

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No. 342

PREVENTION OF RHEUMATIC FEVER

Report of a WHO Expert Committee

CORRIGENDUM

Page 12, fourth line from bottom ;

Page 15, section 6.2.1, lines 15 and 17 ; and

Page 27, Annex 2 and Annex 3, second column of tables

delete dibenzyl penicillin

insert benzathine penicillin G

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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PREVENTION OF RHEUMATIC FEVER

Report of a WHO Expert Committee

WORLD HEALTH ORGANIZATION
GENEVA

1966

**WHO EXPERT COMMITTEE
ON THE PREVENTION OF RHEUMATIC FEVER**

Geneva, 26 April - 2 May 1966

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PREVENTION OF RHEUMATIC FEVER

Report of a WHO Expert Committee

A WHO Expert Committee on the Prevention of Rheumatic Fever met in Geneva from 26 April to 2 May 1966. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General. Professor D. D. Rutstein was elected Chairman; Professor P. Mozziconacci, Vice-Chairman; and Professor E. G. L. Bywaters, Rapporteur.

1. INTRODUCTION

The first WHO Expert Committee on Rheumatic Diseases pointed out that "... there appears to be a possibility that rheumatic fever, a disease in which infection with haemolytic streptococci is believed, on good evidence, to be an important initial factor, can be controlled and perhaps prevented by the use of antibiotics and of sulfonamide drugs. This possibility, if eventually substantiated, will offer an opportunity for preventive action on a world-wide scale, which cannot fail to be a major concern of WHO."¹

Some estimates of mortality, prevalence and incidence rates for rheumatic fever and rheumatic heart disease were given in the report of a second expert committee,² which also reviewed preventive methods of controlling rheumatic fever and made practical recommendations for their further application.

The present Committee was convened to consider what further recommendations on the prevention of rheumatic fever and rheumatic heart disease were justified by the advances in knowledge and practice that had taken place in the 10 years since the last Committee met. Particular attention was given to the changes in the pattern of rheumatic fever and rheumatic heart disease that are occurring in the economically developed countries and to the emergence of what appears to be a serious amount of rheumatic fever and rheumatic heart disease in the developing areas,

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1954, **78**, 17.

² *Wld Hlth Org. techn. Rep. Ser.*, 1957, **126**.

together with practical considerations of preventive methods and organizational techniques applicable to these problems.

Definitions

The term "rheumatic fever" is used in this report to describe the disease that is one sequel of Group A streptococcal infection and that may have one or more of the following major manifestations: acute migratory polyarthritis, carditis, chorea, subcutaneous nodules and erythema marginatum (see Annex 1). The patient is liable to recurrences due to streptococcal infection, and these may further damage the heart.

The term "chronic rheumatic heart disease" as used in this report refers to that form of heart disease which may develop as a sequel to attacks of rheumatic fever but may also occur without a history of such an attack. In general, it is characterized by the occurrence of disease of the valves, particularly of the mitral and less commonly of the aortic valve, usually associated with involvement of the myocardium.

2. EPIDEMIOLOGICAL ASPECTS OF STREPTOCOCCAL INFECTIONS

Group A streptococci are widely distributed in the general population: estimates of carrier rates in childhood sample populations have varied from 5% to 30%. Overt infections occur in all persons from time to time, but rather infrequently—perhaps once in 2 years or once in 5 years, according to age and response. The frequency of subclinical infection is unknown. Although there is unanimous agreement that rheumatic fever is one of the sequelae of Group A streptococcal infection, it is comparatively uncommon. It is not associated, as is glomerulonephritis, with specific streptococcal types, but can be caused by any type. It is probable, therefore, that there are host factors affecting susceptibility about which comparatively little is yet known and even less can be done at the present time.

The frequency with which rheumatic fever follows Group A infections is known to be about 3% in some epidemics in closed military communities. Considerably higher rates were noted in closed communities of convalescent rheumatic fever patients in the days before prophylactic measures were introduced. The frequency seems, however, to be much lower (0.1-0.3%) following sporadic infection in the general population. These variations in the attack rate have been attributed by some to a bacterial factor determining "virulence". Further investigations relating the level of rheumatic fever in a community to virulence and to the

extent of streptococcal infection are needed, as the very striking spontaneous decrease in rheumatic fever in some countries since the turn of the century may well be related to changes in such factors.

3. RHEUMATIC FEVER IN DEVELOPED AND DEVELOPING COUNTRIES

Despite the lack of exact statistics on the incidence and prevalence of rheumatic fever for large areas, the decrease in rheumatic fever in developed countries, noted in the second report of the WHO Expert Committee on Rheumatic Diseases,¹ appears to be continuing. This decrease is evidenced by figures for notification of rheumatic fever in schoolchildren and in the general population of certain developed countries, by mortality figures in the younger age groups, by figures derived from post-mortem examinations of the younger age group population (5-14 years), as well as by the highly dramatic decrease in requests for hospital admission for this acute disease, although this may be due, in part, to other causes. This trend is not of recent origin and has been in progress at least since the beginning of the century in some developed countries. On the other hand, the amount of rheumatic heart disease in those countries assessed by similar rather inexact methods has decreased only to a limited extent and thus still remains an important cause of morbidity and mortality.

