	445	43.2	192	56.8	253
Pounders (78) Oklahoma City	122	43.4	53	56.6	69
Total	6697	46.2	3093	53.8	3604

Figure II. A compilation of various series of sexual incidence of rheumatic fever.

This variation in sexual incidence is consistent; as shown by the chart, there is a 53.8 percent incidence in girls and 46.2 percent in boys. This difference could be accounted for at least partially, by the 2:5:1 ratio of girls to boys in the incidence of Sydenham's chorea.

In summarizing, there is a slight predominence of rheumatic fever in girls. This is of no apparent significance.

AGE DISTRIBUTION

The age incidence of the first attack of rheumatic fever has been worked out by several authors throughout the United States and elsewhere. There is general agreement that it occurs somewhere between the ages of five to thirteen years.

Most of the authors find the peak at seven years.[71,14,58,109] This childhood incidence is found in Oregon,[6] Northern California,[14] St. Louis,[61] Minneapolis,[94] Rochester, New York,[51] Philadelphia,[42,3,98,108,109] New Haven,[58,71] London,[20] and New South Wales.[64] There is some variation in exact incidence, but it is the most common between the ages of six to ten years in New York City,[98] Northern California,[14] and New Haven, Connecticut.[58] Wilson,[108]

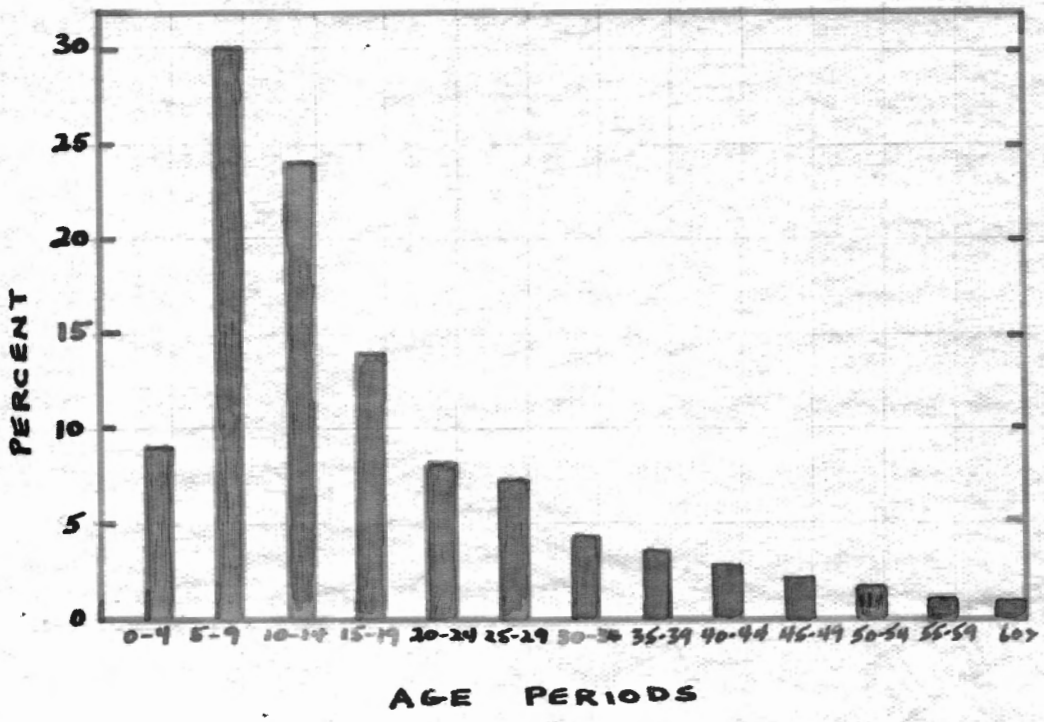

Figure III. Percentage distribution by five year periods of 2,539 first attacks of rheumatic fever with or without rheumatic heart disease, based on present or past history among cases admitted to Philadelphia hospitals from January 1, 1930 to December 31, 1934. From Hedley.[34]

109
has an average age of 7.3 with fifty percent between
20
six and nine years. Coombs, in London, has an average
3
age of ten years in his series. Ash, in Philadelphia,
has 6.8 years as her average age.
42
Hedley, in a large series of cases in Philadelphia, presents a good cross section of age incidence as indicated by Figure III.

The question of whether or not there are any cases before the age of two years is controversial. There are several cases reported with the initial attack in
23 28
infancy. Denzer and Eigen have reported three and one cases respectively. Since the age incidence is between eighteen to twenty-four months, they are
63
borderline cases. McIntosh, in the Babies Hospital at Columbia University, has seen twenty-four cases in the last twenty-five years with first symptoms occurring between the ages of eighteen to thirty-six months.
22 54
According to Denenholz, Kissane and Koons had a case of rheumatic fever in a newborn whose mother had an attack during the pregnancy. This patient died at ten years of age and had the pathological findings consistent with rheumatic fever. Denenholz himself reported a "probable" case of rheumatic fever ten days after birth. In this case also, the mother had an attack of

rheumatic fever during pregnancy.

In summarizing, one can state that rheumatic fever is a disease of adolescents which occurs first after infancy and seldom starts after puberty. There is some question about rheumatic fever in the newborn, but if it is found, it occurs with an attack in the mother during pregnancy.

RACIAL DISTRIBUTION

The problem of racial incidence is difficult to analyze. First, the individuals of the United States are generally of mixed nationalities. Second, authors all interpret the races differently.

Paul,[73] in New Haven, and Sutton,[98] in New York, have compared their general hospital racial percentages with the rheumatic fever racial distribution. They both agree that the Italians and particularly the Irish show a greater incidence in the rheumatic fever clinics in comparison to the general dispensary clinics. For example, the Irish make four percent of Sutton's general clinic and sixteen percent of her cardiac clinic. The high incidence in the Irish is substantiated by Graham[37] and Wilson.[108] Wilson[108] and Ash[3] are able to show a high incidence of Italians in

their clinics, but the latter does not corroborate the findings on the Irish.

Seventeen percent of the patients in Ash's cardiac clinic are negroes; whereas fifty percent of the general hospital admissions are negroes. Wilson and Lingg[109] have only 4.6 percent negroes in a predominately negro district. This low incidence of rheumatic fever in hospital admissions is found by many others.[3,41,44,72,97,98,108,109] Hedley[44] states that the incidence in negroes is very low, but once they have the disease they are more susceptible. This gives a higher mortality figure than would otherwise would be expected.

The Jewish race has a rather high incidence of rheumatic fever but whether or not it is significant is controversial. Paul[73] finds Hebrews are more susceptible. Sutton's[98] findings do not agree with this. Stroud[97] has many Jews under observation, but he is situated in a Jewish district. Wilson[108] and Ash[3] fail to find an increased number of Jewish rheumatics.

In summarizing, one finds that the racial incidence of rheumatic fever is variable in most of the racial groups, with the exceptions of the Negroes, the Italians, and the Irish. The negroes have a

racial immunity but succumb to the disease rapidly once it is contracted. The Irish, especially, and the Italians have an increased susceptibility.

LIVING CONDITIONS

To interpret the living conditions of the rheumatics compared to the non-rheumatics, it is necessary to break them down into component parts; dampness, social and economic relations, and crowding. Nutritional factors will be discussed separately because of their more specific relationship to the disease.

1. Dampness

McSweeney[63] in his study in Great Britain finds that dampness shows a significant difference in his rheumatics and controls. This is based on measuring dampness in the ground floor. Twenty-one percent of the rheumatic homes had damp ground floors in contrast to twelve percent of the controls. Miller,[66] working at the Paddington Green Children's Hospital, finds that the area from which most of the cases of rheumatic fever come is between a canal and a submerged river. These findings in England are substantiated by other English workers.[15,20,65] In Oklahoma, Pounders,[78], who has the greatest number of cases in the winter, attri-

butes his distribution of rheumatic fever to the use of open stoves. He believes the moisture comes from the combustion of natural gas which is the local fuel.

