REVIEW OF THE LITERATURE ON ACUTE RHEUMATISM DURING THE YEARS 1939-1945

BY

C. BRUCE PERRY

Incidence

Glover (1943) has again drawn attention to the decline in the death rate from acute rheumatism and rheumatic heart disease, as shown by the Registrar-General's returns, which has been in progress since the beginning of the century. He shows that this decline was considerably accelerated during the first three years of the war. Glover discusses the possible significance of this, and points out that, while it coincides with a general improvement in the standard of living, it is roughly paralleled by the fall in death rate of streptococcal infections like scarlet fever. Hedley (1939) has shown a similar trend in the United States. He notes the association with an increased standard of living, and points out that the mortality is appreciably higher amongst young negroes than amongst the whites, who certainly live, on the average, under more favourable conditions. Hedley also suggests that the recent widespread practice of tonsillectomy may have had some influence.

It has long been considered that acute rheumatism is a rare occurrence in the tropics. However, Fernando (1939) shows that rheumatic heart disease is responsible for 21.5% of all cardiac admissions to hospital in Ceylon and that rheumatic heart disease was found in 3.6% of all necropsies. He found that the clinical features differed in no material way from those met with in temperate climates, except that chorea was very rare. Reports by Stott (1939) and Kutumbiah (1941) indicate that, while the disease is much rarer in India than in northern countries, it is not unknown. Stott found that about 1% of all hospital admissions in India are due to chronic rheumatic heart disease with valvular lesions. Pestana (1940) states that the disease is not uncommon in Singapore, and reports an incidence of 1.6% of all necropsies performed in 1938. In a study of the incidence in French colonies Sorel (1939) found a very low incidence in Chine du Nord.

From America there have been reports of the incidence from all parts of the United States and from South America. From these it emerges that, broadly speaking, the nearer the equator, the lower the incidence of the disease. For instance, in San José, Costa Rica (latitude 9° N.) Carrillo (1942) found mitral stenosis in 1.0% of 1,000 autopsies, while there were 22 cases in the paediatric wards among 3,771 admissions. In Puerto Rico (latitude 18°-19° N.) Suarez (1945) showed that acute rheumatism is responsible for only 17.4% of all cases of heart disease. However Chavez (1942) reports as many as 41% of all cases of heart disease in Mexico (latitude 19° N.)

as being rheumatic. In Los Angeles (latitude 34° 5' N.) Davis and Rosin (1944) have reported the very low incidence of only 173 cases out of 13,135 admissions to a children's hospital. In Cincinnati (latitude 39° N.) and Louisville, Kentucky (latitude 38° N.), Rauh (1939) and Weiss (1941) found the incidence amongst schoolchildren to be about 0·2% and 0·3% respectively. South of the equator, in the Argentine (latitude 30°–40° S.), Cossio (1943) found 18·2% of heart disease to be rheumatic in origin. (In England and in the northern states of the U.S.A. the incidence is about 35%.) Hedley (1940) has investigated the incidence in Philadelphia, and estimates that rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis—most of which is superimposed on rheumatic heart disease—account for rather more than 1,200 admissions to hospital and for over 50,000 patient-days each year in Philadelphia hospitals, at a cost of over \$272,000.

An interesting study by Sampson and others (1945), in three climatically different communities in California, showed that in the area with a mild, temperate climate 0·57% of the schoolchildren were affected, as compared with 1·1% in a climate comparable with that of Great Britain and the north-east states, and 2% in an area with a cold, damp climate.

Aetiology

AGE, SEX, AND SEASONAL INCIDENCE.—A considerable amount of work on the aetiology of acute rheumatism was published during the war period. Hedley (1940) and Gauld and Read (1940*b*) confirm the well-known age incidence. The maximum incidence of first attacks is between the ages of five and ten years, and first attacks are rare after twenty. Hedley's studies also confirm the generally recognized sex incidence of the disease. He found that in Philadelphia rheumatic fever and rheumatic heart disease were slightly more frequent in females than males, whereas chorea was nearly twice as common among females. Considering their low economic circumstances, the disease was less common amongst negroes than might have been expected. He also (Hedley, 1940) confirmed the seasonal variations in the incidence of rheumatic fever. Admissions to hospital in Philadelphia were highest in April and lowest in October, the maximum and minimum for chorea being May and November, although the seasonal variation in the incidence of chorea was not so marked as that of rheumatic fever.

FAMILIAL INCIDENCE.—A considerable amount of attention has been paid to the familial incidence of acute rheumatism. Pickles (1943) has described an extraordinary family comprising 53 descendants of a man with rheumatic heart disease, 23 of whom had rheumatic fever or rheumatic heart disease. Gauld and others (1939) studied the families of 96 child patients and found that in 43 one or both parents gave a history of rheumatic heart disease, whereas in 33 control families only 4 parents were so affected. They showed that female offsprings of rheumatic mothers exhibited rheumatic manifestations twice as frequently as sons of the same mothers. In a further study of 347 siblings of 95 patients Gauld and Read (1940*a*) noted an increased incidence of the disease after an acute rheumatic episode in the family, but found that the increased incidence might not appear until some time after the acute episode. The authors consider that this observation might be explained on the theory that both hereditary and environmental factors are involved; and that the environmental factor, if it is to give rise to the

disease, must act over a long period, and/or the disease must have a long period of subclinical development before becoming manifest.

Cahan (1941) has also confirmed the marked familial incidence of the disease. In a study of 53 families in which two siblings or one parent and one child were afflicted with the disease, he examined 235 persons and found 171 cases of rheumatic heart disease. Rosenblum (1942), in a study of 70 families at the lower income level, also found that the outstanding observation was the marked familial trend and, contrary to the observation of Gauld and Read, that there was often a simultaneous flare-up of rheumatic manifestations in several members of the same family without any preceding wave of upper respiratory infection. Wilson and others (1943), from a detailed study of 112 families, conclude that the tendency to the development of acute rheumatism is inherited as a single autosomal recessive gene. Wilson (1944), arguing from this conclusion, has urged the closer study of the "potential rheumatic family", both in the interests of the children and in order to determine more closely the aetiological factors.

SOCIAL INCIDENCE.—The social incidence of the disease has also received attention. Most investigators comment on the greater incidence in the poorer districts of cities (Hedley, 1940; Rauh, 1939; Weddum and Weddum, 1944*b*; and Weiss, 1941). Daniel (1942 and 1943) reports the result of an investigation into social and economic conditions and the incidence of rheumatic heart disease in Bristol. This study shows a marked relation between net income and incidence of the disease. Families with incomes below their minimum needs included approximately 40% more cases of rheumatic heart disease than did the average working-class families, and approximately twice as many as the working-class families in the highest net income group. Similarly there was a close correlation with overcrowding. Families with less than 0.6 of a room per person had almost four times as many cases as those with 1.8 rooms or more. Daniel concludes that if the standards of the 30% of the Bristol working-class population with the most inadequate income and housing accommodation were raised to the level of the highest 10% of all working-class families the incidence of the disease would be roughly halved.

Morris and Titmuss (1942) studied the morbidity and mortality of juvenile rheumatism with special reference to the social background of the disease. They stress the importance of the disease, pointing out that it causes 2% of all deaths in England and Wales, and 10% of all deaths between 5 and 45 years of age. They found that the mortality increased with the density of population, which seems to be a function of the greater poverty in the town, the mortality being as high in depressed rural areas as in the worst of the towns. No evidence was found to suggest that the artisan stratum of the population is particularly prone to the disease. The authors consider that the facts elucidated strengthen the view that the whole complex of poverty is involved in the production of juvenile rheumatism.

Dietetic Deficiency.—In an attempt to determine the way in which poverty leads to the disease, various workers have tried to find a dietetic deficiency. Coburn and Moore (1943), in an analysis of the weekly diet of 50 rheumatic children compared with 50 normal children, found that the

diet of the rheumatic children was deficient in many different items (for example, butter, eggs, vitamin A, iron, calcium, etc.) but not deficient in any single component, which made it impossible to evaluate any one essential factor. Further, in a study of 14 unselected rheumatic children in wealthy families they found that 13 had "food fads" or took abnormal diets. In an attempt to study the effect of supplementing the diet of rheumatic children, 17 and 26 cases were given four eggs a day during the 1939-40 and 1940-41 seasons respectively. None of these children exhibited rheumatic relapses despite the fact that they experienced respectively 13 and 11 attacks of haemolytic streptococcal infection during the two periods of observation. The studies were carried further by Shank and others (1944), who studied the vitamin A level in the blood plasma. They found that the vitamin A in the plasma falls markedly with the onset of rheumatic fever, but that the plasma carotene concentration is not similarly affected. The decrease in plasma vitamin A levels is seen in other infections and is not specific for rheumatic fever, but the authors consider that their investigation demonstrates that patients with rheumatic fever show delayed or decreased absorption of vitamin A, or metabolize it in an abnormal manner. The precise significance of this is not clear.

Rinehart (1943) has discussed the relationship between acute rheumatism and nutrition, and has briefly reported the treatment of 3 cases with "vitamin P". No definite claims are made for this. Peete (1944) has also studied the diet of a group of rheumatic families and contrasted it with that of control middle-class families. The rheumatic families averaged 7.5 members, and the controls 4.5 members. He found that poor diet and lack of sunshine are important predisposing factors in rheumatic fever, and suggests that the incidence closely follows that of rickets. The rheumatic families' diet contained less milk, fresh meat, and green vegetables, but more starchy foods and sugar than the controls. Attempts to demonstrate nutritional deficiency have also been made by Epstein and McDonald (1940), who investigated the blood phosphorus which was found to be slightly lower than in normal controls. Schultz (1939*a* and *b*), and Schultz and Rose (1939), have studied the glutathione content of the erythrocytes and the dextrose tolerance and the catalytic potency of the blood in rheumatic fever without any very clear results. Brown and Wasson (1941) have measured the capillary resistance in rheumatic children and found it low. But there were marked seasonal variations, and normal children show such varying degrees of capillary resistance that these findings, too, can hardly be accepted as having any definite significance beyond perhaps pointing to a general nutritional deficiency.

THE PSYCHOLOGICAL FACTOR.—Hubble (1943), in a most stimulating paper, has analysed the "nature" of the rheumatic child in an attempt to evaluate how this child differs from normal. He stresses the emotional instability of the child who develops acute rheumatism, and argues that neither the limitation of the disease to a particular age group, nor its common association with poverty and with infection, refute the theory that nervous instability is part of the rheumatic diathesis. He suggests that the personality of the rheumatic child shows a quantitative increase in emotion and kinesis, and that this nervous instability is an important factor in the development of acute rheumatism.