In developing countries, estimates of the amount of rheumatic fever and of rheumatic heart disease are more difficult to make. With the increase in health facilities, it is becoming evident that in some of these countries both rheumatic fever and rheumatic heart disease are present to a very serious extent. Streptococcal infection in impetigo, chronic leg ulcers and other skin lesions is of frequent occurrence. Information is needed on the role these infections play in the development of rheumatic fever and on the extent to which they are responsible for the frequency of high anti-streptolysin O titres reported from these areas.

Further work is needed to define the size and nature of the rheumatic fever and rheumatic heart disease problem by standardized methods and thence the size and nature of the prevention problem, particularly in the developing countries. While population surveys provide adequate answers, other types of planned assessment, such as multipurpose serological surveys, might provide useful information at a fraction of their cost. Recommendations for further work on this aspect of rheumatic heart disease and its prevention are detailed in section 8 of this report.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1957, 126.

4. SOCIO-ECONOMIC ASPECTS OF RHEUMATIC FEVER

Rheumatic fever and its consequences have long been known to be associated with poor living conditions, in particular with overcrowding and poor housing, which favour the spread of streptococcal infection. In many economically developed countries, the decreasing death rate from rheumatic heart disease has paralleled, over several decades, the improvement in standards of living.

Since it produces crippling heart disease from a young age, rheumatic fever has considerable social and economic consequences, particularly for those countries where it is widespread. On the other hand, of the major cardiovascular diseases, rheumatic heart disease is the one most amenable to preventive measures. These include methods of controlling the spread of streptococcal infections (such as reduction of overcrowding in houses, schools and places of popular assembly), general hygienic measures (such as improvement of washing facilities), health education, and the provision of adequate medical care facilities.

Governments and health authorities should therefore examine the importance of rheumatic fever in their own communities and take steps, such as those outlined in this report, to diminish its impact. Knowledge concerning the nature of rheumatic fever and the available services for prevention and control should be widely disseminated, both to the medical profession and the general public.

5. DIAGNOSTIC CRITERIA

5.1 Criteria for the diagnosis of rheumatic fever

There is unfortunately no single diagnostic symptom, sign or test to establish the diagnosis of rheumatic fever. Nevertheless, before submitting a patient to a prolonged period of treatment to prevent crippling sequelae, it is essential that the diagnosis of rheumatic fever should be made as precisely as possible.

The most useful criteria on which to base this diagnosis are the modified Jones criteria reproduced in Annex 1. These criteria, originally formulated by T. Duckett Jones in 1944, have contributed greatly to the comparability of scientific information on rheumatic fever collected throughout the world.

In certain parts of the world, however, rheumatic heart disease has been reported to follow acute attacks even though only minor diagnostic criteria were present, e.g., migratory polyarthralgia, together with at least two of the following: fever, elevated sedimentation rate, leucocytosis,

increased P-R interval in the electrocardiogram and evidence of antecedent streptococcal infection; these cases would not meet the requirement that at least one major criterion must be present for a diagnosis of rheumatic fever to be made (see Annex 1). Therefore, modification of the criteria may be needed to meet specific local needs, since the Jones criteria were never meant to be a substitute for the wisdom and judgement of the clinician. To ensure comparability in published reports, such modifications should be detailed in full and the results defined both in terms of the group of cases that fulfil the Jones criteria and of those that meet only the locally modified criteria. Furthermore, in developing countries, rheumatic fever will need differentiation also from other diseases, including, for instance, typhoid and typhus fevers or familial Mediterranean fever.¹ These may need to be added to the list of diseases to be excluded given under "Other Manifestations" in Annex 1. This list at present includes "non-specific pericarditis with effusion", but in recent years the question has arisen also of the difficulty of distinguishing between "isolated pericarditis" and the use of "pericarditis" as diagnostic of carditis in the Jones criteria (Annex 1).

It is indeed possible that some further revision of these criteria may be necessary. It is highly desirable that any such change should be justifiable on scientific grounds and be generally and internationally² acceptable. Finally, since the Jones criteria remain empirical, the Committee strongly recommends that their validity be tested by scientific methods.