Hedley,[41,43] in Philadelphia, finds that there is no definite increase in rheumatic fever by waterways. He finds that waterways and poverty are more significant in their correlation.[108] Wilson also places no definite importance on dampness.

2. Economic and social relationship to rheumatic fever.

There is no controversy as to whether or not poverty, in its broadest sense, plays a part in rheumatic fever incidence. There is complete agreement by workers that the disease affects the less well-to-do more frequently. The problem is whether the disease is more common in the destiture or the upper poor class. The factors which make an analysis difficult are numerous. First, the richer people do not, as a rule, seek hospital admission. Second, the terms poor or poorer class used by most authors have no definite meaning.

Glover,[36] in 1930, stated that "Rheumatic fever is thirty times as frequent in poor industrial workers as in those more well-to-do.". This statement is not sub-

stantiated whole-heartedly, but a tendency for incidence of rheumatic fever to be greater in poorer classes has been noticed by numerous workers: Fernando,[31] in Ceylon, Hedley,[41] in Philadelphia, Stroud,[96] Coombs,[20] and Campbell,[12] in England, and Maddox,[64] in New South Wales. The latter includes the word industrial, but Paul[72] finds that industry per se has no relationship to the incidence of rheumatic fever.

Wilson[108] finds that more of her cases come from families whose annual income is $1500.00-2500.00. These findings are corroborated in England by Coats[15] and Miller[65,66] who find the artisan class is most frequently affected.[3] In contrast, Ash states that the destitute and W.P.A. workers make up the greater portion of rheumatics.

Paul,[73] in New Haven, compares the incidence of rheumatic fever at Yale. He divides the students by financial status into four groups based on preparatory schools: I-Expensive boarding schools; II-Less expensive boarding schools; III-Private day schools; and IV-High schools. He takes as his standard the average incidence of rheumatic fever in the north eastern part of the United States as 15/1000 between the ages of

eighteen to twenty-five. He finds the incidence at Yale is 8.2/1000 for undergraduates and 11.4/1000 for graduates. The age of these groups represents nearly the same age as standard groups. The rates per 1000 for the four groups are as follows: I-5.8; II-5.5; III-6.6; IV-12.5. These results whow the tendency for greater incidence as one goes down the financial scale.

In generalizing this problem, Morris[67] finds that no definite group is more susceptible, but that the poverty comples, as a whole, is involved.

3. Crowding

The discussion of crowding and the incidence of rheumatic fever may be divided into three parts: urban and rural differences, number of persons per room, and ventilation and sleeping distance.

First, Hedley,[44] in Philadelphia, reports that the rates of rheumatic fever in cities over 100,000 in population, and especially those of 500,000, were higher than in more rural areas. Maddox[64] found a similar situation in New South Wales.

Second, Perry, Roberts,and Fraser,[77] in determining the incidence of rheumatic fever in Bristol, England, found a correlation coefficient of 0.84 with the number of persons per room. They used the various wards

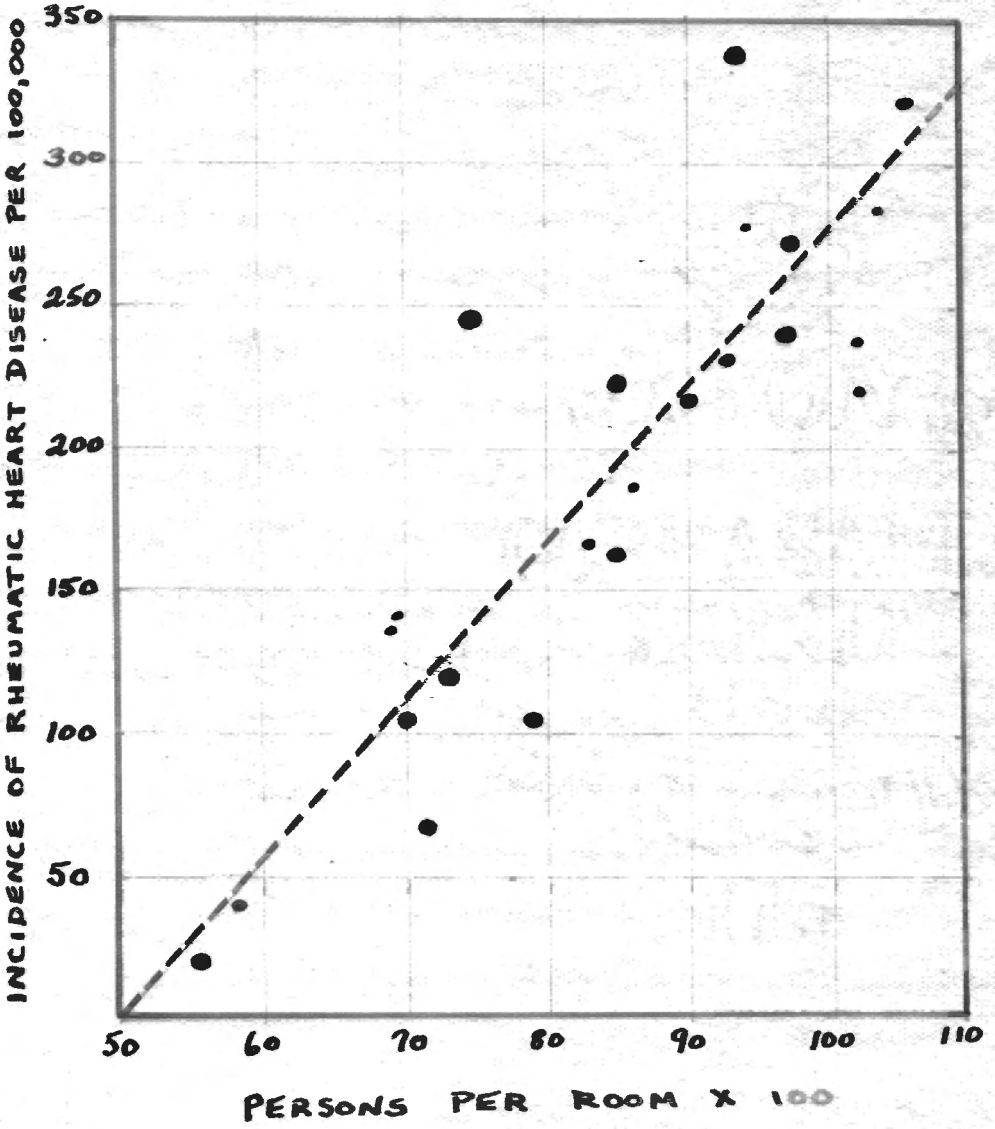

Figure IV. The correlation between the incidence of rheumatic heart disease per 100,000 and the number of persons per room (X 100) in various districts of the city of Bristol, England. The size of the dots roughly indicate the comparative size of the district.

65

Perry and Roberts

in the city for comparison. See Figure IV.

Third, Thomson and Glazebrook,[102] in Edinburgh, studied rheumatic fever in large institutions of 1000-1500 adolescents in crowded, poorly ventilated dormitories, with an outbreak of tonsillitis followed by rheumatic fever. This epidemic was fed by new recruits every two weeks and it continued. They were unable to control it until the beds were moved further apart and the ventilation was improved.

In more general studies, these facts are substantiated.[20,31,36,73,67] In a review of mortality statistics, Atwater[4] found that the urban death rate was consistently higher than in the rural areas (10,000 or lower) for the period between 1910-1925. Other authors find no correlation between rheumatic fever and crowding.[63,66,108]

In summarizing these findings on living conditions, it is apparent that dampness, poverty, and overcrowding coincide with the incidence of rheumatic fever. These facts have the same relationship to streptococcic infections as they do to rheumatic fever.