Theories of an Infective Agent

THE VIRUS THEORY.—The interest in a possible virus cause of acute rheumatism, which was aroused in 1935 by the description of Schlesinger and others, of particles having the properties of elementary bodies in rheumatic exudates, has largely died down. Repeated attempts to infect animals by these particles have failed. Eagles and Bradley (1939) studied the agglutination of these particles by the sera of patients with rheumatic fever, rheumatoid arthritis, and other arthropathies. They found that agglutination occurred equally well with all these groups of sera, and there was no relationship between agglutination and clinical activity. It thus

appears that these particles can no longer be considered the causative virus of rheumatic fever.

However, MacNeale and others (1945) have re-aroused interest in the virus theory. They found that a filtrate of pericardial fluid from a patient dying with rheumatic fever, when injected into rabbits produced scattered foci of inflammation in the myocardium and valves. Attempts to repeat these experiments gave inconstant results, but changes were noted in most of the animals' hearts. Inoculation of embryonated eggs with blood of the experimental animals gave rise to a non-lethal inflammation which could be propagated in series in the eggs. When the allantoic fluid of the infected eggs was injected intravenously into rabbits, more pronounced cardiac lesions resulted. Another possible causal organism has been described by Swift and Brown (1939), who cultivated a pleuropneumonia-like organism on chorio-allantoic membranes inoculated with exudates from patients with rheumatic fever and from lung lesions produced in mice by injections of rheumatic exudates. However, Jones (1939) reports that further work suggests that the organisms occur spontaneously in mice, and that the growth direct on the membranes from the rheumatic exudates was an artefact. Sabin and Johnson (1940) have also investigated these pleuropneumonia-like organisms and found that they may be obtained from certain "carrier" mice, and on injection into other mice may produce a disease somewhat resembling acute rheumatism; but they were unable to isolate the organism from children with acute rheumatism. Cecil (1940), too, failed to find these organisms.

Copeman (1944b) has tried to elucidate the problem by the inoculation of human volunteers with blood from an adult with acute arthritis. In two of the five volunteers this produced no effect, but in the other three there occurred slight fever and vague limb pains. Blood from two of these was pooled and injected into four more volunteers, one of whom developed indefinite muscle pains. Blood from one of the original volunteers was again injected into four more, one of whom exhibited muscle pain two days later. Blood from this patient was again injected into four more volunteers, one of whom exhibited fever and vague pain on the next day. It is doubtful if a true arthritis was produced in any volunteer, and the results must be regarded as inconclusive.

STREPTOCOCCAL INFECTION.—A great deal of attention has naturally been paid to the relationship between acute rheumatism and infection with the haemolytic streptococcus. This work falls into three main groups, the isolation of streptococci from rheumatic lesions, the occurrence of acute rheumatism in epidemic form in association with epidemics of streptococcal infection, and the demonstration of antibodies to the haemolytic streptococci in the blood of patients with acute rheumatism.

Green (1939) isolated haemolytic streptococci at necropsy from the affected valves in 8 out of 9 cases of acute rheumatism. In one case *Strep. viridans* was grown. In no case were organisms grown from the heart blood or from the non-affected valves. In five of the cases the same organism had been obtained from the patient's throat during life. Haemolytic streptococci were isolated from the valves and heart blood in only two of 22 non-rheumatic necropsies. Collis (1939) reported the recovery of haemolytic streptococci from 22 affected valves in 17 cases of acute rheumatism.

These observations were repeated by Thomson and Innes (1940) in 10 cases, and they found haemolytic streptococci in the damaged valves in 5, in 2 of which the same organism was isolated from the blood and in one from the spleen. Other types of streptococci and coliform organisms were also isolated from both damaged and undamaged valves, but more frequently from the former. They discuss the possible significance of their findings and suggest two alternative explanations. First, the haemolytic streptococcus may be the cause of rheumatic fever and is responsible for the valvulitis by an actual infection of the valve; in which case it is curious that the joint lesions should so frequently prove sterile. The absence of organisms in the blood and other healthy tissues might be due to the bactericidal effect of the blood and tissues, which defences

might be absent in the avascular vegetations. The alternative hypothesis is that the abnormality of the valves allows organisms to lodge and persist there after a transient bacteraemia. The discovery of other types of streptococci and other organisms in the damaged valves far more often than in the undamaged valves would support this view. These observations, which are clearly of great interest, deserve further study.

In 1935 Wilson and others, reporting on the effect of upper respiratory infection in rheumatic children, concluded that "while the occurrence of respiratory infection in a rheumatic child may not be a fortuitous event, it would seem to bear no more specific aetiological relationship to rheumatic disease than would be attributed to similar episodes in the tuberculous child". This conclusion, so much at variance with the accepted view, has stimulated further study into the relationship between infection of the upper respiratory tract with haemolytic streptococci and the development of an attack or recurrence of acute rheumatism. Jones and Mote (1939) observed 749 patients with rheumatic fever for one year. They found that 58% of first attacks of acute rheumatism were preceded by upper respiratory infections (66% of these were sore throats and 33% colds). In 271 recurrences, two-thirds were associated with upper respiratory tract infection. When 512 patients with inactive rheumatic infection were observed through a respiratory-tract infection, 180 (of whom 84 (47%) relapsed) had a sore throat, and 332 (of whom 97 (29%) relapsed) had colds. The authors conclude that there is strong evidence that rheumatic recurrences are usually associated with haemolytic streptococcus infections (although they may occur without any such association being demonstrable clinically or serologically), and that, therefore, haemolytic streptococcus infection must be regarded as important precipitating agents in rheumatic fever.

Bazan and Maggi (1939) have re-studied the arthritic sequelae of scarlet fever, and find that early in the course of the disease there may occur a simple polyarthritis which on rare occasions becomes suppurative—due to the general infection—whereas later, or during convalescence, there may be arthritis and carditis indistinguishable from acute rheumatism. Reyersbach and others (1941) studied an epidemic of influenza B in a group of rheumatic children, and found that the influenzal epidemic did not enhance the virulence of a group A beta-haemolytic streptococcus of proved pathogenicity present in the community, and did not precipitate rheumatic recurrences. Kuttner and Krumwiede (1941) report a three-years' observation of a group of rheumatic children. Attacks of infection due to a single type of Group A beta-haemolytic streptococcus occurred in each of the three years, but in each epidemic a different type was involved. In the three epidemics the incidence of subsequent rheumatic relapses varied from none to a large proportion of the cases. No rheumatic relapses were observed amongst the children escaping the streptococcal infection. The authors put forward a new hypothesis as to the relationship between haemolytic streptococcal infection and acute rheumatism, and suggest that the streptococcal infection may be an indication accompanying the invasion of the rheumatic agent, and that the infectivity of the streptococcus may be increased by the entrance or reactivation of the rheumatic agent, just as the virus of herpes simplex is stimulated by certain diseases which appear to lower the resistance of the patient.

Studies of Streptococcal Epidemics.—The war has provided great opportunities for the study of epidemics of streptococcal infection and acute rheumatism in semi-closed communities like barracks and training ships. Thomson and Glazebrook (1941a) observed an epidemic of haemolytic streptococcal tonsillitis lasting four terms in a training ship with an average population of 1,200 boys aged 15 to 17. During the period of observation, 2,095 boys passed through the ship and there were 1,903 attacks of tonsillitis and 115 cases of acute rheumatism. Rheumatism did not occur in boys resident in the community for a long time or in those who had several attacks of tonsillitis, but amongst the newcomers to the ship. The epidemic of rheumatism did not appear until the second term, and subsided a fortnight before the streptococcal infection. There was some evidence that the incidence of rheumatism was higher in boys recruited from poorer parts of the country. Glazebrook and Thomson (1941b), in the same epidemic, noted that in 11 cases the first joint affected was the site of recent trauma.

Green (1942) made a similar study in a training centre, and found that an epidemic of haemolytic streptococcal infection (1,466 cases) was associated with an outbreak of acute rheumatism (162 cases). He, too, found that the incidence of rheumatism in boys from a depressed area (Tyneside) was nearly twice as high as in boys from the rest of the country, the incidence being 101.3 per 1,000 and 52.8 per 1,000 respectively. During the same period outbreaks of rubella, measles, chicken-pox, and the common cold occurred, but without influence on the incidence of rheumatic fever. Ditkowsky and others (1943) report a similar epidemic in a school. There were 241 cases of sore throat, and 88 of rheumatism. Of the rheumatic cases, 51 occurred after tonsillitis, 21 after an upper respiratory infection other than tonsillitis, and 16 with no preceding infection. The onset of the rheumatic fever epidemic was six weeks after that of the streptococcal one, and it reached its peak eight weeks after. There were 20 families with two or more children in the school, the majority of the siblings living in different houses; yet there was a marked familial incidence which would appear to be due to a specific susceptibility. Before the attack 61 of the affected children had cardiac murmurs mostly classified as "functional" and of no significance. This suggests that these murmurs may actually have indicated a pre-existing cardiac lesion, and that the attack of rheumatism was really a relapse. Boisvert and others (1943) reported a similar epidemic; and Massel and Jones (1944) suggest that the knowledge of this relationship between the two diseases might well be made use of prophylactically, and they discuss the value of the sulphonamides in this respect. Watson and others (1945) observed 110 cases of scarlet fever in young adults. Clinical rheumatic fever developed in 8; 4 had a mild transitory rheumatism; and 7, while exhibiting no evidence of rheumatism, had a period of fever and raised sedimentation rate during convalescence. They conclude that the difference between these three groups is quantitative rather than qualitative, and all appeared to suffer from the same fundamental tissue injury.

Holbrook (1944), studying the incidence of rheumatic fever in the United States Army Air Force, found that this varied enormously in different areas. For instance, in a camp in Colorado there were 25 cases per 1,000, and in California less than 1 per 1,000. In every instance rheumatic fever occurring in a high incidence was preceded by a high incidence of haemolytic streptococcal infection. Rantz and others (1945) observed 15 cases of acute rheumatism amongst 410 cases of Group A haemolytic streptococcal upper respiratory infection. No rheumatism was seen after non-streptococcal infection. Apart from the typical cases of acute rheumatism, many men failed to return to full health and some of these showed electrocardiographic changes during this period. There was some evidence that re-infection with a different strain of streptococcus was particularly associated with the development of rheumatism. The authors conclude that rheumatic fever is invariably induced by infection with a Group A haemolytic streptococcus, that the syndrome of rheumatic fever is only part of the whole "post-streptococcal" state, that these manifestations are the result of an altered sensitivity of the tissue to the products of the streptococcus, and that repeated infection with different types of streptococcus may be necessary for the development of this state. Despite this strong support for the rôle of haemolytic streptococcus, at least as a precipitating factor, it must be noted that Juster (1942) finds no direct relationship between upper respiratory infection and rheumatic activity as measured by leucocyte counts, and suggests that a far larger amount of latent active rheumatic infection exists in the community than is realized, and that upper respiratory infection may complicate, rather than initiate, a pre-existing active rheumatic process.