5.2 Criteria for the recognition of Group A streptococcal infection

For the purpose of a practical rheumatic fever programme, a Group A streptococcal infection is defined in terms of those clinical, epidemiological and laboratory features that are easily recognized by a practising physician. Many streptococcal infections capable of precipitating an attack of rheumatic fever are not characteristic or are so mild as to be practically unrecognizable, and some cannot easily be differentiated from viral infections of the upper respiratory tract. However, there is a group of clinical and epidemiological syndromes in which rheumatic fever may be prevented by adequate penicillin treatment. These are as follows :

- (1) scarlet fever;
- (2) pharyngitis, with or without tonsillitis, manifested by local redness, oedema, exudate, pain and elevated temperature, and associated with enlarged tender lymph-nodes at the angle of the jaw, leucocytosis, or a positive throat culture;

¹ In English-speaking countries, familial Mediterranean fever is sometimes referred to as "periodic fever".

² Recently, a further modification of the Jones criteria was proposed in the USA; see *Circulation*, 1965, 32, 664.

(3) complications of upper respiratory diseases or syndromes that are frequently due to streptococci, such as otitis media, mastoiditis and erysipelas and other skin lesions;

(4) upper respiratory infection occurring in individuals living in the same households or in close contact with patients with obvious streptococcal disease;

(5) symptoms suggestive of streptococcal disease in known rheumatic patients or their familial household contacts.

It is important for the physician to recognize the above-described manifestations of Group A streptococcal infection so that he may institute adequate penicillin treatment.

Certain laboratory examinations are useful in assisting the physician in differentiating streptococcal disease from other varieties of upper respiratory infection. Determination of the white blood count is probably the simplest because it is unusual in adults to find a marked leucocytosis in viral infections of the upper respiratory tract. A nose and throat culture is also very helpful in diagnosis, if properly performed and interpreted.

It would be desirable to define in precise quantitative terms the criteria for differentiating, by the use of throat cultures, between an acute streptococcal infection, the carrier state, and the total absence of streptococci in the throat. However, this is not possible, because the results of a throat culture depend upon many factors that are difficult to control.

The best available technique involves such procedures as the careful swabbing of both tonsils and the pharyngeal wall, the use of nasal swabs in addition to throat swabs, the rapid transfer to a sheep-blood-agar plate before the swab can dry out, careful streaking with a wire loop to ensure adequate distribution of the organisms, and the use of a suitable nutrient agar base to which blood has been added. The use of filter-paper slips as the transport medium for throat or nasal smears is recommended. When facilities are available, it may be useful to establish with certainty the presence of Group A streptococci by isolation and further identification of haemolytic colonies. The use of the fluorescent antibody method permits accurate and more rapid detection of Group A streptococci, but like other methods does not distinguish between infection and the carrier state.

In general, it can be stated that the following will be true under optimal conditions :

(1) throat cultures obtained from 70-90% of patients with acute streptococcal sore throat will show a heavy predominance of Group A streptococci;

(2) throat cultures from carriers will only infrequently show comparable numbers of organisms.

It is therefore advisable to consider the recovery of large numbers of streptococci as diagnostic of streptococcal sore throat. When smaller numbers are recovered, the decision as to treatment will have to be based on the clinical findings. The absence of streptococci in a single culture is good evidence against acute infection but does not eliminate the possibility of the carrier state.

A rising titre of antistreptolysin O in sera taken in the convalescent stage as compared with those taken in the acute stage confirms the diagnosis of recent streptococcal infection. The titres should be determined by a standard laboratory procedure and based on comparison with standard sera. The result of a single specimen is indicative of a recent streptococcal infection only if the titre is over 200. The use of other antibody determinations increases the percentage of positive results, but so far this procedure has been used mainly in research studies.

Pursuant to the recommendations in the second report of the WHO Expert Committee on Rheumatic Diseases,¹ the World Health Organization, with the co-operation of the Statens Seruminstitut of Denmark, established an international reference standard and a recommended procedure for antistreptolysin titration. As a result, comparability of antistreptolysin titrations among the research laboratories of the world has been greatly facilitated. However, most practising physicians do not yet have easy access to reliable and standardized measurements of the antistreptolysin titre.

WHO now has plans under way for the creation of an international network of streptococcal reference laboratories to which specimens for antistreptolysin titration may be sent by other laboratories for comparison with their own results. A network of reference laboratories should also yield basic knowledge, so that eventually there should be more efficient and practical methods for the precise diagnosis of group A streptococcal infections.

The Committee strongly supports the establishment of such a network of reference laboratories; it recommends that, when the network has been created, national governments establish appropriate liaison with the nearest reference laboratory and when necessary create appropriate laboratory facilities to assure reliable and standardized antistreptolysin measurements for aid in the diagnosis of acute rheumatic fever.

6. PREVENTION OF RHEUMATIC FEVER

It is clear that, if Group A streptococcal infection could be eradicated, rheumatic fever would disappear. The prevention of rheumatic fever is possible today only by prevention or early treatment of Group A streptococcal infections.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1957, 126.