NUTRITION

Malnutrition, in general, is discussed much the

same as living conditions. Numerous workers state that evidence of general malnutrition seems to coincide with cases of rheumatic fever.[31,36,96] This deserves the same explanation as was summarized under Living Conditions. More specific work has been done on Vitamin C.

Rinehart[84] carried out experiments with guinea pigs which he divided into three groups. To the first group he gave adequate Vitamin C, to the second group inadequate Vitamin C, and to the third group inadequate Vitamin C and a streptococcus infection. He obtained his streptococcus from the lymph nodes of a guinea pig with lymphadenitis. He found at autopsy that the third group showed connective tissue proliferation in the valves, heart, joints, and subcutaneous tissues (nodules). These were similar to rheumatic fever. In a later report Rinehart[85] states that his Vitamin C blood plasma level in rheumatic fever patients was below 0.5 millegrams per 100 cubic centimeters. It was higher in his controls. The experimental findings were substantiated by Stimson and Hedley[95] who used Vitamin C deficiency and streptococcus exotoxin.

In a discussion of Rinehart's earlier paper of

1936, H. F. Swift[84] confirmed his findings but believed them due to severe scurvy. M. J. Shapiro[84] in the same discussion expressed the same idea as Swift.

In attempting to determine a Vitamin C deficiency in the rheumatic fever patient, Faulkner[29] gave twenty seven rheumatic fever patients increased Vitamin C in the form of fruit juices and crystaline ascorbic acid orally and intravenously. The dose was for 200-300 millegrams of ascorbic acid or 530 cubic centimeters of orange juice. Previously only three patients were on an adequate Vitamin C diet. This was done for four weeks. The reticulocyte count went up in most of the patients, but no clinical improvement was noted.

Sendroy[93] used the urinary output method of determining the ascorbic acid retained. He used very careful methods but found no consistent figures in the rheumatic fever patients. There was no difference in his control group of other diseases. Perry[76] confirmed these findings.

Schulz[89] divided fifty-four patients into two groups. One group received 100 millegrams of ascorbic acid and the other an equal amount of lactose. The capillary fragility was greater in the latter, the control group, but there were fewer recurrences.

Therapeutically, he obtained no results.

A slight increase in the ascorbic acid excretion was found in rheumatic fever, but sodium salycylate and sodium bicarbonate give similar results. Thus, Keith[53] was able to find no evidence for Vitamin C deficiency as an etiological basis of rheumatic fever.

Recently a new field in the relation of diet to rheumatic fever has been entered. Coburn[17] tested fifty well individuals, twenty-five less susceptible, and twenty-five more susceptible people. The susceptibility was not measured by the diet nor was it a factor in the choice. The diet was judged in calories, calcium, phosphorus, iron, and Vitamins A, B Complex, C, and D. He found a significant difference in the rheumatic fever patient's diets in contrast to the controls in protein, Vitamin A, calcium, and iron. An unusual finding was that the rheumatic fever patients were nearly unanaimous in the rarity with which they ate eggs. The girls in very expensive girl's schools who had rheumatic fever had various idiocyncrasies concerning eggs and refused to eat them. The poor couldn't afford eggs, or least they didn't eat them.

In summarizing, one can state that malnutrition is important only as a predisposing factor to infection.

Vitamin C deficiency is incidental in rheumatic fever and follows this disease as it does any infection. The work on the importance of protein in relation to rheumatic fever needs more investigation. It may be important in the formation of antibodies and in the development of immunity to rheumatic fever. This will be discussed in detail later.

TRAUMA AND BASAL METABOLIC RATE

There have been many attempts to correlate various factors with rheumatic fever. Glazebrook and Thomson[35] were able to show a relationship between trauma and polyarthritis in eleven out of 115 cases of rheumatic fever. The polyarthritis first occurred in the traumatized joint. These findings were minimized because there was an epidemic of tonsillitis at the same time.

Brown and Wasson[9] determined the basal metabolic rate in ninety-seven cases. The results were: forty-three patients below minus ten percent, nine below minus twenty percent, and two above plus ten percent. They also found a general decrease in the basal metabolic rate from January to July.

In summarizing, one can state that trauma is

relatively unimportant, as one would expect 114 out of 115 boys to bump their joints while playing. Also, the findings were accompanied by a tonsillitis epidemic.

The statistics on the tendency of rheumatic fever patients to be hypothyroid are of interest in the light of the recent report[80] on the reproduction of rheumatic fever-like lesions in adrenalectomized animals given an overdosage of desoxycorticosterone acetate. These lesions are more readily reproduced if the animals are thyroidectomized and the environment is cold. This will be discussed later.

BASIC FACTORS

The term basic is used in preference to exciting because in the writer's opinion, there are no exciting factors per se. Rheumatic fever is caused by a combination of conditions, heredity, streptococcus hemolyticus and state of allergy, all of which must be present for an individual to contract the disease. Heredity transmits the susceptibility of an individual to the hemolytic streptococcus which produces a state of allergy. This combination is responsible for the production of the disease. These conditions are discussed in detail below.

HEREDITY

Heredity is discussed as a basic factor because it is important not just as a tendency but as a definite inherited susceptibility that is necessary to bring on the disease.

In this discussion a list of the family incidence in rheumatic families and non-rheumatic femilies is given in Figure V. From this chart one can see that there is a definite family trend in this disease. Coates and Thomas,[15] in England, came to the same conclusion, but no figures are presented here. Wilson,[111]

	Percentage of cases of rheumatic fever with positive family history excluding original rheumatic.	Percentage of cases of rheumatic fever with negative family history.
Abeloff[1] New York City	25.8	14.7
Maddox[64] New South Wales	12.0*	
Christie[14] Northern California	32.4*	
Shapiro[94] Minneapolis	46.2	14.7
Coombs[20] London	50.0#	
Campbell and Warner[12] England	58.0*	22.0
Poynton[79] Australia Group I	53.0*	
Group II	40.0	

* Not excluding original case

\# An approximation

Figure V. A compilation of the results of various authors.

was able to find no evidence of family history in only twenty-eight percent of her cases.

It is better to approach the problem by dividing the family history into three groups: neither parent with rheumatic fever, one parent with rheumatic fever, and both parents with rheumatic fever.

Gauld, Ciocco, and Read[33] divided their cases in this manner and found a gradual increase in the number of cases as the number of rheumatic parents increases. Draper's[25] series gave the same results.

Wilson[108] in an intensive study of 122 families has presented the facts in various ways. In comparing the environment with the heredity, she divided her families into four classes: Group I, favorable living conditions; Group II, poor living conditions only; Group III, poor dietary habits only; and Group IV, poor dietary habits and living conditions. The percentage of rheumatic children under these conditions showed no significant variation. Another method used in comparing the two conditions was the age at which the primary and secondary attack occurred in the same family. She found that in measles the disease started in the school children and spread to the pre-school children. In rheumatic fever this was not true. The disease occur-

Family history of rheumatic fever	Number of Families*	Children	Rheumatic Children Observed	Expected
Both parents negative	59	251	101 (40.2%)	90 (35.9%)
One parent positive	52	224	129 (58.0%)	121.1 (54.0%)
Both parents positive	4	15	14#	15

* Family size one to nine

\# Non-rheumatic child only ten years old

Figure VI. Modified from Table 16 and page 56, Wilson.[108]

red at approximately the same age regardless of the number of previous cases in the family. Paul[4] corroborated this finding.

In attempting to determine the type of inherited factor involved, Wilson tried to predict the number of cases she would expect and compared that figure with the actual number of cases observed. In predicting the number of cases, she used a sex-linked gene, a single recessive gene, a double recessive gene, and a double dominant gene hypothesis. The best correlation was obtained by using a single recessive gene. A number of corrections had to be made because the only families she could use were those that came to the cardiac clinic. Consequently, every family had at least one child with rheumatic fever. The size of the family, especially the smaller ones, changed the percentage. The age was important as the greatest number of cases occurred between five and twelve years.