Skin Tests.—Skin tests, and demonstration of immune bodies in the patient's serum, have also been used in studying the relationship between acute rheumatism and infection with the haemolytic streptococcus. Taran and others (1944), using the "M" fraction of haemolytic streptococci, found that 65% of normal children and 88% of rheumatic children showed positive skin tests. Normal siblings of rheumatic children showed the same incidence of positive reactions as the rheumatic children themselves, and there was no correlation between rheumatic activity and incidence or strength of the positive reaction. The significance of their findings is obviously far from clear.

Streptolysin O and Streptolysin S.—Todd and others (1939) have described two distinct varieties of streptococcal haemolysin, one sensitive to oxygen—streptolysin O—and one soluble or extractable in serum—streptolysin S. In response to haemolytic streptococcal infection there normally occurs a rise in the level of anti-streptolysin S (ASS) titre. This also occurs in rheumatic children who do not develop a rheumatic relapse; but in children with active rheumatic infection, while the ASS titre may be higher than normal, it tends to remain relatively low. The titre in the active cases of rheumatism tended to be lower than in the same children during a quiescent period, and the more severe the attack the lower the titre. On the other hand anti-streptolysin O (ASO) titres were higher after a streptococcal infection in rheumatic than in non-rheumatic children and higher still during the acute phase of rheumatism. There is thus a striking difference in the ASO and ASS titres in acute rheumatic fever. Bunim and McEwen (1940) found that the majority of patients with acute rheumatism showed a high anti-streptolysin titre, but that the height of the titre bore no relationship to the various clinical manifestations beyond the fact that active cases had a higher titre than inactive, and the latter higher titres than normal children. They also showed that cases of active rheumatic infection and chorea tended to have a higher titre than did normal children after a streptococcal infection.

Green (1941 and 1942) confirmed these observations. He found that following scarlet fever and streptococcal pharyngitis the ASO titre was usually, but not always, raised, reaching its maximum in three to four weeks. In active rheumatism 79.9% showed a significant rise at about the height of the infection, and on the average this was higher than occurred in non-rheumatic subjects after a streptococcal infection. However, this rise in ASO titre was not constant, 10.1% of patients in an attack of acute rheumatism showing no change, and 3.6% actually having a reduced titre. Mote and Jones (1941), in a study of the incidence of anti-streptolysin O, antifibrinolysin, and haemolytic streptococcal precipitins, confirmed these findings that every normal patient after a streptococcal infection does not show a significant rise in ASO titre although the majority do, and the more severe the infection the higher the titre tends to rise. In moderate cases of scarlet fever, for example, 85% showed some antibody response, and in 78% the rise in titre was significant. They found no significant difference in antibody mechanism between patients during a primary attack of acute rheumatism and non-rheumatic patients convalescent from a haemolytic streptococcal infection. They state that the serological evidence that first attacks of rheumatic fever are associated with haemolytic streptococcal infection is as strong as is the serological evidence that scarlet fever is a streptococcal disease. In the case of rheumatic recurrences, mild, moderate, or severe relapses may occur without serological evidence of a previous streptococcal infection; however, 74% of severe relapses show evidence of this association. Further, Mote and Jones could find no evidence that the magnitude or duration of the antibody response following haemolytic streptococcal infections differed in rheumatic and non-rheumatic subjects. They consider that their findings indicate that haemolytic streptococcal infections are an important factor in rheumatic fever, but whether or not they are the only factor involved must remain uncertain for the present.

Perry (1939), studying streptococcal antifibrinolysin in the sera of patients with acute rheumatism, found that 78% showed a marked antifibrinolysin. This is about the same incidence as in normal patients after a streptococcal infection. He found no correlation between the duration or severity of the rheumatic attack and the persistence or occurrence of antifibrinolysin, and concludes that the appearance of antifibrinolysin in the patient's blood is not an essential part of the rheumatic process. Boisvert (1940 and 1941), too, found that the majority of patients with acute rheumatism and chorea showed a high titre of antifibrinolysin, but that in these cases the antifibrinolysin tended to persist for much longer than after uncomplicated streptococcal infection. He suggests that this fact may possibly be of diagnostic value; but, since not every case of rheumatic fever shows antifibrinolysin, its value must be very limited. Lichty (1941) on the other hand found that as many as 28% of the 73 children he studied had typical rheumatic fever without any appreciable increase in antifibrinolysin. The patients could be divided into those with high, intermediate, or low antibody titre, and there was no correlation between these groups and the

clinical state except that possibly the patient with lower antibody level tended to have less severe arthritis and was more apt to have carditis, but this was not definite. These findings are thus in close agreement with Perry's.

There is thus a difference of opinion as to the nature and significance of streptococcal antibodies in acute rheumatism. According to Coburn and Pauli (1939*b*) and Coburn (1940) the marked and maintained streptococcal antibody titre is of great significance. They consider that it is different in degree and duration in rheumatic patients and indicates a subclinical persistence of the streptococcal infection. Coburn suggests that heredity and environment produce an individual who is unable to deal with a streptococcal infection in the normal manner. The result is an inadequate immune response to the primary infection, with a persistence of viable organisms in the tissues. The cells of the reticulo-endothelial system become sensitized and retain antigen within them, the persistent organisms release more antigen into the circulation, and the contact of this with the residual antibody within the reticulo-endothelial cells gives rise to an abnormal reaction. The result is an intense inflammatory reaction with changes in the vascular permeability in the visceral tissues. When wandering cells infiltrate these damaged areas the evolution of the rheumatic lesion is completed. Support for this theory is provided by the description by Coburn and Pauli (1939*a*) of the development of a mutual precipitation between sera from patients in the "silent interval" following a streptococcal pharyngitis, and the same patient a week or ten days later at the height of a rheumatic relapse. They explain this by postulating the presence of an antigen in the serum during the interval, and the development of antibody to this antigen at the time of the relapse. They also show that this reaction is not "patient-specific", that is, that serum from patient A during the silent interval (Coburn, phase II) will react with serum from patient B in an acute attack (Coburn, phase III). (Coburn, Phase I is the acute streptococcal infection.) This work, if repeated and confirmed, may possibly provide the long awaited test for acute rheumatism.

Visceral Lesions.—Rather similar concepts of the nature of the rheumatic lesion have been reached by other workers approaching the subject from different aspects. Rich (1942) and Rich and Gregory (1943*a* and *b*, and 1944) have shown that visceral lesions identical with those of peri- or polyarteritis nodosa may be met with in severe reactions in man and also in experimentally produced serum sickness in animals. They were surprised to find that some of their experimental animals showed changes in the myocardium and heart valves which in their basic characteristics closely resembled those of acute rheumatism.

Relation to Glomerulo-nephritis.—The Caveltis (1945*a*, *b*, and *c*) suggest that human glomerulo-nephritis may be due to the action of auto-antibodies to kidney incited by homologous kidney rendered antigenic by combination with frequent antigens—particularly streptococci and their products. Acting on this assumption they claim to have produced such antibodies by immunization of the animal by combination of streptococci and homologous kidney. Further, it is stated that these antibodies act as a pathogenic agent and produce glomerulo-nephritis in the experimental animal by their reaction with the kidney. The antibodies can be demonstrated *in vitro* in the serum by the collodion particle technique. Turning their attention to rheumatic fever (1945*d*) they suggest that a similar mechanism may explain the carditis—the streptococcus combining in some way with heart muscle to produce an antigen which produces auto-antibodies which react with the heart muscle. They claim to have demonstrated such auto-antibodies to human heart in the sera of 27 out of 36 patients with rheumatic fever. This is clearly a most interesting claim, as, apart from its implications as to the mechanism of rheumatic fever, it might provide a specific test for the disease. However, this work obviously needs careful checking before it can be accepted.

Seegal and Earle (1941) discuss the biological differences between rheumatic fever and glomerulo-nephritis. It is well known that these two diseases frequently follow haemolytic streptococcal infection and yet are rarely seen together. They note that there is much less difference in the incidence of nephritis at different latitudes than in acute rheumatism. Acute nephritis occurs, they claim, twice as often in males as in females. Acute nephritis is apt to occur

after "deep" streptococcal infections complicated by adenitis, otitis media, mastoiditis, etc., while in acute rheumatism the preceding infection is often a superficial and evanescent pharyngitis. The latent period between preceding infection and the development of nephritis is rather shorter than in acute rheumatism (7 to 21 days, compared with 14 to 21 days) and in relapses this is more marked (1 to 4 days compared with 14 to 21 days). Further, relapses in the healed state of acute glomerulo-nephritis are rare, whereas they are very common in acute rheumatism. Theirs is a stimulating and interesting paper, but the statements made need careful corroboration and further study. It is perhaps worth noting that some of Rich and Gregory's animals showed, in addition to peri-arteritis nodosa and carditis, an acute glomerulo-nephritis.

Pathology

Little has been added to the broad picture of the histological characteristics of acute rheumatism. Clawson (1940) has studied 796 post-mortem cases of rheumatic heart disease at Minneapolis. He distinguishes four types or phases of the disease, acute rheumatic endocarditis, recurrent rheumatic endocarditis, valvular deformities, and adherent pericardium. Nearly three-quarters of the cases fell into the third group. His study leads him to conclude that the calcified nodular aortic valve lesion found in males in the fourth decade is rheumatic in origin. In fact he believes that all non-specific aortic valve lesions leading to heart failure are due to acute rheumatism. He (1941) has also attempted to determine the origin of the "Anitschkow" myocyte, the significance of which in the cardiac lesion of acute rheumatism has been so often discussed. He concludes that this cell develops, not from the myocardial muscle fibres, but from the interstitial tissues of the heart. This is often the chief cell to respond in both rheumatic inflammation and experimental inflammation of the heart, but it cannot be regarded as a characteristic cellular response in rheumatic inflammation as it is not found in subcutaneous nodules.

Interesting papers by Aschoff (1939*a* and *b*) reiterate his views on the specificity of the cell formation which is commonly known by his name. He does not consider the fibrinoid change in the ground-substance of the myocardial lesion so stressed by Klinge as being particularly characteristic, but views the granuloma and cell formation as being specific to, and exclusively seen in, acute rheumatism. McKeown (1945) has studied the evolution of the "Aschoff nodule" and describes it as starting as a necrotic lesion of the fibrous tissue, which is soon followed by an acute non-specific inflammatory infiltration; this gives way to a focal aggregation of a peculiar type of histiocyte, and these cells evolve into fibroblasts with the production of collagen, the end result of this being the formation of a scar. She also stresses the widespread distribution of these lesions throughout the cardiovascular system. She suggests that, while the heart is usually the site of maximal damage, all tissues of mesenchymal origin, especially vascular mesenchyme, are liable to be involved in the rheumatic process.