In rheumatic patients, prevention of recurring attacks may be accomplished by continuous prophylaxis (see section 6.1) and, should prophylaxis break down, by adequate early penicillin treatment of any ensuing streptococcal infection (see section 6.2). Adequate treatment of streptococcal infection in non-rheumatic cases will also prevent rheumatic fever; in addition, measures for the prevention of rheumatic fever are particularly important in epidemics in closed population groups (schools, camps, hospitals and other institutions). Furthermore, it is always desirable that, in order to protect the individual, prophylaxis should be instituted as soon as the presence of rheumatic fever or chronic rheumatic heart disease is recognized, and that acute Group A streptococcal infection should be adequately treated.

In any country, the form of programme developed to prevent rheumatic fever must depend on its relative importance compared with other health problems.

6.1 Prevention of recurrent attacks of rheumatic fever in known rheumatic patients

It has been demonstrated that the continuous administration of sulfonamides, of penicillin in various forms, or of broad-spectrum antibiotics is effective in preventing streptococcal infection and hence recurrences of rheumatic fever.

The prophylactic value of sulfonamides given by continuous oral administration (0.5 g per day in children, 1.0 g per day in adults) has been demonstrated repeatedly. Sulfonamide prophylaxis has the advantage of low cost but the disadvantage of toxic manifestations, such as skin eruptions and blood disorders, particularly agranulocytosis. These are, however, infrequent; if prophylaxis is established, as it should be, during the acute phase of rheumatic fever, when the patient is under constant medical supervision, the risk of such complications is slight, since they rarely occur after more than 8 weeks' prophylaxis. Another disadvantage is the development of resistant Group A streptococci in the throat, although this has not created difficulties (except in closed communities where uncontrollable epidemics occurred in pre-penicillin days). The long-acting sulfonamides, sulfadimethoxine and sulfamethoxypyridazine, are associated with highly undesirable side-effects, such as erythema multiforme, and should not be used in the prevention of rheumatic fever.

Prophylaxis with penicillin by mouth (200 000 IU of penicillin G or 100-125 mg of penicillin V twice a day) or by injection (1.2 million IU of dibenzyl penicillin intramuscularly once a month for children) has proved as effective as prophylaxis with sulfonamides or, under certain circumstances, more effective. In adults, intramuscular injection every 3 weeks is more desirable (see Annex 2). Allergic reactions to penicillin

consist of urticaria, oedema and joint inflammation. Fatalities following injection have been very rare—one in many tens of thousands—but penicillin injections should be discontinued after any general reaction and should not be given to people who have shown reactions after any previous penicillin treatment; in such instances prophylaxis should be maintained by other means, e.g., by sulfonamides. Dibenzyl penicillin should not be given by mouth, as it is less effective by that route than penicillins G or V. It is unwise to provide patients with more than enough penicillin for one month's supply, since under certain conditions of storage potency can deteriorate rapidly.

As yet, no Group A streptococcus has been confirmed as penicillin-resistant. However, continuous penicillin administration has resulted in the development of antibiotic resistance in other throat bacteria, particularly *Staphylococcus aureus*, although this has only rarely caused practical difficulties. The effect of continuous penicillin prophylaxis on etiological agents of subacute endocarditis must also be noted. During prophylaxis, *Streptococcus viridans* in the throat may become slightly resistant, but no strain has been found to be resistant to the levels of penicillin used in the treatment of subacute bacterial endocarditis. In practice the coverage of dental extraction, tonsillectomies and other procedures¹ by administering bactericidal doses of penicillin to patients already on prophylactic penicillin dosage has had very few untoward results. However, oral strains of Group D streptococci (enterococci) have become resistant to high levels. It might be better, therefore, to use another combination of antibiotics for the prevention of subacute bacterial endocarditis in patients subject to these procedures (see section 6.6).

Broad-spectrum antibiotics, especially erythromycin or chlortetracycline (250 mg daily) are effective in continuous prophylaxis but less efficient than penicillin and sulfonamides. Their use over long periods may be limited by the possible appearance of resistant organisms and fungus infections and by their higher cost. They should be given only to patients who cannot tolerate penicillin or sulfonamides.

The selection of the prophylactic agent and its method of administration will depend on such factors as the tolerance of the patient to a monthly intramuscular injection, the economic status of the family, the availability of the drugs, the ability of the patient or parent to accept responsibility for daily oral administration, and drug sensitivity.

Under conditions of excessive exposure to streptococci, such as occurs in wards of hospitals or in semi-closed communities, the maintenance of prophylaxis in rheumatic patients is of the highest importance, and for these cases the Committee recommends a dosage double that listed in Annex 2. Known rheumatic patients should, on admission, have

¹ Including genito-urinary, gastro-intestinal and obstetric procedures.

a "priming course" of penicillin in bactericidal dosage before the dosage is lowered to prophylactic levels. Intensive prophylaxis with high dosage should be administered to patients admitted to hospital for cardiac surgery and should be continued at least until discharge from the hospital. The personnel of institutions should be aware of the possible dangers associated with a breakdown of protection and should use bactericidal penicillin treatment to abort a rheumatic fever attack in susceptible subjects. Such protection should be maintained for as long as exposure remains excessive. Education of the patient, particularly in regard to the avoidance and recognition of streptococcal infection, is essential.