In calculating the expected number of rheumatic children, Wilson used the Lenz-Hogben method[45] with the single recessive gene as her basis. See Figure VI.

It is readily seen that no significant difference is noted in the observed and expected incidence of rheumatic fever. Especially important are the children

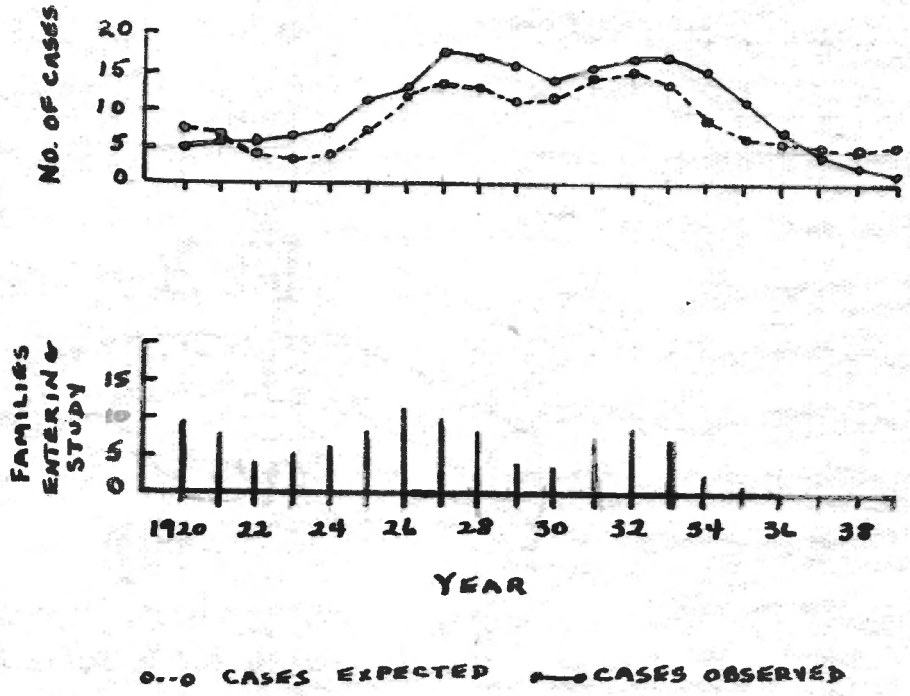

Figure VII. Annual incidence of cases expected and observed during a twenty year period, 1920-1939, in 102 rheumatic families.

Wilson, Lubschez, and Schweitzer (110)

with both parents positive. Only one child had not contracted rheumatic fever and that child was still in the susceptable age group.

If a single recessive gene is the factor involved, one might expect identical twins to be alike as to whether or not they have rheumatic fever. If they are fraternal twins, one would expect the same ratio as normal siblings. Wilson[108] studied seven sets of twins, two sets of identical and five sets of fraternal twins. The four individuals in the identical sets all had rheumatic fever. Of the five fraternal sets, only two pairs were alike and three pairs were unalike (one with and one without rheumatic fever). Irvine-Jones[47] has found similar results in another small series. Kaufmann and Scheerer[52] have studied seventy-two sets of twins and also have had the same findings.

Wilson, Lubschez, and Schweitzer,[110] in 1943, reported on 102 families from 1920-1939. They used age and genetic factors combined in determining the expected number of cases for each year as the families grew up. This contrasted to the actual number of cases observed shows a striking correlation as shown in Figure VII.

In summarizing, it is apparent that the family

relationship is important. There is no evidence that environment is the basis, but Wilson has conclusively illustrated that it is a hereditary factor, probably a single recessive gene, which is responsible for the susceptibility of rheumatic fever. It would be clarifying to have other authors analyze their cases in a similar manner.

VIRUS

The virus is discussed at this time, not because it is a basic factor, but because there has been considerable work done concerning it as the causitive agent of rheumatic fever. Both sides of the question are presented.

The method used in demonstrating the presence of a virus is that of Ledingham and Aberst.[57] They used as the antibodies the sera of animals who had had vaccinia or fowl pox. As the antigens they used a homogeneous suspension in formalized saline of elementary bodies which were derived from lesions of animals with this disease. On mixing the immuned serum and the suspension of elementary bodies, they were able to show aggluttination.

Schlesinger, Signy, and Amies[88] used deposits of

of pericardial fluid (in one case pleural fluid) to obtain elementary bodies. They centrifuged it and prepared it in the same manner as Ledingham. With this suspension of elementary bodies they were able to produce agglutination with sera from patients with active rheumatic fever. There was no agglutination with sera from quiescent or non-rheumatic patients. They concluded that these were the infective agents.

Eagles, Evans, Fisher, and Keith[26] went further and obtained these "bodies" from exudates from the pericardium, pleura, joints, and subcutaneous nodules, also blood plasma, urine, and cerebral spinal fluid of the rheumatic patient. They used exudates from lesions of patients with rheumatoid arthritis and chorea also. They were able to demonstrate strong agglutination when mixing sera and elementary bodies that were both from rheumatic fever patients, rheumatoid arthritis patients, or chorea patients. Moderate agglutination was shown on cross mixing sera and elementary bodies of these three types of conditions. There was no agglutination with other diseases.

In attempting to produce the disease, these same authors[27] inoculated Macacus rhesus monkeys intrapericardially, intraperitoneally, intratracheally, intra-

muscularly, intravenously, and into the joints and nasal mucosa. They did it with the suspension alone and in association with streptococcus. They were not able to obtain any lesions which simulated rheumatic fever.

Swift,[99] in 1936, attempted to produce the disease by injecting, in different ways, exudates from various types of rheumatic lesions, with and without association with streptococcus, but was unsuccessful. He also raised the question of specificity of these elementary bodies. This is illustrated by lack of specificity (1) in the heterophile antigen test for infectious mononucleosis and (2) with Proteus X 19 agglutinating sera from typhus fever patients. Van Roozen[103a] was unable to corroborate the earlier work of Schlesinger done on virus. Jones[49] states that these same elementary bodies are found in normal body fluid.

In summarizing, it is apparent that the virus plays no definite part in the etiology; therefore it is not considered a basic factor.

STREPTOCOCCUS

The search for the etiology of rheumatic fever has been in progress for many years. Poynton,[80] in

1900, first attempted to show that a bacteria was the cause, a diplococcus. This started much research, and many other types of organisms were discussed.[100] Swift, in 1917, was early in centering the attention toward a streptococcus.

The occurrence of rheumatic fever following streptococci infection has been recognized by numerous writers.[18,24,38,50,55,72,73,87,102] Coburn and Pauli[18] have compared rheumatic fever to the streptococcus in many manners to show their relationship. Using the well accepted predisposing factors to rheumatic fever, they demonstrated that streptococcic infection had a similar distribution. The seasonal, geographical, and social distribution of rheumatic fever corresponded to a rise in streptococcic throat cultures in these patients.

Coburn[18] continued by demonstrating the relationship of a hemolytic streptococcus to a local outbreak of rheumatic fever. In all student nurses at Pennslyvania, with good living conditions, he found negative throat cultures in the fall. In the spring he obtained four pure cultures of hemolytic streptococci and many other positive cultures. One month later the nurses with the pure cultures succumbed to rheumatic fever.

Coburn also demonstrated the relationship of hemolytic streptococcus to recrudescences. One patient with inactive rheumatic fever from New York City went to Puerto Rico for a considerable period of time. He had no recurrence of the disease. On his return to New York, the disease again became active.