THE RHEUMATIC LUNG.—The question of the "rheumatic lung" has been studied by Epstein and Greenspan (1941), who are convinced that a characteristic series of changes occur in the lung in rheumatic fever. They consider that this series results from damage to the pulmonary capillaries, with consequent alteration in vascular permeability. These successive changes are

oedema and alveolitis followed by a haemorrhagic consolidation; the consolidated alveoli are infiltrated with large mononuclear cells, and hyaline membranes may be seen on the walls of the respiratory bronchioles and alveolar ducts. Finally the lesion heals by organization and fibrosis.

THROMBO-PHLEBITIS AND RHEUMATISM.—Russek and Abbott (1943) have produced further support for the view that thrombo-phlebitis in acute rheumatism is due to a specific rheumatic inflammation of the vein.

PSYCHOSES AND RHEUMATISM.—Bruetsch and Bahr (1939) and Bruetsch (1940) found that 9% of autopsies on cases of dementia praecox showed chronic rheumatic heart disease and changes in the blood vessels of the brain which are regarded as rheumatic in origin. These vascular lesions consisted of a recurrent process of an obliterating endarteritic type. Bruetsch has coined the phrase "chronic rheumatic brain disease" for these changes, and considers that they are clearly distinguishable from cerebral embolism occurring in patients with mitral stenosis. In a series of papers (1942*a* and *b*, and 1944) he discusses a possible causal relationship between acute rheumatism and some types of mental disease. Dublin (1941) has reported two cases with the clinical picture of schizophrenia, in which chronic rheumatic heart disease and vascular lesions in the brain as described by Bruetsch were present. It is clearly important that the real nature of these vascular lesions in the brain should be clarified, and also their relationship to acute rheumatism.

RHEUMATOID ARTHRITIS AND RHEUMATIC FEVER.—Considerable interest had been aroused by the report by Baggenstoss and Rosenberg (1941) that in 14 out of 25 autopsies on patients with rheumatoid arthritis at the Mayo Clinic cardiac lesions were found identical with those of rheumatic fever. This report immediately brought into prominence the question of the similarities between rheumatoid arthritis and rheumatic fever, and the so-called "unity of the rheumatic diseases". Later (Rosenberg and others, 1943 and 1944) the figures from the Mayo Clinic have been increased, and in 30 cases of rheumatoid arthritis 16 have been found to have cardiac lesions indistinguishable from rheumatic carditis. It should be mentioned that 8 of the 30 showed non-rheumatic heart disease, and 11 showed chronic lung diseases such as bronchiectasis. Fingerman and Andrus (1943) studied 61 cases of rheumatoid arthritis at necropsy, and found 19 with rheumatic heart lesions. Bayles (1943) however, found only 6 cases with changes in the heart in 23 cases of rheumatoid arthritis, and considered that the discovery of the two diseases together was merely a coincidence and no indication that the two conditions were causally related. Further, Bennett (1943), in 48 autopsies on rheumatoid arthritis, found 2 cases of bacterial endocarditis and 3 of non-specific myocarditis, but no undoubted example of rheumatic carditis. On the other hand Young and Schwedel (1944) found 25 cases of rheumatic heart disease in post-mortem studies of 38 adults with rheumatoid arthritis. This association is clearly of great interest and needs further study. Some light on its significance may be provided by the report of Hall and Anderson (1943) on the discovery of "rheumatic stigmata" in "non-rheumatic" hearts. In 112 hearts free from valvular lesions as commonly understood, about 90% showed "signs" of rheumatic infection in the form of thickening of mitral or other valve leaflets, shortening of the chordae tendineae, or changes in the myocardium consisting of "Aschoff bodies" (in 33) and "Aschoff-like collections of cells" (in a further 34), and other changes. Positive healed minimal rheumatic infection was diagnosed in 68 (60.7%) and probable healed minimal lesions in 36 (32.1%). This paper clearly raises the whole question of the specificity of such lesions when they are found in such a high proportion of non-rheumatic patients.

The other feature which is often held to denote a similar aetiology and pathology for rheumatoid arthritis and rheumatic fever is the occurrence of subcutaneous nodules in both diseases. By some it has been held that these nodules are histologically similar. However, Bennett and others (1940) have made a careful study of this problem and find that the "nodules of rheumatoid arthritis and rheumatic fever differ as much from one another as do the granulomas of syphilis and tubercle", and point out that this clearly suggests that they may well be due to quite different agents. The main difference noted was that nodules from rheumatoid arthritis contain a large

central area with well-marked necrosis and, in some cases, areas of calcification, whereas the centres of the nodules of rheumatic fever show a marked "fibrinoid" change in the collagen but no necrosis.

Clinical Features

On the clinical side Copeman (1944a) has studied an epidemic of 42 cases of rheumatic fever in an isolated community. Most of the patients had some antecedent illness but this was not always streptococcal. He suggests that the relationship between antecedent infection and acute rheumatism may not be very intimate, and that its main effect is to lower the patient's resistance to the rheumatic infection. From this view-point the frequent finding of an antecedent streptococcal infection might mean no more than the frequent occurrence of streptococcal infections in general. Copeman describes three clinical types. First, the classical acute arthritis moving from joint to joint. It was only in these that carditis was observed (two cases). Secondly, a benign type characterized by an acute febrile myalgia with some, but not marked, joint involvement. Lastly, a type starting acutely, but merging into a chronic "fibrositis" with long persisting painful and tender areas in muscles and ligaments. Not everyone would agree that the last two types were really examples of acute rheumatism, although their occurrence in the isolated epidemic is obviously suggestive.

ABDOMINAL PAIN.—Langmann (1941) and Berger (1945) have both drawn attention to the occurrence of abdominal pain in acute rheumatism. This is no new observation, but is not perhaps as well recognized as it should be. Langmann reports findings in 262 patients with acute rheumatism, 19 of whom were admitted to hospital as suffering from acute appendicitis. In 10 the appendix was removed but the remainder were not operated on. The true diagnosis was made by the development of arthritis and carditis within a few days. In 4 of those operated on the appendix showed non-specific histological changes, and in 1 case it contained oxyuris. The remaining 14 are described as cases of "pseudo-appendicitis". Berger describes 4 patients only 1 of whom was operated on, and in whom a generalized inflammatory peritoneal reaction was found. It is clear that this rheumatic syndrome occurs not infrequently, as pointed out by Davis and Rosin (1944) and by Jones (1944), who found abdominal pain and appendicitis one of the commonest causes of confusion in the early diagnosis of acute rheumatism. Nevertheless, if there is doubt it is wiser to perform a laparotomy, since Langmann has shown that children with acute rheumatism may also develop acute appendicitis.

SUBCUTANEOUS NODULES.—Interest was aroused in 1937 by the claim of Massel and Jones that subcutaneous nodules could be produced in rheumatic patients by the injection of the patient's own blood into subcutaneous tissues, as, for instance, around the elbows. Hart (1939) attempted to repeat these experiments but with no success, despite the fact that several of the patients developed spontaneous nodules while under observation. The significance of rheumatic nodules has been discussed by Hayes and Gibson (1942). They confirm the well-known fact that nodules are frequently symmetrical in their distribution, develop days and weeks after the onset of the rheumatic attack, and last days, weeks, or months, often persisting after other evidence of infection has disappeared. Struthers and Bacal (1942), struck by this last fact, suggest that the occurrence of nodules probably indicates the onset of subsidence of that particular attack and should be regarded as a sign of recovery. They agree, however, that they are usually seen in patients with severe attacks, usually with carditis, and that the ultimate outlook in patients with nodules is grave. Hayes and Gibson found that the mortality was twice as high in patients with nodules as in those without. This, of course, confirms the present view of their grave significance. Urbach and Bleier (1940) have discussed erythema annulare and agree that this is a specific rheumatic manifestation.

ACUTE CARDITIS.—Clinical features of acute carditis in rheumatic patients have been described by Glazebrook and Thomson (1941*a*). They have found that bradycardia is a frequent occurrence in the acute attack in adolescents and young men. Electrocardiograms showed that this bradycardia was a simple sinus bradycardia associated in some cases with a prolongation of the P-R interval. This bradycardia seemed to have some prognostic significance, as half the patients showing it developed permanent cardiac damage, compared with only 30% of those without it. They consider that the findings suggest over-stimulation of the vagal nerve endings by the rheumatic toxin, and that it serves as some index to the degree of toxæmia. Glazebrook and Thomson (1941*b*) also discuss the changing heart murmurs in acute rheumatism and note the early appearance of a presystolic murmur in some cases. In 3 cases it developed within 4, 6, and 9 weeks of the onset of the disease. They also confirm the fact that aortic diastolic murmurs may disappear. Quinlan (1942) has drawn attention to the fact that early acute rheumatic carditis may be responsible for sudden death.

It has long been considered that changes in the P-R interval are a valuable sign of active carditis in acute rheumatism. Heffer (1941) has investigated the electrocardiogram in children with chorea, and finds that it may provide valuable corroborative evidence of involvement of the heart. The main changes he noted were prolongation of the P-R and Q-T intervals. However, Reyersbach and Kuttner (1940), from a study of the A-V conduction in normal and in rheumatic children, have thrown doubt on the significance of this. They found P-R intervals of 0.20 seconds or more in 5.7% of 140 rheumatic children with no demonstrable evidence of active infection. Moreover, spontaneous variations in the P-R interval were observed in both normal and rheumatic children. They conclude that the P-R interval is not in itself a reliable index of myocardial involvement and that the significance of a change in the P-R interval in rheumatic children remains doubtful. Robinson (1945) investigated the effect of atropine on the prolonged A-V conduction time of acute rheumatic fever and of normal "vago-tonics". He found that atropine markedly reduced the conduction time in both, and that it was thus of no value in distinguishing between the two conditions. This provides further evidence for the increased vagal tone in acute rheumatism postulated by Glazebrook and Thomson. Brown and Wasson (1942) have reported the frequent occurrence of chronic sinusitis in rheumatic children, but as this study appears to have been uncontrolled by a similar investigation in non-rheumatic children the significance of their findings is uncertain.

DIAGNOSIS.—Jones (1944) has discussed at some length the diagnosis of rheumatic fever. He points out that it is essential that strict diagnostic criteria should be employed if false diagnoses are to be avoided. A mere arthralgia without joint swelling should be viewed with scepticism unless some other more definite rheumatic manifestation is present. Fever alone he regards as a useless diagnostic sign, and he doubts the value of the administration of salicylates diagnostically. A history of recent haemolytic streptococcal infection, or a history of previous undoubted attacks is of great help in diagnosis.