Under ordinary conditions, where the rheumatic subject is liable only to casual exposure, prophylaxis should be continued for long periods of time. It is important, first that the diagnosis of rheumatic fever should be clearly established, and second that both the physician and the patient understand the necessity for continuous prophylaxis and be prepared to undertake the responsibility. They should also both be aware of the possible side-effects, particularly in the early stages of prophylaxis. Periodic medical checks are necessary, not only to ensure maintenance of good health, but in particular to reinforce the patient's will to continue prophylaxis. It is natural for patients, in the absence of instruction, to feel apathetic about taking tablets daily for years if there are no immediate signs of danger to health. Continual encouragement by the physician and his paramedical personnel is necessary to maintain satisfactory long-term prophylaxis.

The duration of prophylaxis cannot be precisely defined in the present stage of knowledge, but it would appear reasonable for prophylaxis at a dosage level such as that suggested in Annex 2 to be continued without interruption at least up to the age of 18 years or for a minimum period of 5 years following the end of the last recognizable attack, whichever is longer. Prophylaxis should not be discontinued after surgical treatment for the correction of juvenile mitral stenosis. Moreover, prophylaxis should be resumed in any patient exposed to unusual risk of infection, for example, when a young man with a history of rheumatic fever is called up for military service. While some have advocated seasonal prophylaxis, this Committee strongly recommends continuous year-long prophylaxis. Some specialists, having observed recurrences of rheumatic fever late in life, have recommended continuous life-time prophylaxis.

For all these reasons, educational programmes must be established for all concerned in the care of the rheumatic patient. Information must be provided in medical schools, medical societies, and medical journals to enable the physician to carry out his share of preventive responsibility. Paramedical personnel, particularly those visiting the patient at home, must be well informed so that they may independently encourage the patient and his family to continue prophylaxis and be able to recognize

warning signs when they appear. Representatives of community agencies, including the public health and social welfare departments, voluntary medical and social agencies, institutions such as hospitals, and finally the patient himself must be aware of the dangers of streptococcal disease and the benefits of prophylaxis.

6.2 Treatment of streptococcal infections

6.2.1 *In rheumatic patients*

Not all patients with rheumatic fever or rheumatic heart disease are placed on a prophylactic regimen; in others the regimen fails to provide adequate protection, or prophylaxis breaks down owing to failure to take the drug. In such circumstances, prompt recognition and treatment of the streptococcal infection, if undertaken within 9 days of the onset, may well avert a recurrence of rheumatic fever. In rheumatic patients, treatment of sore throats should be started immediately, without waiting for laboratory confirmation of streptococcal infection. Treatment must, however, be adequate: it is all too frequently terminated after 2 to 4 days, when the classical symptoms of streptococcal infection have disappeared. Special attention must be given to the importance of prolonging treatment for 7-10 days to ensure elimination of the streptococcus. Penicillin has proved the most effective agent. The following dosages are recommended: (a) penicillin G, 200 000 IU, or penicillin V, 100-125 mg, by mouth, 3 or 4 times a day for 7 to 10 days; (b) dibenzyl penicillin, a single injection of 1.2 million IU; (c) a combination of crystalline penicillin G, procaine penicillin and dibenzyl penicillin given as a single intramuscular injection of 1.2 million IU (see Annex 3).

It is important to emphasize that, in the treatment of streptococcal infections, sulfonamides, even though they may suppress the symptoms and signs of pharyngitis, have been quite ineffective in the prevention of rheumatic fever, presumably because they are unable to eliminate streptococci from the upper respiratory tract. Sulfonamides should not be used for the treatment of streptococcal infections, despite the fact that they have been found effective in the prevention of such infections.

6.2.2 *In non-rheumatic patients*

Streptococcal infection can be eliminated in the individual, whether or not he has already had rheumatic fever. However, successful prevention of first attacks of rheumatic fever has been reported only in closed communities, such as military establishments, often with a high rate of streptococcal infection. The prevention of rheumatic fever in the general population by treatment of sporadic streptococcal infection has not yet been adequately accomplished or documented; there are difficulties

involved in the differentiation of streptococcal sore throats from non-streptococcal sore throats, owing to the often symptomless way in which the former may appear and the failure of some patients to consult their doctors.

Nevertheless, when cases are recognized, they should be treated as described in the previous section.

It may be economic for appropriate community agencies to provide an adequate supply of penicillin for treatment if this is not otherwise available, in order to avoid the expense of prolonged care of an attack of rheumatic fever. While the decrease of streptococcal infection (and thus of rheumatic fever) in the community has in the past depended on environmental improvement, with better hygiene, less overcrowding, better nutrition and less opportunity for cross-infection, today these long-term measures can be supplemented by specific antistreptococcal measures.