Coburn demonstrates statistically in 200 cases of rheumatic fever the correlation between hemolytic streptococci in throat cultures and recrudescences as follows:

	Number of cases
Hemolytic streptococci with recrudescences	77
No hemolytic streptococci with no recrudescences	71
No hemolytic streptococci with recrudescences	17
No hemolytic streptococci with no recrudescences	25
Undetermined	30

Paul,[72,73] in the New Haven hospital, found the same relationship that Coburn did. He stated that 302 out of 526 of his cases of rheumatic fever had known precursors. Tonsillitis, upper respiratory disease, grippe, and scarlet fever were the most common ones stated in the hospital records. The seasonal relationship of the several streptococcic diseases and rheu-

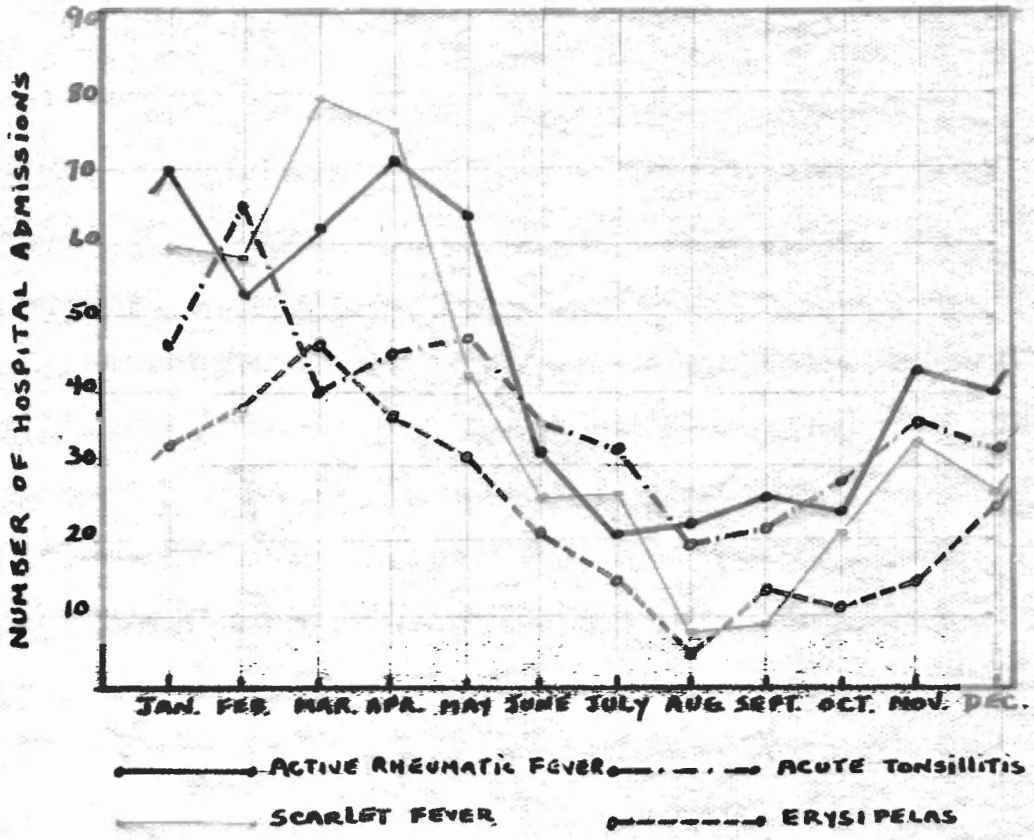

Figure VIII. Seasonal occurrence of the onset of hospitalized cases of rheumatic fever and of three streptococcus diseases in New Haven County. The rheumatic fever series consists of 526 cases, the scarlet fever series of 458, the acute tonsillitis of 443, and the erysipelas of 285. Paul[73]

matic fever is illustrated in Figure VIII. It shows definite correlation.

Studying rheumatic fever in a training center of 1900 individuals, Green[38] found that the new recruits were more susceptible to streptococcic infections. He had 1466 cases of throat infections, 132 cases of scarlet fever, and 162 cases of rheumatic fever. The majority of the scarlet fever cases occurred during the first three months of the recruits' training, but the opposite was true in rheumatic fever. He also found that neither rubella, measles, chicken pox, coryza, nor diphtheria were related to rheumatic fever. Kuttner[55] and Reyersback[82] demonstrated these facts to be true. Thomson and Glazebrook[102] with conditions similar to Green's had 115 cases of rheumatic fever following 1903 cases of tonsillitis caused by a hemolytic streptococcus. Dithowsky[24] had eighty-eight cases of rheumatic fever following an epidemic of 241 cases of tonsillitis.

Other workers found that numerous cases of rheumatic fever attacks or recurrences were preceded by hemolytic streptococcic infections. Jones[50] demonstrated hemolytic streptococcus in 58.7 percent of 750 cases of rheumatic fever. He obtained an immune re-

sponse in many of the other cases. Kaiser[36] had seventy-five percent in 200 cases; Schlesinger[54] had many cases of rheumatic fever that were preceded by throat infection which occurred from ten to twenty-one days previously.

Colonel Holbrook[46] in the army air forces and Commander Coburn[16] in the navy have compiled the results with the use of sulfonamides prophylactically in their respective services. They have used controlled experiments, giving tens of thousands of men the drug and withholding it from a similar number. Their reports showed that epidemics of hemolytic streptococcic infections were stopped in the treated groups and at the same time, it was just as severe in the control groups. They also stated that with this decrease in hemolytic streptococcic infections, there was a corresponding decrease in incidence of rheumatic fever in the prophylactically treated men.

Collis[19] in studying seventeen cases of rheumatic fever at autopsy found hemolytic streptococci in the center of fourteen of fifteen tonsils, in thirteen of twenty-seven lymph nodes, and in twenty-two of forty-two heart valves. He stated that he tried to be aseptic but the sources of error were numerous.

In 1927, Coburn[18] used three immune reactions which demonstrated the presence of antibodies produced by streptococcic products. One, the antistreptolysin titre in the sera of rheumatic fever patients rose early in the disease and remained high for long periods. Two, the agglutination reaction was not sensitive enough to be used. Three, the precipitins in the serum rose gradually during the duration of the activity of the disease and fell with recovery. A hemolytic streptococcus infection occurring one to five weeks before the attack of rheumatic fever caused the antistreptolysin titre to rise at that time.

Todd and Coburn[103] described two antistreptolysins: one, Antistreptolysin O sensitive to oxygen and consequently difficult to determine, and two, Antistreptolysin S extracted in the serum. The titre of the latter is increased with hemolytic streptococcic infections in the non-rheumatic and in inactive rheumatic children. It is low in the active rheumatic child with a similar infection. This is in contrast to the antistreptolysin O which increases with hemolytic streptococcus infection and shows greater increase with active rheumatic fever.

An average Antistreptolysin O titre of seventy-

nine units was determined by Green.[39]

	Antistreptolysin O titre average
Scarlet fever	300
Hemolytic streptococcus pharyngitis	263
Active rheumatic fever	444
Inactive rheumatic fever	210

In 110 attacks of rheumatic fever, eighty percent were accompanied by a significant increase in titre reaching its maximum proportions at the height of clinical activity.

Mote and Jones,[68] studying the same problem, found that the Antistreptolysin O is a more sensitive determination than the antifibrinlysin titre determination or the precipitin test. They were unable to find any basic difference in antibody response between rheumatic fever and streptococcal infections. Bunim[10] and Rantz[81] corroborated these findings, and noticed a great variation in values, although the general trend was up in both hemolytic streptococcus infection and rheumatic fever. Wilson[108] was unable to find a consistent rise in her antistreptolysin titre determinations in rheumatic fever. Swift[99] stated (1) she may have mixed hemolytic streptococcus Group A and B antigen, (2) the organism may have been in the tonsils without producing

symptoms but giving high titres, and (3) that twenty percent fail to show a response anyway.

Wasson and Brown[106] have immunized their patients for nine years with thirty-eight injections each winter. They use a hemolytic streptococcic filtrate. They report ten to fifteen percent fewer recurrences in the treated group than in the control group. Recently[78] they have tried this immunization with four injections, but have not yet reported the results.