As has already been mentioned, abdominal pain and "pseudo-appendicitis" occur commonly. Hansen (1943), too, has found such symptoms the commonest cause of confusion. Laboratory findings are of little help. Shapiro (1939) discusses the differential diagnosis of acute rheumatism from non-rheumatic "growing pains". His main points are that "growing pains" tend to occur at the end of the day or during the night and are usually situated in the muscles of the legs, thighs, and arms. On the other hand the pain of acute rheumatism is present all the time but is better in bed and is situated in the joints; and as a rule the joints are slightly swollen, although this may be overlooked by both patient and parent. No evidence of active infection such as raised erythrocyte sedimentation rate or leucocytosis is, of course, found in "growing pains". It is well known that the early pain of acute anterior poliomyelitis may give rise to a mistaken diagnosis of acute rheumatism. However, Poynton (1943), in a paper written shortly before his death, describes the occurrence of an acute painful arthritis occurring either early or late in poliomyelitis. The arthritis was extremely painful at first, and in some cases persisted for weeks or months but occurred only in paralysed limbs. It occurred both in cases receiving skilled treatment and

splinting from the onset, and in those which had received no such treatment. Poynton concluded that the arthritis was probably a manifestation of the virus infection. Kaiser (1943) describes a clinical syndrome of uncertain nature resembling mild rheumatic fever in children. This is characterized by mild fever, muscle and joint pain, fatigue, and irritability. No cardiac involvement has been noted, and the erythrocyte sedimentation rate is normal throughout.

Indications of Activity

A need in the diagnosis of acute rheumatism is a reliable and specific test. Up to date this has not been found, but great help as to the activity of the disease is provided by the non-specific erythrocyte sedimentation rate. It had been hoped that the formol-gel test might give further help in this way, and Green and others (1939) found that it fairly closely paralleled the sedimentation rate and that it was a useful supplement. Klein and others (1941), however, compared the erythrocyte sedimentation rate, the formol-gel test, and the Weltmann coagulation reaction, and found that the formol-gel was the least sensitive and least valuable. Butterworth and Poindexter (1942) have confirmed this and have found that the formol-gel test is essentially a test for hyperglobulinaemia and is of little or no value in the diagnosis of acute rheumatism. As for the Weltmann reaction, Klein and others (1940) claim that it reflects three phases of rheumatic activity, the exudative, the proliferative, and the fibrotic. The reaction may return to normal before the sedimentation rate if the patient is convalescing and in the proliferative stage. Scherlis and Levy (1943) found that in a single observation a normal Weltmann reaction and a normal sedimentation rate was equally accurate in excluding active disease. They found no relationship, however, between a persistently abnormal Weltmann reaction and progressive development of rheumatic heart disease. It would appear that the best single laboratory guide to the activity and progress of a case of acute rheumatism is still the erythrocyte sedimentation rate. This is the conclusion reached by Wasson and others (1941), who suggest that a white blood cell count with special reference to the non-filamented neutrophil count is next in value. They also investigated the capillary resistance, but found marked variations in both active and inactive phases of the disease and at different seasons of the year. Juster (1939) considers that the best method of dividing patients with rheumatic heart disease into groups of varying degrees of activity is by a consideration of the percentage number of abnormal leucocyte counts. This is based on frequent and repeated white blood cell counts. Hubbard and McKee (1939), noting the association of a secondary anaemia with active phases of acute rheumatism, suggest that anaemia may often be an indication of continued activity.

Prognosis

Much follow-up work has been published on the end-results of acute rheumatism, particularly as this affects the heart. Brown and Wolff (1940) have shown that it is not uncommon for patients to recover with no permanent cardiac damage. In their own series this occurred in 50%. Further there was no relationship between the apparent severity of the illness or the number of recurrences and the development of permanent heart disease. Patients showing no evidence of permanent heart changes in the first attack are more likely to escape in subsequent attacks. This is confirmed by Ash (1941*a*), who found that the course also depended on the type of onset. Cases with acute carditis have a poor prognosis, while those with uncomplicated chorea do much better. In her series, 50% had obvious signs of rheumatic heart disease at the end of three years, 7% died by the end of the first year, and 10% by the end of the third year.

De Lee and others (1943) showed that the age of onset of the disease is a very important factor in determining the severity. Of those cases whose first attack of polyarthritis occurred before

O*

the age of 12, 28% recovered with permanent cardiac lesions; but when the age of onset was over 25 only 7% developed persistent heart lesions. Cohn and Lingg (1943), in an exhaustive study, support this finding that when the rheumatic heart disease starts in childhood only 5% survive beyond the age of 45, whereas if the onset is in adolescence 21% live beyond 45. They find that half the patients die within 9 years of the onset. They also find that recurrences are most common during childhood and are most prevalent before puberty rather than during the first 5 years after onset. They confirm that the type of onset is significant prognostically. When the first manifestation of rheumatic fever in childhood is carditis, the chances are three to one that the illness will be "severe". With joint symptoms or chorea and no carditis the chances are three to two that the infection will be "mild". In adult life, whatever the mode of onset, the illness is "mild" in nine out of ten cases. Couper (1943) found that just over half the children with acute arthritis developed cardiac lesions whereas about two-thirds of those with chorea escaped.

Cotton (1942), discussing the outlook in rheumatic carditis, found that the degree of cardiac enlargement was a far better index than the valve deformity of the severity of the infection. Progressive cardiac enlargement must be taken as an important sign of active infection. However, the death rate over 10 years is much higher in children with aortic and mitral lesions than in those with mitral systolic murmurs only. Keith and Brick (1942) and Taussig and Goldenberg (1941) have also studied the question of heart size. They found that cardiac enlargement in rheumatic heart disease is not inevitable and progressive. It does not depend primarily on the valvular lesion but is directly related to the severity and persistence of rheumatic activity. Increase in heart size is a bad, and a decrease in size a good prognostic sign.

Ash (1942), in considering the various signs of carditis in childhood, has drawn attention to the mid-diastolic murmur which is so often heard in the acute attack and which disappears with improvement. She suggests that this may be due in part to the relative inelasticity of the acutely inflamed mitral valve. She confirms the ominous significance of the development of an aortic diastolic murmur. Twenty-nine per cent. of her cases developing this sign in a first attack died, and a further 37% died in subsequent recurrences. Pericardial friction was of even more serious significance, 60% of the patients dying in the illness in which the rub was first heard. However, Massie and Levine (1939) found that although 16.3% of patients with pericarditis died in the acute attack, 36% of those who survived finally recovered with no clinical evidence of organic heart disease.

The importance of recurrences in the maintenance and increase in cardiac lesions has been stressed by Ash (1941*b*). Bland and Jones (1939) also point out that the development of heart disease after apparent recovery from the acute illness is due in the majority of cases to recurrent rheumatic fever and to persistent subclinical rheumatic activity. Console (1942) found that death from rheumatic heart disease tends to occur at two peak periods. The first is in childhood and corresponds with deaths from cardiac failure resulting from active infection; the second peak occurs between the ages of 40 and 60 and is associated with deforming valvular lesions but no evidence of active rheumatic infection.

Walsh and Sprague (1941*b*) have studied the clinical features of heart failure in children with active rheumatic fever. They think that most of the features—puffiness of the face, enlarged tender liver, rapid gain in weight, and oedema—must be due to right ventricular failure. Dyspnoea is rarely a striking feature. In support of this theory of a predominant failure of the right ventricle they describe a shift in the electrical axis in the electrocardiogram, which may disappear with recovery, and the development in a few cases of a well-marked diastolic gallop rhythm along the upper left sternal border. The reason for this disproportionate failure of the right ventricle is obscure.

Treatment

SALICYLATES.—Boas and Ellenberg (1940) state that salicylates are of great value in the treatment of rheumatic pericarditis with effusion. They make no claim that these drugs have any effect on the course of the myocarditis, and they

suggest that the rapid absorption of the pericardial exudate and the control of the fever is analogous to their effect on the arthritis. Coburn (1944) reopened the whole question of the effect of salicylates on rheumatic fever. He claimed that, if given in sufficiently large doses—intravenously if necessary—to maintain a blood plasma level of at least 350 gamma per millilitre, they not only control the fever and arthritis but have a striking effect on the whole course of the disease and considerably reduce the incidence and severity of the carditis. He states that the arthritis and fever may be controlled by smaller doses giving a plasma level of 200 gamma or less. If this is true it is clearly of the greatest importance; however, it should be noted that Coburn's cases were young adults in whom the ultimate prognosis and course of the disease is much less severe than in children, as has already been stressed. Unfortunately these claims have not been substantiated. Wegria and Smull (1945), Murphy (1945), and Keith and Ross (1945) all found that full dosage as recommended by Coburn did not significantly affect the course of the disease when compared with controls receiving inadequate or no salicylate therapy. Murphy observed progression of the disease with drug levels in the plasma above those advised by Coburn.

Not only is the disease not materially affected by the larger doses, but the risk of toxic effects is naturally much higher. Keith and Ross frequently noted nausea and vomiting, and severe hyperpnoea developed in 3 patients. Meyer and Howard (1943) showed that the administration of salicylates in any form consistently produced hypoprothrombinaemia and impaired coagulability of the blood. They suggest that the haemorrhagic manifestation occasionally met with in acute rheumatism may be due to the administration of salicylates. This effect of salicylates can be prevented by the simultaneous administration of vitamin K. Fashena and Walker (1944) describe a fatal case of salicylate poisoning in a negro boy aged 9 years treated with 8 g. of salicylates a day. This lead them to study the toxic effects. They confirmed the hypoprothrombinaemia, and found that quite small doses reduced the alkali reserve of the blood. The hyperpnoea of salicylism they found to be out of all proportion to the bicarbonate deficit, and they suggest that it may be due to central stimulation by the salicyl radicle. They conclude that, in children, in order to achieve the blood levels advocated by Coburn it is necessary to give doses which border on the toxic, and that all cases treated by the large doses should be controlled by frequent blood estimations. Sable (1945) has also studied the toxic effects of salicylates and finds that tolerance to the drug is acquired in most cases so that toxic effects are most marked early in the course. Although finding that the hyperpnoea is probably not due to an acidosis, he recommends the simultaneous administration of sodium bicarbonate whenever large doses of salicylates are given.

Smull and others (1944) studied the effect of the simultaneous administration of sodium bicarbonate with salicylates on the blood level of salicylates. They found that the sodium bicarbonate prevented the establishment of as high a level of serum salicylates as was obtained with the same dose of salicylates without the bicarbonate. The mechanism of this is not clear. The bicarbonate may interfere with the absorption of salicylates, may increase extra-cellular fluid, leading to a decrease of salicylates in the blood, or may increase the renal excretion of salicylates. It has in the past been suggested that the effect of salicylates in acute rheumatism might be due to its alleged inhibiting effect on antibody formation. Perry (1941) was unable to demonstrate any effect on the development of antibodies in response to typhoid inoculation by the administration of acetylsalicylic-acid.

ASCORBIC ACID AND SUCCINATES.—Gubner and Szucs (1945), in a comparative study of different methods of treatment in acute rheumatism, found that the administration of ascorbic acid with salicylates reduced toxic effects more than did the more usual sodium bicarbonate.