At the present time, the prevention of first attacks of rheumatic fever consists of the above procedures, supported by the activities of the public health agency, by the control of the spread of streptococcal infection in closed communities and by lay education to encourage patients who might have streptococcal infection to report to their physicians. This applies particularly to certain groups, such as members of families of known rheumatic fever patients, in whom there is an increased risk of developing rheumatic fever in response to streptococcal infection.

Since the prevention of first attacks of rheumatic fever will depend ultimately on the earliest recognition and adequate treatment of streptococcal disease, it is recommended that appropriate programmes, adapted to the special conditions of particular communities, be established, using whatever means give greatest promise of effective streptococcal case-finding.

Education both of the public and of the medical profession in the consequences of streptococcal infection, its recognition and the great value of early treatment, should be undertaken by special publicity programmes.

6.3 Control of epidemics of streptococcal infections

Epidemics may occur in closed communities with a large turnover of streptococci through new arrivals (as in a recruiting centre) and also in communities where close intimate contact is inevitable, as in schools, children's homes or large families. The best and quickest method of control is intramuscular injection of 1.2 million IU of dibenzyl penicillin for the total population, i.e., infected cases and carrier cases as well as individuals who are apparently unaffected. Measures short of this, such as isolation and treatment of carriers and infected persons, are often unsuccessful, since persons who are non-carriers one week may be carriers the next.

Oral administration of penicillin for 10 or more days is also effective. Environmental measures should include strict hygiene, including frequent hand-washing and the use of disposable paper handkerchiefs, which should be properly and promptly disposed of. Currently available air-disinfection or dust-control systems will not prevent the spread of streptococcal infection, as this takes place by means of intimate contact.

Once the epidemic is under control it is possible to prevent infection building up again by a single injection of combined short- and long-acting penicillin for new members of the community on arrival.

6.4 Prophylaxis in patients with inactive rheumatic heart disease

Since recurrences may be associated with an increase in heart damage, it would seem reasonable to protect persons found to have established inactive heart disease by continuous prophylaxis, even if they have never suffered an overt attack of rheumatic fever. This is particularly important in the younger age groups, i.e., in persons under the age of 18 years. It is also wise to protect persons with rheumatic heart disease undergoing surgery by prophylaxis covering the operative period, as described below under section 6.6.

6.5 Prophylaxis in patients with "probable rheumatic fever" not meeting the Jones criteria

Prophylaxis in patients with an illness not meeting the Jones criteria but thought by their physician to have rheumatic fever need special consideration. For example, it is well documented that some persons with apparently lone ("pure") chorea, manifesting no carditis when first seen, will sometimes later develop mitral stenosis. While there is no proof that these developments are always due to further streptococcal infection, it is perhaps wise to protect such patients as well as others exhibiting only minimal criteria, for example, patients with "febrile polyarthralgia". The decision is a difficult one and depends upon many different circumstances of which the patient's physician is usually the sole judge. Evidence of previous streptococcal infection may be helpful.

6.6 Prevention of bacterial endocarditis in patients with rheumatic heart disease

Subacute bacterial endocarditis may result from dental and other surgical procedures¹ in patients with chronic rheumatic heart disease, owing to the colonization of the damaged valves by dissemination of

¹ See page 13, footnote.

local bacteria. Such patients should therefore be protected by administration of antibiotics in therapeutic doses.

Whether or not they are on regular penicillin prophylaxis, patients should be protected by the intramuscular administration of procaine penicillin, 600 000 IU, and penicillin G (crystalline), 600 000 IU in a single injection, together with streptomycin, 1 g, 1 to 2 hours before the operation. Subsequently, procaine penicillin, 600 000 IU, and streptomycin, 1 g, should be given intramuscularly daily for 2 days. Oral protection is less certain and is not recommended.

Because of the possible presence of penicillin-resistant organisms in persons receiving penicillin prophylaxis, some authorities have recommended other combinations of drugs in these cases, including erythromycin, streptomycin, vancomycin and cefaloridine.

Patients who are sensitive to penicillin should receive erythromycin, 250 mg, 4 times a day for 3 days, starting 8 hours before the operation.

7. IMPLEMENTATION OF PREVENTIVE PROGRAMMES

Each country will need to evaluate the importance of rheumatic fever relative to its other health problems and to decide the degree to which its resources can be allocated to meet this need. While there is no substitute for accurate data on the extent of the rheumatic fever problem, their collection should not delay the application of a preventive regimen for known cases.

The establishment of a practical programme will depend, in all countries, on the efficient use of all available and potential resources. Initially, efforts might well be concentrated on a pilot programme which, as opportunities permit, can be expanded locally and extended to other areas. An essential component of the programme, at every stage, is the education of professional personnel, health agencies and the public.