In attempting to determine the type of streptococcus involved, it is apparent that the hemolytic streptococcus is the one as shown by nearly all the authors referred to above. That it is a Group A is presented by Coburn,[16,18] Rantz,[81] and Kuttner.[55] The type in Group A seemed to vary with epidemics.[75] There has been no definite evidence that rheumatic fever is caused by one specific type of hemolytic streptococcus.

In summarizing, one can state that the predisposing factors, discussed previously, reflect mainly the incidence of hemolytic streptococcus infection. The close association of this organism with rheumatic fever hasbeen shown by numerous approaches and means. From this we can deduce that some type of the Group A hemolytic streptococcus must be present in all cases of

rheumatic fever.

STATE OF ALLERGY

In explaining the term used, a definition of allergy is needed. In general, allergy is a condition of unusual susceptibility to a substance which is harmless in similar amounts for the majority of members of the same species.[94a] It is the state of allergy in the body that results in the production of the lesions of rheumatic fever. This state is produced by the two preceeding basic factors, heredity and streptococcus hemolyticus.

Vaughan[104] in an address in 1940, on the future of allergy, expressed the accepted theory of allergy. He stated that the inherited factor is the cellular maturation of antibodies. They are normally produced and "shed" from the cell into the blood stream. If this cellular maturation of antibodies is not functioning properly, the antibodies are not "shed" or produced in normal amounts. When these abnormal antibodies combine with an antigen there is an "H" substance liberated which produces the clinical manifestations of allergy. An additional concept of allergy is that it is poorly developed immunity.[105] This will help later in

explaining the mechanics of the etiology.

One striking relationship between rheumatic fever and allergy is the similarity of the former to serum sickness. In both conditions there is an incubation period after the initial infection before the manifestation of these diseases occur. In rheumatic fever this varies from one to five weeks.[18,73,87,102] Also both conditions are characterized by transient migratory joint pains (polyarthritis).

Opie[70] stated that the Aschoff body also has some characteristics in common with the lesions from serum sensitization. Rich and Gregory[83] have produced lesions in rabbits similar to rheumatic carditis by the injection of horse serum resulting in production of a hypersensitive anaphylactic reaction.

Swift[99] has shown rheumatic patients to have marked hypersensitivity to streptococcal protein or vaccines when introduced either intracutaneously or intravenously. Animals subjected to focal injection of streptococcus show a hyperergic (allergic) reaction. When they are injected intravenously, they show a hypoergic (immuned) response. Opie[70] also found that skin sensitization tests with filtrates or nucleoproteins of streptococci are more positive in rheumatic than in

non-rheumatic children. He produced a reaction in rheumatic patients by giving them streptococcic products intravenously. This simulated the reaction produced by giving tuberculin intravenously to tubercular patients. Schick[86] confirmed this latter finding and added that the joint lesions of rheumatic fever are an allergic reaction.

Wasson and Brown[106] have noted no marked reaction in their immunization of rheumatic patients, but the improvement noted in these patients with immunization shows a partial change from the allergic state over to an immuned state.

Another correlative between allergic diseases and rheumatic fever is the type of tissue involved. There is a well known correlation between epithelial allergies such as urticaria, bronchial asthma, hay fever, and others. In rheumatic fever the type of tissue involved is mesodermal[60] as shown by Lichtwitz. These are serous membranes, joint structures, connective tissue in the myocardiam valves of the heart, blood vessel walls, and in the fascia, subcutaneous nodules. Arey[2] states that the microglial tissue of the brain is of mesodermal origin. It may be the factor in production of gramulomatous lesions in the brain

producing chorea. Thus, rheumatic fever may be called a "mesodermal allergy".

In summarizing, one can state that rheumatic fever and allergic reactions are clinically similar in their incubation period and in the manifestation of polyarthritis, and pathologically similar in the characteristics of the granulomatous lesions and joint changes. Cutaneous and intravenous injections of streptococcus resulting in tuberculin-like reactions are manifestations of allergy. The partial ability to immunize is characteristic of allergic conditions. The production of rheumatic-like lesions by horse serum injections and the involvement of only one type of tissue illustrate this point. Therefore, one can conclude that a state of allergy is present in rheumatic fever.

DISCUSSION

In postulating a theory which will bring together the factors involved in the etiology of rheumatic fever, one must start first with the heredity of the individual concerned. This person must have a hereditary defect of the cellular maturation of antibodies. This makes him "susceptible" to some specific antigen.

Certain other factors modify this defect. Both lack of thyroxine and cold weather will decrease the cellular metabolism. This decrease in cellular metabolism results in decrease in antibodies produced. Proteins in the diet are also necessary for production of antibodies, because they apparently contain the substances which are converted into antibodies by the cells. This illustrates the condition of the "soil" and the factors involved in varying that condition.

The hemolytic streptococcus (Group A) provides the antigen for which the cells are unable to produce a specific antibody in normal amounts and in a normal manner. These factors produce a state of allergy in the individual. Therefore, one would expect a low specific antibody titre in the serum in an acute case. The rise in the antistreptolysin O content of the blood in an active case appears contradictoy. Because the

streptococcus liberates many exotoxins as well as endotoxins, one can not say to which antigen it is that the individual is susceptible. For example, it may be the antistreptolysin S, the titre of which fails to rise during an acute phase of the disease.

The susceptible individual exposed to the hemolytic streptococcus for a period of time produces abnormal unshed antibodies. These antibodies combine with the antigen and thus liberate an "H" or unknown substance. This combination may act by producing a physiological change in the cell that results in the production of this substance. This unknown substance acting directly on the mesodermal tissue produces the lesions of rheumatic fever, a mesodermal allergy.

Reviewing the new work in the production of rheumatic fever by hormones, one might say that desoxycorticosterone may be the substance liberated or may be over produced by this "unknown" substance and thus produce rheumatic fever.

One may state that due to a hereditary deficiency an individual produces an abnormal antibody response to the stimulus from a specific antigen from the hemolytic streptococci Group A. This creates an allergic state in which abnormal unshed antibodies are produced.

The combination of the antigen and unshed antibodies liberates a toxic substance which produces the lesion of rheumatic fever.

CONCLUSION

1. Rheumatic fever has certain definite predisposing factors.
2. The basic factors necessary to produce the disease are heredity, hemolytic streptococcus, and a state of allergy.
3. The mechanism by which these factors work is patterned on an allergic basis.
4. More work is needed to substantiate this mechanism.
5. If the postulated theory is true, many other diseases of unknown etiology may fit into this pattern.

BIBLIOGRAPHY

1. Abeloff, A. J. and Sobel, I. P.: Communicability of Rheumatic Disease. Arch. of Ped., 43:576, 1926.

2. Arey, L. B.: Developmental Anatomy. Philadelphia and London, W. B. Saunders Co., 1941.

3. Ash, R.: Prognosis of Rheumatic Infection in Childhood. Am. J. Dis. Child., 52,Pt. I: 280, 1936.

4. Atwater, R. M.: Studies in Epidemology of Acute Rheumatic Fever and Related Diseases in the U. S. Based on Mortality Statistics. Am. J. Hyg., 7:343, 1927.

5. Baneyea (Banerjea) J. C.: Rheumatic Heart Disease in Childhood. Indian J. Ped., 2:279, 1935, quoted by Carruthers (13).

6. Bilderback, J. B. and Overstreet, R. M.: Incidence of Rheumatic Infection in Children in Oregon. Northwest Medicine, 37:390, 1938.

7. Boas, E. P. and Schwartz, S. P.: Modes of Infection of Rheumatic Fever. Am. Heart J., 2:375, 1927.

8. Boyd, W.: The Pathology of Internal Diseases. Philadelphia, Lea and Fiberger, 1941.

9. Brown, E. E. and Wasson, U. P.: Basal Metabolism in Rheumatic Children. J. of Ped., 23:19-23, July 19, 1943.

10. Brown, E. E. and Wasson, U. P.: Immunization in Rheumatic Fever. J. of Ped., 23:23, July 19, 1943.

11. Bunim, J. J. and McEwer, C.: Antistreptolysin titres in Rheumatic Fever, Arthritis, and Other Diseases. J. Clin. Invest., 19:75, 1940.