They found that a calcium double salt of benzoic acid and succinic acid benzyl ester gave much better results than salicylates. They suggest that in rheumatic fever there is evidence of widespread interference with various constituents involved in tissue oxidation, and that the succinates, as active reducing agents, may prevent the inactivation of respiratory enzymes.

TONSILLECTOMY.—The old discussion on the advantages and disadvantages of tonsillectomy, both as a prophylactic and as a method of treatment, continues. Bach and others (1939) found no evidence that tonsillectomy prevents acute rheumatism, but consider that it influences the severity. They found the incidence of permanent cardiac lesions to be 24·6% in children whose tonsils had not been removed, as compared with 18·9% in tonsillectomized children. Meiks (1940), on the other hand, found that tonsillectomy either before or after the onset did not modify the course of the disease, and points out the established fact that tonsillectomy may be followed immediately by a relapse. (The tonsillectomy wound presumably becomes infected by haemolytic streptococci and has the same effect as a pharyngitis.) He considers that rheumatic heart disease is not in itself an indication for the operation. Ash (1941*a*), too, noted that a conservative attitude towards tonsillectomy had no unfavourable influence on the course of the disease. Watkins (1944) wisely advocates that the tonsils should be judged on their own merits as in a non-rheumatic child, bearing in mind the special danger to the child with a damaged heart (the risk of a rheumatic relapse and of an engrafted bacterial endocarditis).

CHEMOTHERAPY.—The uselessness of sulphonamides in the treatment of acute rheumatism has been confirmed by Hopkins (1941), and penicillin has proved equally disappointing (Foster and others, 1944; Watson and others, 1944). The first observers also showed that the administration of penicillin to patients with haemolytic streptococcal infection does not prevent the subsequent development of rheumatic fever.

It is well known that any operation on the mouth or throat (dental extraction, tonsillectomy, etc.) gives rise to a transient bacteraemia which in a patient with rheumatic heart disease may lead to bacterial endocarditis. Pressman and Bender (1944) have shown that the administration of sulphanilamide, while not preventing the bacteraemia, considerably decreases its duration. They advocate the use of sulphanilamide as a prophylactic in such cases. However, the better measure now would appear to be the administration of penicillin for 24 hours before and after the operation.

PYRIDOXINE HYDROCHLORIDE.—Schwartzman and others (1941) have given a preliminary report on the treatment of chorea with vitamin B₆—pyridoxine hydrochloride. The 3 cases studied showed marked improvement in two or three days.

FEVER THERAPY.—Fever therapy previously used in chorea has been employed by Simmons and Dunn (1939) in rheumatic fever. They claim prompt and complete relief of joint pain in almost all cases. It was not possible to determine the effect on the cardiac lesions, but the period of subclinical activity appeared to be shortened and in no case was the cardiac lesion aggravated by the therapy.

“RHEUMATIC ANTIBODIES.”—Green (1940) has shown that the intradermal injection of joint fluid from patients with acute rheumatic arthritis into a normal individual produces a brisk reaction. This effect can be neutralized in some cases by serum taken from the same patient later in the attack, which would appear to indicate the development in the patient of some “rheumatic” antibodies. Green and others (1940) were thus led to treat a series of patients with “convalescent serum”. Nine of the fifteen cases appeared to be benefited, but it was difficult to assess the results with certainty as the attack was mild in all patients. Two patients showed rather alarming partial collapse within a short period of receiving the serum. The nature of this is uncertain. Rettani (1939) claimed benefit from blood transfusion in patients with persistently active carditis.

XANTHINE DERIVATIVES.—Walsh and Sprague (1941*a*) have discussed the treatment of congestive heart failure in children with active rheumatic fever. They found the xanthine derivatives, especially theobromine calcium salicylate and theobromine sodium acetate, of great value, with digitalis as the second choice.

INSTITUTIONAL TREATMENT.—Many workers have stressed the value of long-stay institutional sanatorium type of treatment for rheumatic heart disease (Hubbard and Griffin, 1940; Weddum

and Weddum, 1944). Stroud and Twaddle (1940) believe "that the available educational facilities, attention to hygiene, adequate medical supervision and the ability to adjust the child physically and emotionally to his handicap are factors to justify such convalescent institutional care. . . ." Taran (1941) finds that such treatment not only minimizes the permanent effect of the rheumatic attack, but also reduces the risk of recurrences after discharge (0.22 per child per year, compared with 0.55 per child per year in control children not given the institutional treatment). He also stresses the marked gain in weight of the children under treatment, which was two or three times that of the controls. Martin (1941), confirming the value of institutional care of these children, draws attention to the need for adequate supervision after discharge. Weddum and Weddum (1942) have attempted to assess the number of beds required in order to provide adequate care of this type, and suggests that in New York one bed for every 550 children between the ages of 7 and 15 would be the minimum. Obviously these needs will vary in different localities according to the incidence of the disease.

Kohen and McEldowney (1944) have stressed the value of special schools for children with more severe cardiac lesions. Of 233 children who attended such a school in Chicago, 56 had died. Of the remainder, only 5 had never worked or were not working at the time of re-examination. Bland (1941) and Ebert (1941) have tried an experiment by which rheumatic children were treated at home under close medical and social supervision. In cases where the home conditions were very unsuitable foster homes were found for some of the children. This has the obvious advantage of maintaining the child's home life, to the child's greater contentment and the development through education and encouragement of the family's and the patient's confidence and competence in handling the problem of chronic illness. The authors state that the end results showed no difference when compared with similar children treated in hospital (at the Home of the Good Samaritan). This is a most interesting and stimulating study.

Rutstein (1944) has drawn attention to the need for, and value of, the cardiac clinic as the centre round which any programme for the care and management of acute rheumatism should be built. An extremely valuable and interesting report on the care of rheumatic children was published in 1944 jointly by the Cardiac Society of Great Britain and Ireland and the British Paediatric Association (*Archives of Disease in Childhood*, 1944, 19, 96). In this report the need for clinics to act as the centre for any organization for the care of children with acute rheumatism is stressed. These clinics should act as sorting and diagnostic centres, and should provide supervision and follow-up facilities for all affected children. Linked to the centre should be a hospital school for long-stay treatment of all children with manifestations of active disease. On account of the importance of early diagnosis and treatment it is suggested that acute rheumatism, chorea, and rheumatic heart disease under the age of sixteen should be compulsorily notifiable.

Prevention

The prevention of acute rheumatism is clearly a most important problem; and the fact that children once they have had an attack are very liable to a recurrence makes it possible to study the effect of different measures in reducing the incidence of such relapses.

VITAMIN PROPHYLAXIS.—Kuttner (1944) administered large doses of vitamins A, B, C, and D to a group of rheumatic children and compared them with an equal group of untreated controls. There was no evidence to suggest that the administration of the vitamins reduced the incidence either of upper respiratory infections or of acute rheumatism.

ACETYSALICYLIC ACID.—Coburn and Moore (1942) attempted to prevent the development of rheumatic relapses following haemolytic streptococcal pharyngitis by the administration of 4 to 6 g. of acetylsalicylic acid daily for four weeks after the pharyngitis. Of 47 treated patients 1 only developed a rheumatic relapse and there was some doubt as to whether the prophylaxis had been carried out properly in this case. On the other hand 57 of 139 untreated control cases

developed rheumatic fever. This experiment would appear to support strongly the claim previously put forward by Schlesinger and others for this form of prophylaxis.

IMMUNIZATION BY STREPTOCOCCAL TOXIN.—Acting on the assumption that rheumatic fever is due to an abnormal reaction to the haemolytic streptococcus, Wasson and Brown (1940 and 1942) have attempted to prevent recurrences by “immunizing” rheumatic children with haemolytic streptococcal toxin. (They used a filtrate of NY5 strain streptococcus.) For the 1939–40 and 1940–41 periods they report relapse rates of 12% and 4·7% in treated cases, compared with 40·2% and 33% in untreated controls. It should be noted that the average age of the treated children was over three years older than that of the controls. This in itself would considerably reduce the risk of relapses. In 1943 they reported that better results were obtained by using a tannic acid precipitated toxin of the same strain (NY5) streptococcus. In 1941–42, using this technique, the relapse rate was 2 out of 31 treated compared with 6 out of 29 untreated. In these groups the average age was more nearly the same. Wasson and Brown found no ill effects from the treatment.

PROPHYLACTIC CHEMOTHERAPY.—Considerable interest was aroused by the report by Thomas and France (1939) that the continuous administration of sulphanilamide to rheumatic children prevented their developing haemolytic streptococcal infections and relapses of acute rheumatism. None of 30 patients treated had a major rheumatic attack, whereas 4 of the 30 controls developed severe attacks, and one of them two. This was quickly followed by a similar report by Coburn and Moore (1939), who also showed that the treatment of haemolytic streptococcal infections with sulphanilamide does not prevent subsequent rheumatic relapses, a fact confirmed by Glazebrook and Thomson (1942). In later reports Coburn and Moore (1940 and 1941) describe 100 children who received prophylactic sulphanilamide during 1936–9 and were given no treatment during 1939–40. While under treatment none had a streptococcal pharyngitis, and no rheumatic relapse occurred. In the twelve months without treatment 32 contracted streptococcal upper respiratory infections, and of these 40% developed rheumatic fever.

It soon became clear that, as might have been expected, the prolonged administration of sulphonilamide was not without dangers. Fortunately most of the toxic effects noted were mild—mainly rashes—but Stowell and Button (1941) reported a death from agranulocytosis and stated that in their opinion “sulphanilamide can be a lethal drug when used prophylactically in rheumatic patients”. At the present state of our knowledge the drug should not be used in ambulatory rheumatic children and adolescents. However, Thomas, and others (1941) published a further series in which they found toxic reactions few and slight. No rheumatic relapses occurred amongst 55 patients between 1936–40 during 79 person-seasons, but fifteen major attacks of rheumatic fever were seen in 67 untreated patients during the same time (150 person-seasons). Hansen and others (1942) gave a similarly encouraging report, and Thomas (1942), reviewing her own work and the other studies reported, advocates this form of prophylaxis and suggests that the drug should be taken all the year round for four or five years instead of only during the “rheumatic season” each year.

Enthusiastic reports of the success of sulphanilamide prophylaxis of rheumatic relapses continued to appear (Chandler and Taussig, 1943; Kuttner, 1943; Kuttner and Reyersbach, 1943; Messeloff and Robbins, 1943; Dodge and others, 1944; Feldt, 1944; Pennoyer and Hansen, 1944; Thomas, 1944). There is no doubt that sulphonamide will materially reduce the incidence of haemolytic streptococcal infections, especially in epidemics in semi-closed communities (Holbrook, 1944). Fullerton (1945) reports that in the United States Navy the administration of sulphadiazine to all personnel in doses of 0·5 g., twice daily, reduced the incidence of haemolytic streptococcal infection by 85%, only 1 case of acute rheumatism occurring for every 14 in untreated controls.