The first steps in the programme are the registration, prophylaxis and surveillance of those cases of rheumatic fever and rheumatic heart disease already identified in hospital, in the clinic, and in the practice of individual physicians. Surveillance must provide for the prompt identification of Group A streptococcal infections occurring in patients in whom prophylaxis was discontinued or ineffective and for adequate treatment with penicillin.

The next step in an evolving programme is the identification of previously unknown cases by co-operation with physicians and through examination of special population groups, such as schoolchildren.

As soon as feasible, efforts should be directed toward the identification and treatment of streptococcal infection in the general population in

an attempt to prevent *initial* attacks of rheumatic fever. This stage of the programme would be concerned with cases of streptococcal infection presenting themselves to the practising physicians as well as with cases identified in epidemics.

In addition to prevention through the control of streptococcal infection, an evolving programme must give consideration to facilities for rehabilitation, vocational guidance and job placement of patients after cardiac surgery as well as those handicapped by heart disease.¹

The Committee recommends that WHO should urge every country with a significant rheumatic fever problem to develop at least a pilot programme and to extend services to the entire country as rapidly as possible.

8. IMMEDIATE RESEARCH NEEDS

Although much can be achieved in the prevention of rheumatic fever by the application of existing methods, the effectiveness of these programmes is still limited by lack of knowledge in certain spheres. There is need for a clearer understanding of the pattern of streptococcal infections and the resultant cardiac sequelae in various communities, particularly in those parts of the world where rheumatic heart disease still poses a prominent problem. The Committee suggests that the following lines of research deserve particular attention :

(1) Epidemiology of streptococcal infections in relation to rheumatic fever, with particular reference to the role of (a) mild and asymptomatic infections and (b) skin infections.

(2) Better methods for the diagnosis of recent streptococcal infections, especially :

(a) Serological methods for the diagnosis of streptococcal infections, with particular reference to standardization of techniques; application of these methods in field surveys; and practical problems, such as the collection, storage and transport of specimens, and their use in multi-purpose surveys.

(b) Rapid diagnostic procedures, including the fluorescent-antibody technique.

(3) Further assessment of the value of prophylactic measures in improving the prognosis of cardiac lesions in patients with established rheumatic heart disease.

(4) A study of the effects of host factors on the occurrence of streptococcal infections, rheumatic fever and rheumatic heart disease. The

¹ For further details, see *Rehabilitation of patients with cardiovascular diseases : Report of a WHO Expert Committee (Wld Hlth Org. techn. Rep. Ser., 1964, 270)*.

study of genetic factors may lead to the identification of susceptible groups. The effects of other factors, e.g., nutritional, climatic, and socio-economic, also deserve further internationally co-ordinated investigation in different areas.

(5) Study of the clinical features of rheumatic fever in different parts of the world in order to assess the applicability of the revised Jones criteria. This would be of particular interest in those areas where the clinical picture apparently differs from the classical form of the disease, and also in areas where the pattern seems to have changed in recent years.

(6) The organization of medical services for the prevention of rheumatic fever in different settings and its evaluation.

(7) The application of mass screening methods for the detection of cases of established rheumatic heart disease, e.g., mechanized analysis of phonocardiograph patterns.

(8) Search for other methods of preventing streptococcal infection and rheumatic fever, e.g., immunoprophylaxis.

(9) The international monitoring of untoward reactions to drugs and also of drug stability and formulation.

9. SUMMARY

1. This report reviews the changes in the natural history of rheumatic fever and rheumatic heart disease over the past 10 years, the epidemiology of rheumatic fever, and the control of group A streptococcal infection. It presents an up-to-date evaluation of the present state of knowledge in this field and its application to the prevention of rheumatic fever.

2. The continued international use of the modified Jones criteria for the diagnosis of rheumatic fever is recommended. Local exceptions are recognized, and the suggestion is made that, to ensure universal comparability, all published reports should note exceptions to the criteria.

3. The present state of knowledge of the prevention of rheumatic fever through prevention and treatment of group A streptococcal infection in rheumatic patients and normal individuals is summarized, dosage schedules defined, and a practical programme outlined. A note on the prevention of subacute bacterial endocarditis is included.

4. Immediate research needs to promote rheumatic fever prevention are proposed.

5. The following recommendations are particularly emphasized :

(a) the Jones criteria should be validated by scientific methods in developing and economically developed countries;

(b) pilot centres for preventive programmes of rheumatic fever should be established in individual countries, with expansion of services as rapidly as possible.

ACKNOWLEDGEMENT

The Committee acknowledges the special contributions made during its discussions by the following members of the WHO Secretariat : Dr K. Raska, Director, Division of Communicable Diseases and Dr J. H. Dingle, Consultant, Division of Communicable Diseases.