12. Campbell, M. and Warner, E. C.: Rheumatic Disease in Children. Lancet, 1:61, 1930

13. Carruthers, L. G.: Rheumatic Heart Disease in Bombay, Deccan. Indian Med. Gaz., 71:137, 1936.

14. Christie, A.: Rheumatic Fever in Northern California. Am. Heart J., 12:153, 1936.

15. Coates, U. and Thomas, R. E.: Rheumatic Infection in Childhood. Lancet, 2:326, 1925.

16. Coburn, A. F.: Paper read at A. M. A. meeting in Chicago, June, 1944.

17. Coburn, A. F. and Moore, L. V.: Nutrition as a Conditioning Factor in Rheumatic State. Am. J. Dis. Child., 65:744-56, May, 1943.

18. Coburn, A. F. and Pauli, R. H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic process. J. of Exp. Med., 56: 609, 1932.

19. Collis, W. R. F.: Bacteriology of Rheumatic Fever. Lancet, 2:817, 1939.

20. Coombs, C. F.: Rheumatic Infection of Childhood. Lancet, 1:579 and 624, 1927.

21. Cooper, E. L.: A Note on Incidence of Rheumatic Infection in Australia. Med. J. of Australia, 1:714, 1935.

22. Denenholz, E. J. and Rambar, A. C.: Rheumatic Fever in the Newborn Infant. Am. J. Dis. Child. 61:1044, 1941.

23. Denzer, B. S.: Rheumatic Heart Disease in Infancy. J. Am. Med. Assn., 82:1243, 1924.

24. Ditkowsky, S. P., Stevenson, E., and Campbell, J. M.: Epidemology of Rheumatic Fever in Children's Institutes. J. Am. Med. Assn., 121.2:991-5, March, 1943.

25. Draper, G.: Heredity and Environment: the Disease Makers. Am. J. Med. Sci., 171:803, 1926.

26. Eagles, G. H., Evans, P. R., Fisher, H. G. T., and Keith, A. D.: A Virus in the Etiology of Rheumatic Disease. Lancet, 2:421, Aug. 21, 1937.

27. Eagles, G. H., Evans, P. R., Fisher, H. G. T., and Keith, A. D.: Infection Experiment with Virus-like Bodies from Rheumatism. J. Path. and Bacti., 41:481-93, May, 1938.

28. Eigen, L. A.: Juvenile Rheumatic Fever. Am. Heart J., 16:363, 1938.

29. Faulkner, J. M.: Effect of Administration of Vitamin C on the Reticulocyte in Certain Infectious Diseases. N. Eng. Med. J., 213:19, 1935.

30. Faulkner, J. M. and White, P. E.: The Incidence of Rheumatic Fever, Chorea, and Rheumatic Heart Disease with Especial Reference to its Occurrence in Families. J. Am. Med. Assn., 83:425, 1924.

31. Fernando, P. B.: Rheumatic Heart Disease as Met with in Hospital Practice in Ceylon. Quart. J. Med., n.s. 8:261, 1939.

32. Fisher, V. E.: Rheumatic Heart Disease at One Year. Am. J. Dis. Child., 48:590, 1934.

33. Gauld, R. L., Ciocco, A., and Read, F. E. M.: Further Observations on the Occurrence of Rheumatism Manifested in Families of Rheumatic Patients. J. Clin. Invest., 18:213, 1939.

34. Gauld, R. L. and Read, F. E. M.: Familial Association and Aggregation in Rheumatic Disease. J. Clin. Invest., 19:393, 1940.

35. Glazebrook, A. J. and Thomson, S.: Acute Rheumatism and Trauma. Edinburgh Med. J., 48.2: 674, Oct., 1941.

36. Glover, J. A.: Milroy Lectures on the Incidence of Rheumatic Diseases. I. Incidence of Acute Rheumatism. Lancet, 1:499, 1930.

37. Graham, R. S. and Paul, J. R.: Studies in Rheumatic Fever. Bull. Ayer Clin. Lab., 10:44, 1926.

38. Green, C. A.: Epidemiology of Hemolytic Streptococcus. J. Hyg., 42:365-92, July, 1942.

39. Green, C. A.: Observation on the Antistreptolysin O Titre in Relation to the Mechanics of Acute Rheumatic Fever. J. Path. and Bact., 53:223-241, Sept., 1941.

40. Harrison, T. R. and Levine, S. A.: Notes on the Regional Distribution of Rheumatic Fever and Rheumatic Heart Disease in the U. S. Southern Med. J., 17:914, 1924.

41. Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. Pub. Health Rep., 55:1809, 1940.

42. Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. Pub. Health Rep., 55:647, 1940.

43. Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. Pub. Health Rep., 55:1845, 1940.

44. Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality from Heart Disease among Persons from Five to Twenty-Four Years of Age in the U. S. During Recent Years. Pub. Health Rep., 54:2271, 1939.

45. Hogben, L.: Factorial Analysis of Small Families with Parents of Undetermined Genotype. J. of Genetics, 26:75-79, July, 1922. Quoted from Wilson (108).

46. Holbrook, Col.: Paper read at A. M. A. Meeting in Chicago, June, 1944.

47. Irvine-Jones, E.: Acute Rheumatism as a Familial Disease. Clin. J. Dis. Child., 45:1184, 1933.

48. Jones, T. D.: Paper read at A. M. A. Meeting in Chicago, June, 1944.

49. Jones, T. D.: Etiology of Rheumatic Fever. J. of Ped., 15:772, 1939.

50. Jones, T. D.: Heart Disease in Childhood. Am. J. of Pub. Health, 28:637, 1938.

51. Kaiser, A. D.: Factors that Influence Rheumatic Heart Disease in Children. J. Am. Med. Assn., 103:886, 1934.

52. Kaufman, O. and Scheerer, E.: Heredity of Acute Articular Rheumatism; Studies on Seventy-Two Sets of Twins. Ztshr. f. menschv. f. Vererb. u. Konshtutionslehve, 21:687-96, May 21, 1938. Quoted by Wilson (108).

53. Keith, J. D. and Hickman, E. M.: Vitamin C Excretion in Children with Particular Reference to Rheumatic Fever. Arch. Dis. Child., 13: 125-136, June, 1938.

54. Kissane, R. W. and Koons, R. A.: Intra-Uterine Rheumatic Heart Disease. Arch. Int. Med., 52:905-910, Dec., 1933.

55. Kuttner, A. G. and Krumwiede, E.: Observations on the Effect of Streptococcus Upper Respiratory Infection on Rheumatic Children: A Three Year Study. J. of Clin. Invest., 20:273, 1941.

56. Kutumbrah, P.: Clinical Study of Rheumatism in Childhood. Indian J. of Ped., 2:215, 1935. Quoted by Carruthers (13).

57. Ledingham, J. C. G. and Albert, M. B.: Etiological Importance of Elementary Bodies in Vaccinia and Fowl Pox. Lancet, 2:525, 1931.

58. Leonard, M. D.: Puberty and Prognosis in Rheumatic Fever. Am. Heart J., 14:192, 1937.

59. Lewis, M. J.: Study of the Seasonal Relationship of Chorea and Rheumatism for a Period of Fifteen Years, 1876-1890 Inclusive. Trans. of Assoc. of Am. Physicians, 7:249, 1892.

60. Lichtwitz, L.: Rheumatic Fever. New York, Greene and Stratton Inc., 1944.

73. Paul, J. R.: Rheumatic Fever in New Haven. Lancaster, Pennslyvania, The Science Press Pringing Co., 1941.

74. Paul, J. R. and Leddy, P. A.: The Social Incidence of Rheumatic Heart Disease. (A Statistical Study in Yale University Students.) Am. J. Med. Sci., 184:597, 1932.