The striking thing to an English reader about all these reports from the United States is the very high incidence of rheumatic relapses met with each year in the untreated control groups. Thus in Dodge and others' controls observed for 138 patient-seasons there were nineteen serious recurrences with two deaths and seven more probable mild relapses. Wilson and Lubschez

(1944) made a large statistical analysis of the risk of rheumatic recurrences in relation to age and time since the last attack in 499 individuals studied for a total of 5,677 person-years. They found that the over-all risk for a major recurrence was 25% for all patients between the ages of 4 and 13 years, 8.6% between the ages of 14 and 16 years, and 3.7% for patients between the ages of 17 and 25 years. The risk was two or three times greater in the year immediately following an attack than after one or two years of freedom from rheumatic activity. Further, there was no significant difference in the recurrence rate between those living under relatively favourable and unfavourable environmental conditions. In fact, the only factors found to influence the risk of future recurrence were age and interval of time elapsing since the last attack. On the basis of these findings Wilson and Lubschez seriously criticize most of the published work on sulphonamide prophylaxis and state that the control groups did not meet the basic requirements for a proper statistical analysis. They consider that final judgement on the value of this form of prophylaxis must be deferred. Up to date most of the reports have come from America, but Anderson (1945) has issued a preliminary report from Australia. One doubtful relapse occurred in 160 children taking the drug, and thirty definite attacks of acute rheumatism occurred in 100 children who did not attend the clinic during the same six months. However, there was a bias in the selection of the treated patients since these were chosen partly because it was thought they would attend regularly. In Great Britain a similar experiment has been organized, but the results have not yet been published. Further work on this will obviously be awaited with interest.

Conclusion

From this review it will be seen that despite the war a considerable amount of work has been done on the urgent problem of acute rheumatism. Much has been learnt, but the real cause of the disease has still to be determined.

BIBLIOGRAPHY

- Anderson, S. G. (1945). *Med. J. Austral.*, 1, 635.
 Aschoff, L. (1939a). *Arch. Kinderheilk.*, 116, 145.
 — (1939b). *Annals of the Rheumatic Diseases*, 1, 161.
 Ash, R. (1941a). *Amer. Heart J.* 22, 439.
 — (1941b). *Pennsylvania Med. J.*, 44, 484.
 — (1942). *Amer. J. Dis. Child.*, 63, 1.
 Bach, F., Hill, N. G., Preston, T. W., and Thornton, C. E. (1939). *Annals of the Rheumatic Diseases*, 1, 210.
 Baggenstoss, A. H., and Rosenberg, E. F. (1941). *Arch. intern. Med.*, 67, 241.
 Bayles, T. B. (1943). *Ann. intern. Med.*, 19, 113.
 Bazan, F., and Maggi, R. (1939). *Arch. Argent. Pediat.*, 12, 376.
 Bennett, G. A. (1943). *Ann. intern. Med.*, 19, 111.
 —, Zeller, J. W., and Bauer, W. (1940). *Arch. Pathol.*, 30, 70.
 Berger, H. (1945). *Ann. intern. med.*, 22, 97.
 Bland, E. F., and Jones, T. D. (1939). *J. Amer. med. Ass.*, 113, 1380.
 — (1941). *New Engl. J. Med.*, 224, 629.
 Boas, E. P., and Ellenberg, M. (1940). *J. Amer. med. Ass.*, 115, 345.
 Boisvert, P. L. (1940). *J. clin. Invest.*, 19, 65.
 — (1941). *J. Pediat.*, 18, 357.
 —, Dawson, M. H., Schwenker, F. F., and Trask, J. D. (1943). *Ann. intern. Med.*, 19, 107.
 Brown, E. E., and Wasson, V. P. (1941). *J. Pediat.*, 18, 328.
 — (1942). *Arch. Pediat.*, 59, 735.
 Brown, M. G. and Wolff, L. (1940). *New Engl. J. Med.*, 223, 242.
 Bruetsch, W. L. (1940). *Amer. J. Psych.*, 97, 276.
 — (1942a). *Ibid.*, 98, 727.
 — (1942b). *Trans. Amer. Neurol. Ass.*, 68, 17.
 — (1944). *Arch. intern. Med.*, 73, 472.
 —, and Bahr, M. A. (1939). *J. Indiana. med. Ass.*, 32, 445.
 Bunim, J. J., and McEwen, C. (1940). *J. clin. Invest.*, 19, 75.
 Butterworth, J. S., and Poindexter, C. A. (1942). *Amer. J. med. Sci.*, 203, 278.
 Cahan, J. M. (1941). *Pennsylvania med. J.*, 44, 481.
 Cardiac Society and British Paediatric Association (1944). "The Care of Rheumatic Children." *Brit. Heart J.*, 6, 99.
 Carrillo, E. G. (1942). *Amer. Heart J.*, 23, 171; *Arch. Dis. Childh.*, 19, 96.
 Cavelti, P. A. and E. S. (1945a). *Arch. Pathol.*, 39, 148.
 — (1945b). *Ibid.*, 40, 158.
 — (1945c). *Ibid.*, 40, 163.
 — (1945d). *Proc. Soc. exp. Biol., N.Y.*, 60, 379.
 Cecil, R. L. (1940). *Minnesota Med.*, 23, 533.
 Chandler, C. A., and Taussig, H. B. (1943). *Johns Hopk. Hosp. Bull.*, 72, 42.
 Chavez, I. (1942). *Amer. Heart J.*, 24, 88.
 Clawson, B. J. (1940). *Ibid.*, 20, 454.
 — (1941). *Arch. Pathol.*, 32, 760.

- Coburn, A. F. (1940). *Trans. Stud. Coll. Phys., Philadelphia*, 8, 91.
 — (1944). *Canad. med. Ass. J.*, 51, 366.
 —, and Moore, L. V. (1939). *J. clin. Invest.*, 18, 147.
 —, — (1940). *Med. Clin. N. America*, 24, 633.
 —, — (1941). *J. Amer. med. Ass.*, 117, 176.
 —, — (1942). *J. Pediat.*, 21, 180.
 —, — (1943). *Amer. J. Dis. Child.*, 65, 744.
 —, and Pauli, R. H. (1939a). *J. exp. Med.*, 69, 143.
 —, — (1939b). *J. clin. Invest.*, 18, 141.
 Cohn, A. E., and Lings, C. (1943). *J. Amer. Med. Ass.*, 121, 1.
 Collis, W. R. F. (1939). *Lancet*, 2, 817.
 Console, A. D. (1942). *Arch. intern. Med.*, 69, 551.
 Copeman, W. S. C. (1944a). *Annals of the Rheumatic Diseases*, 4, 11.
 — (1944b). *Ibid.*, 4, 37.
 Cossio, P. (1943). *Amer. Heart J.*, 25, 145.
 Cotton, T. F. (1942). *Brit. med. J.*, 2, 473.
 Couper, E. C. R. (1943). *Arch. Dis. Childh.*, 18, 88.
 Daniel, G. H. (1942). *J. roy. Statist. Soc.*, 105, 197.
 — (1943). *Bristol med.-chir. J.*, 60, 13.
 Davis, D. B., and Rosin, S. (1944). *J. Pediat.*, 24, 502.
 De Lise, E. M., Dodge, K. G., and McEwen, C. (1943). *Amer. Heart J.*, 26, 681.
 Ditkowsky, S. P., Stevenson, E., and Campbell, J. M. (1943). *J. Amer. med. Ass.*, 121, 991.
 Dodge, K. G., Baldwin, J. S., and Mortimer, W. W. (1944). *J. Pediat.*, 24, 483.
 Dublin, W. B. (1941). *Dis. Nerv. System*, 2, 390.
 Eagles, G. H., and Bradley, W. H. (1939). *Quart. J. Med.*, 32, 173.
 Ebert, V. B. (1941). *New Engl. J. Med.*, 224, 634.
 Epstein, E. Z., and Greenspan, E. B. (1941). *Arch. intern. Med.*, 68, 1064.
 —, N., and McDonald, F. C. (1940). *New Engl. J. Med.*, 222, 943.
 Fashena, G. J., and Walker, J. N. (1944). *Amer. J. Dis. Childh.*, 68, 369.
 Feldt, R. H., (1944). *Amer. J. med. Sci.*, 207, 483.
 Fernando, P. B. (1939). *Quart. J. Med.*, 32, 261.
 Fingerman, D. L., and Andrus, F. C. (1943). *Annals of the Rheumatic Diseases*, 3, 168.
 Foster, F. P., McEachern, G. C., Miller, J. H., Ball, F. E., Higley, C. S., and Warren, H. A. (1944). *J. Amer. med. Ass.*, 126, 281.
 Fullerton, C. W. (1945). *Canad. med. Ass. J.*, 52, 559.
 Gauld, R. L., Ciocco, A., and Read, F. E. M. (1939). *J. clin. Invest.*, 18, 213.
 —, and Read, F. E. M. (1940a). *Ibid.*, 19, 393.
 —, — (1940b). *Ibid.*, 19, 729.
 Glazebrook, A. J., and Thomson, S. (1941a). *Edinb. med. J.*, 48, 619.
 —, — (1941b). *Ibid.*, 48, 674.
 —, — (1942). *J. Hyg., Camb.*, 42, 20.
 Glover, J. A. (1943). *Lancet*, 2, 51.
 Green, C. A. (1939). *Annals of the Rheumatic Diseases*, 1, 86.
 — (1940). *Proc. roy. Soc. Med.*, 33, 421.
 — (1941). *J. Path. Bact.*, 53, 223.
 — (1942). *J. Hyg. Camb.*, 43, 365, 371, and 380.
 —, Thomson, S., and Glazebrook, A. J. (1939). *Annals of the Rheumatic Diseases*, 1, 180.
 —, Glazebrook, A. J., Thomson, S., and Hopkins, W. A. (1940). *Proc. roy. Soc. Med.*, 33, 275.
 Gubner, R., and Szucs, M. (1945). *New Engl. J. Med.*, 233, 652.
 Hall, E. M., and Anderson, L. R. (1943). *Amer. Heart J.*, 25, 64.
 Hansen, A. E. (1943). *J. Amer. med. Ass.*, 121, 988.
 —, Platou, R. V., and Dwan, P. F. (1942). *Amer. J. Dis. Childh.*, 64, 963.
 Hart, F. D. (1939). *Annals of the Rheumatic Diseases*, 1, 196.
 Hayes, R. M., and Gibson, S. (1942). *J. Amer. med. Ass.*, 119, 554.
 Hedley, O. F. (1939). *Publ. Hlth. Rep., Wash.*, 54, 2271.
 — (1940). *Ibid.*, 55, 1599, 1647, 1809, and 1845.
 Heffer, E. T. (1941). *J. Pediat.*, 18, 363.
 Holbrook, W. P. (1944). *J. Amer. med. Ass.*, 126, 84.
 Hopkins, W. A. (1941). *Annals of the Rheumatic Diseases*, 2, 233.
 Hubbard, J. P., and Griffin, W. A. (1940). *New Engl. J. Med.*, 223, 968.
 —, and McKee, M. H. (1939). *J. Pediat.*, 14, 66.
 Hubble, D. (1943). *Brit. med. J.*, 1, 121.
 Jones, T. D. (1939). *J. Pediat.*, 15, 772.
 — (1944). *J. Amer. med. Ass.*, 126, 481.
 —, and Mote, J. R. (1939). *Ibid.*, 113, 898.
 Juster, I. R. (1939). *Amer. Heart J.*, 17, 669.
 — (1942). *Ann. intern. Med.*, 16, 1137.
 Kaiser, A. D. (1943). *N. Y. St. J. Med.*, 43, 1937.
 Keith, J. D., and Brick, M. (1942). *Amer. Heart J.*, 24, 289.
 —, and Ross, A. (1945). *Canad. med. Ass. J.*, 52, 554.
 Klein, R. I., Levinson, S. A., and Rosenblum, P. (1940). *Amer. J. Dis. Childh.*, 59, 48.
 —, Levinson, S. A., and Stulik, C. K. (1941). *J. Pediat.*, 18, 337.
 Kohen, K. H., and McEldowney, R. P. (1944). *Amer. Heart J.*, 28, 491.
 Kuttner, A. G. (1943). *N. Y. St. J. Med.*, 43, 1941.
 — (1944). *J. clin. Invest.*, 19, 809.
 —, and Krumwiede, E. (1941). *Ibid.*, 20, 273.
 —, and Reyersbach, G. (1943). *Ibid.*, 22, 77.
 Kutumbiah, P. (1941). *Indian J. Paediat.*, 8, 204.
 Langmann, A. G. (1941). *J. Pediat.*, 18, 599.
 Lichty, J. A. (1941). *Amer. J. Dis. Childh.*, 62, 92.
 McKeown, F. (1945). *Ulster med. J.*, 14, 97.
 MacNeale, W. J., Blevins, A., Slavkin, A. E., and Scanlon, H. (1945). *Science*, 101, 415.
 Martin, A. T. (1941). *J. Amer. med. Ass.*, 117, 1663.
 Massel, B. F., and Jones, T. D. (1944). *Amer. Heart J.*, 27, 575.
 Massie, E., and Levine, S. A. (1939). *J. Amer. med. Ass.*, 112, 1219.
 Meiks, L. T. (1940). *J. Indiana med. Ass.*, 33, 666.
 Messeloff, C. R., and Robbins, M. H. (1943). *J. Lab. clin. Med.*, 28, 1323.