75. Pauli, R. H. and Coburn, A. F.: Studies on Serological Typing of Streptococcus Hemolyticus. J. of Exp. Med., 65:595, 1937.

76. Perry, C. B.: Rheumatic Heart Disease and Vitamin C. Lancet, 2:426, 1935.

77. Perry, C. B. and Roberts, J. A. F.: Study on the Variability in the Incidence of Rheumatic Heart Disease within the City of Bristol. Suppl., Brit. Med. J., 2:154, Aug. 28, 1937.

78. Pounders, C. M. and Gray, J. K.: Juvenile Rheumatism. So. Med. J., 32:471, 1939.

79. Poynton, J. F.: Notes on Social Aspects of Rheumatism. Med. J. of Australia, 1:555-557, 1938.

80. Poynton, F. J. and Paine, A: Etiology of Rheumatic Fever. Lancet, 2:861, 932, 1900.

81. Rantz, L. A.: Group A Hemolytic Streptococcus Antibodies. Arch. of Int. Med., 73:238, March, 1944.

82. Reyersbach, G., Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurred with an Outbreak of Streptococcus Pharyngitis. Clinical and Epidermiological Observation. J. of Clin. Invest., 20:289, 1941.

83. Rich, A. R. and Gregory, J. F.: Experimental Evidence that Lesions with the Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity. Bull. John Hopkins Hosp., 72:239, Oct., 1941.

61. McCulloch, H. and Irvine-Jones, E.: Role of Infection in Rheumatic Children. Am. J. Dis. Child., 37:252, 1929.

62. McIntosh, R. and Wood, C. L.: Rheumatic Infection Occurring in the First Three Years of Life. Am. J. Dis. Child., 49.2:835, 1935.

63. McSweeney, C. J.: Acute Rheumatism in Childhood. Lancet, 1:959, 1928.

64. Maddox, K.: Metropolitian and Rural Incidence and Distribution of Acute Rheumatism and Rheumatic Heart Disease in New South Wales. Med. J. of Australia, Part I, pp. 394, 425, 464, 499, 1937.

65. Miller, R.: Problems of Rheumatic Infection in Childhood. Brit. Med. J., 2:23, 1926.

66. Miller, R.: Rheumatism in Childhood. Suppl., Brit. Med. J., Dec. 10, 1927.

67. Morris, J. N. and Titmuss, R. M.: Epidemiology of Jewish Rheumatics. Lancet, 2:59-63, 1942.

68. Mote, J. R. and Jones, T. D.: Studies of Hemolytic Streptococcus in Control Groups.of Rheumatic Fever and Rheumatic Arthritis. J. of Immunology, 41:35-60, 61-85, 87-118, May, 1941.

69. Nichols, E. S.: Geographic Distribution of Rheumatic Fever and Rheumatic Heart Disease in the U. S. J. Lab. and Clin. Med., 21:588, 1936.

70. Opie, E. L.: Significance of Allergy in Disease. Medicine, 15:489-509, Dec., 1936.

71. Paul, J. R.: Age Susceptibility to Familial Infection in Rheumatic Fever. J. Clin. Invest., 10:53, 1931.

72. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of its Public Health Aspects. New York, Metropolitan Life Insurance Co. Press, 1943.

84. Rinehart, J. F.: An Outline of Studies Relating Vitamin C.Deficiency in Rheumatic Fever. J. Lab. and Clin. Med., 21:597, 1936.

85. Rinehart, J. F.: Vitamin C and Rheumatic Fever. International Clinic, 2:22,1937.

86. Schick, B: The Problem of Allergy in Rheumatic Disease. Mount Sinai Hosp. J., 8:991-4, 1942.

87. Schlesinger, B.: Relationship of Throat Infection to Acute Rheumatism in Childhood. Arch. Dis. Child., 5:411, 1930.

88. Schlesinger, B, Signy, A. G., and Amies, C. R.: Etiology of Acute Rheumatism-Virus. Lancet, 1:1145, 1935.

89. Schultz, M. P.: Studies on Ascorbic Acid and Rheumatic Fever. J. of Clin. Invest., 15:385, 1936.

90. Seegal, D. and Seegal, B. C.: Studies in the Epidemiology of Rheumatic Fever. J. Am. Med. Assn., 89:11, 1927.

91. Seegal, D, Seegal, B. C., and Jost, E. L.: Comparative Study of Geographic Distribution of Rheumatic Fever, Scarlet Fever, and Acute Glomerulonephritis in Two New York Hospitals and Four Southern Hospitals. Am. J. Med. Sci., 190:383, 1935.

92. Selye, H, Sylvester, O., Hall, C. E. and Leblond, C. P.: Hormone Production of Arthritis. J. Am. Med. Assn., 124.4:201, Jan., 1944.

93. Sendroy, J. and Schultz, M. P.: Studies on Ascorbic Acid and Rheumatic Fever. J. of Clin. Invest., 15:369, 1936.

94. Shapiro, M. J.: Natural History of Childhood Rheumatism in Minnesota. J. Lab. and Clin. Med., 21:564, 1936.

94. (a) Shrewsbury, E. E.: A Review of Allergy. West Virginia Med. J., 39:121-26, April, 1943.

95. Stimson, A. M., Hedley, O. F., and Rose E.: Notes on Experimental Rheumatic Fever. Pub. Health Rep., 49:361, 1935.

96. Stroud, W. D., Goldsmith, M. A., Polk, D. S., and Thorpe, F. Q.: Ten Years Observation of Children with Rheumatic Heart Disease. J. Am. Med. Assn., 101:502, 1933.

97. Stroud, W. D. and Twaddle, P. H.: Fifteen Years Observation of Children with Rheumatic Heart Disease. J. Am. Med. Assn., 114:629, 1940.

98. Sutton, L. P.: Observations on Certain Etiological Factors in the Rheumatic (Including Chorea). Am. Heart J., 1:145, 1928.

99. Swift, H. F.: Nature of Rheumatic Fever. J. Lab. and Clin. Med., 21:551, 1936.

100. Swift, H. F.: Rheumatic Fever. Med. Clin. of No. Am., 1:641, Nov., 1917.

101. Thompson, E.: Rheumatic Fever in Nebraska. Nebr. Med. J., 24:347-49, 1939.

102. Thomson, S. and Glazebrook, A. J.: Infectious Diseases in a Semi-Closed Community. J. Hyg., 41:570, 1941.

103. Todd, E. W., Coburn, A. F., and Hill, A. B.: Antistreptolysin S Titre in Rheumatic Fever. Lancet, 2:1213, 1939.

103. (a) Van Roozen, C. E.: Transactions of the Second International Congress for Microbiology. London, 1936. Quoted from Jones (49).

104. Vaughan, W. T.: The Future of Allergy. J. of Allergy, 11:584, Sept., 1940

105. Vaughan, W. T.: Theory of the Mechanism of Allergic Response. J. Lab. and Clin. Med., 21:629, 1936.

106. Wasson, V. P. and Brown, E. E.: Further Studies in Immunization Against Rheumatic Fever. Am. Heart J., 23:291-305, March, 1942.

107. White, P. D.: Treatment of Heart Diseases. Modern Med., August, 1944.

108. Wilson, M. G.: Rheumatic Fever. New York, The Commonwealth Fund, 1940.

109. Wilson, M. G., Lingg, C., and Croxford, G.: Statistical Studies Bearing on Problems in the Classification of Heart Disease. Am. Heart J., 4:164, 1928.

110. Wilson, M. G., Lubschez, R., and Schweitzer, M. D.; Integration of Genetics and Epidemiological Methods of Analysis in Rheumatic Fever. Science, 97: 335-6, April 9, 1943.

111. Wilson, M. G. and Schweitzer, M. D.: Rheumatic Fever as a Familial Disease. Environment, Communicability and Heredity in their Relation to the Observed Familial Incidence of Disease. J. of Clin. Invest., 16: 555, 1937.