- Meyer, O. O., and Howard, B. (1943). *Proc. Soc. exp. Biol.*, N.Y., 53, 239.
- Mote, J. R., and Jones, T. D. (1941). *J. Immunol.*, 41, 35.
- Morris, J. N., and Titmuss, R. M. (1942). *Lancet*, 2, 59.
- Murphy, G. E. (1945). *Johns Hopk. Hosp. Bull.*, 77, 1.
- Peete, D. C. (1944). *Ann. intern. Med.*, 21, 44.
- Pennoyer, M. M., and Hansen, A. E. (1944). *Journal—Lancet*, 64, 139.
- Perry, C. B. (1939). *Arch. Dis Childh.*, 14, 32.
- (1941). *J. Path. Bact.*, 53, 291.
- Pestana, A. V. (1940). *Brit. med. J.*, 1, 589.
- Pickles, W. N. (1943). *Lancet*, 2, 241.
- Poynton, F. J. (1943). *Ibid.*, 2, 433.
- Pressman, R. S., and Bender, I. B. (1944). *Arch. intern. Med.*, 74, 346.
- Quinlan, J. T. (1942). *Brit. med. J.*, 2, 695.
- Rantz, L. A., Boisvert, P. J., and Spink, W. W. (1945). *Arch. intern. Med.*, 76, 131.
- Rauh, L. W. (1939). *Amer. Heart J.*, 18, 705.
- Rettani, G. (1939). *Gazz. Osped. Clin.*, 60, 803.
- Reyersbach, G., and Kuttner, A. G. (1940). *Amer. Heart J.*, 20, 573.
- , Lenert, T. F., and Kuttner, A. G. (1941). *J. clin. Invest.*, 20, 289.
- Rich, A. R. (1942). *Johns Hopk. Hosp. Bull.*, 71, 123.
- , and Gregory, J. E. (1943a). *Ibid.*, 72, 65.
- , — (1943b). *Ibid.*, 73, 239.
- , — (1944). *Ibid.*, 75, 115.
- Rinehart, J. F. (1943). *Annals of the Rheumatic Diseases*, 3, 154.
- Robinson, R. W. (1945). *Amer. Heart J.*, 29, 378.
- Rosenberg, E. F., Baggenstoss, A. H., and Hench, P. S. (1943). *Ann. intern. Med.*, 19, 114.
- , — (1944). *Ibid.*, 20, 903.
- Rosenblum, A. and R. L. (1942). *Amer. Heart J.*, 23, 71.
- Russek, H. I., and Abbott, G. A. (1943). *Ibid.*, 26, 542.
- Rutstein, D. D. (1944). *J. Amer. med. Ass.*, 126, 484.
- Sabin, A. B., and Johnson, B. (1940). *Proc. Soc. exp. Biol.*, N.Y., 44, 565.
- Sable, H. Z. (1945). *Canad. med. Ass. J.*, 52, 153.
- Sampson, J. J., Hahman, P. T., Halverson, W. L., and Shearer, M. C. (1945). *Amer. Heart J.*, 29, 178.
- Scherlis, S., and Levy, D. S. (1943). *Ibid.*, 26, 355.
- Schlesinger, B., Signy, A. G., Ames, C. R., and Barnard, J. E. (1935). *Lancet*, 1, 1145.
- Schultz, M. P. (1939a). *Publ. Health Rep., Wash.*, 54, 264.
- (1939b). *Ibid.*, 54, 305.
- , and Rose, E. J. (1939). *Ibid.*, 54, 343.
- Schwartzman, J., Dragutsky, D., and Rook, G. (1941). *J. Paediat.*, 19, 201.
- Seegal, D., and Earle, D. P. (1941). *Amer. J. med. Sci.*, 201, 528.
- Shank, R. E., Coburn, A. F., Moore, L. V., and Hoagland, C. L. (1944). *J. clin. Invest.*, 23, 289.
- Shapiro, M. J. (1939). *J. Pediat.*, 14, 315.
- Simmons, E. E., and Dunn, F. L. (1939). *Arch. Phys. Therap.*, 20, 547.
- Smull, K., Wegria, R., and Leland, J. (1944). *J. Amer. med. Ass.*, 125, 1173.
- Sorel, F. P. J. (1939). *Bull. off. Internat. d'hyg. pub.*, 31, 617.
- Stott, H. (1939). *Ibid.*, 31, 623.
- Stowell, D. D., and Button, W. H. (1941). *J. Amer. med. Ass.*, 117, 2164.
- Stroud, W. D., and Twaddle, P. H. (1940). *Ibid.*, 114, 629.
- Struthers, R. R., and Bacal, H. L. (1942). *Canad. med. Ass. J.*, 46, 376.
- Suarez, R. M. (1945). *Amer. Heart J.*, 29, 339.
- Swift, H. F., and Brown, T. M. (1939). *Science*, 89, 271.
- Taran, L. M. (1941). *J. Pediat.*, 18, 737.
- , Jablon, J. M., and Weyr, H. N. (1944). *J. Immunol.*, 49, 209.
- Taussig, H. B., and Goldenberg, M. (1941). *Amer. Heart J.*, 21, 440.
- "The Care of Rheumatic Children." (1944). *Brit. Heart J.*, 6, 99.
- Thomas, C. B. (1942). *Bull. N.Y. Acad. Med.*, 18, 508.
- (1944). *J. Amer. med. Ass.*, 126, 490.
- , and France, R. (1939). *Johns Hopk. Hosp. Bull.*, 64, 67.
- , —, and Reichsman, F. (1941). *J. Amer. med. Ass.*, 116, 551.
- Thomson, S., and Glazebrook, A. J. (1941). *J. Hyg. Camb.*, 41, 570.
- , and Innes, J. (1940). *Brit. med. J.*, 2, 733.
- Todd, E. W., Coburn, A. F., and Hill, A. B. (1939). *Lancet*, 2, 1213.
- Urbach, E., and Bleier, A. (1940). *Arch. Derm. Syph., Chicago*, 41, 515.
- Walsh, B. J., and Sprague, H. B. (1941a). *J. Amer. med. Ass.*, 116, 560.
- (1941b). *Amer. J. Dis. Child.*, 61, 1003.
- Wasson, V. P., and Brown, E. E. (1940). *Amer. Heart J.*, 20, 1.
- (1942). *Ibid.*, 23, 291.
- (1943). *J. Pediat.*, 23, 24.
- , and Weintraub, C. (1941). *Amer. Heart J.*, 22, 342.
- Watkins, A. G. (1944). *Practitioner*, 153, 161.
- Watson, R. F., Rothbard, S., and Swift, H. F. (1944). *J. Amer. med. Ass.*, 126, 274.
- (1945). *Ibid.*, 128, 1145.
- Weddum, A. G. and B. G. (1942). *Amer. J. publ. Hlth.*, 32, 1237.
- (1944a). *Amer. J. Dis. Child.*, 67, 182.
- (1944b). *Amer. J. publ. Hlth.*, 34, 1065.
- Wegria, R., and Smull, K. (1945). *J. Amer. med. Ass.*, 129, 485.
- Weiss, M. M. (1941). *Amer. Heart J.*, 22, 112.
- Wilson, M. G. (1944). *J. Amer. med. Ass.*, 124, 1188.
- , Ingerman, E., Dubois, R. O., and Spock, B. McL. (1935). *J. clin. Invest.*, 14, 325.
- , and Lubschez, R. (1944). *J. Amer. med. Ass.*, 126, 477.
- , M. G. Schweitzer, M. D., and Lubschez, R. (1943). *J. Pediat.*, 22, 468.
- Young, D., and Schwedel, J. B. (1944). *Amer. Heart J.*, 28, 1.

The following general reviews have also been published during the period 1939-45 :

- Clarke, P. J. H. (1940). *Irish J. med. Sci.*, p. 97.
- Miller, R. (1942). *Lancet*, 2, 563.
- Parkinson, J. (1945). *Ibid.*, 2, 657.
- Ritchie, W. T. (1939). *Ibid.*, 2, 582.