Annex 1

**JONES CRITERIA (MODIFIED) FOR GUIDANCE IN THE
DIAGNOSIS OF RHEUMATIC FEVER ¹**

MAJOR CRITERIA	MINOR CRITERIA
I. Carditis	I. Fever
II. Polyarthritits	II. Arthralgia
III. Chorea	III. Prolonged P-R Interval in the Electrocardiogram
IV. Subcutaneous Nodules	IV. Increased Erythrocyte Sedimentation Rate, Presence of C-reactive Protein or Leukocytosis
V. Erythema Marginatum	V. Evidence of Preceding Beta-hemo- lytic Streptococcal Infection
	VI. Previous History of Rheumatic Fever or the Presence of Inactive Rheumatic Heart Disease

In 1944, the late Dr. T. Duckett Jones published criteria for the diagnosis of rheumatic fever which have been generally accepted in the United States and in many parts of the world. Subsequently Dr. Jones guided revision of his criteria for use in the United Kingdom-United States Co-operative study on "The Relative Effectiveness of ACTH, Cortisone and Aspirin in the Treatment of Rheumatic Fever" and, just prior to his death, he participated in a conference on the revision of his original suggestions for use by the practicing physician. These modified Jones criteria are based in great measure upon his suggestions.

¹ This is a report of the Committee on Standards and Criteria for Programs of Care of the Council of Rheumatic Fever and Congenital Heart Disease of the American Heart Association and is reproduced, by permission, from *Circulation*, 1956, 13, 617.

Rheumatic fever is related to previous infection with Group A β -hemolytic streptococci, but the mechanism of the disease is unknown. Its boundaries are indefinite, and its differentiation from other diseases is sometimes impossible. There is no specific laboratory diagnostic test. The diagnosis must therefore be arbitrary and empirical. Criteria herein set forth are aimed at identifying those individuals who have had or are having an attack of rheumatic fever. They make no attempt to measure rheumatic activity at any given time or to diagnose inactive rheumatic heart disease. Thus, following the designation of an illness as rheumatic fever, the existence of continued activity or the presence of inactive rheumatic heart disease may be indicated by criteria different from those outlined below.

Criteria are necessary in order to minimize both overdiagnosis and underdiagnosis. The tendency to label as rheumatic fever a chronic febrile illness for which no obvious cause can be found is to be deplored. The tragedy which may lie in the wake of the false diagnosis of rheumatic fever may be even greater than the possible harm of missed recognition in questionable cases. The institution of effective prophylactic regimens requiring prolonged administration of sulfadiazine or antibiotic agents places a grave responsibility on the physician in the diagnosis of this illness.

In this statement, the diagnostic features of the disease are divided, as originally proposed by Jones, into major and minor categories, dependent upon their relative occurrence in rheumatic fever and in other disease syndromes from which this disease must be differentiated. Thus, chorea is included among the major criteria while fever, a symptom common to many diseases, is placed in a minor category. *These major and minor categories have no significance beyond their diagnostic import either as to prognosis, amount of "rheumatic activity" or severity of acute illness.* Indeed, a severe manifestation of rheumatic fever, such as rheumatic pneumonia, is not included because it is difficult to differentiate from congestive cardiac failure and because it almost always occurs in patients whose rheumatic fever is so obvious as to offer no difficulty in diagnosis.

The presence of two major criteria or one major and two minor criteria indicates a high probability of the presence of rheumatic fever (with one notable exception, see Other Manifestations). In addition to the major and minor criteria to be used in the recommended formula, other manifestations have been listed which may be used to support the diagnosis. These criteria are not meant to substitute for the wisdom and judgment of the clinician. They are designed only to guide him toward a diagnosis of the disease with the suggestion that he follow carefully all questionable cases and restrict the diagnosis of rheumatic fever to illnesses which meet acceptable criteria.

MAJOR DIAGNOSTIC CRITERIA

I. *Carditis*

As evidenced by any one of the following :

A. The presence of a significant apical systolic murmur,¹ apical mid-diastolic murmur² or basal diastolic murmur³ in an individual without a history of previous rheumatic fever or in whom there is good reason to believe there was no pre-existing rheumatic heart disease; or a change in the character of any of these murmurs under observation in an individual with previous history of rheumatic fever or rheumatic heart disease.

B. Obviously increasing cardiac enlargement determined by x-ray study.

C. Pericarditis manifested by a friction rub, pericardial effusion or definite electrocardiographic evidence.

D. Congestive heart failure present (in a child or young adult under 25) in the absence of other causes.

II. *Polyarthritis*

Polyarthritis tends to be migratory and is manifested by pain *and* limitation of active motion, or by tenderness, heat, redness or swelling of two or more joints. Arthralgia alone without objective evidence of joint involvement is not a major manifestation.

¹ A *significant apical systolic murmur* is long, filling most of systole; is heard best at the apex; is as well transmitted toward the axilla as over the precordium; and does not change with position or respiration. It must be differentiated from an innocent (functional) murmur which is frequently found in normal people. This innocent murmur is systolic, occasionally harsh, is heard best along the left sternal border and usually changes with position and respiration. Borderline systolic murmurs, intermediate in location and nature, occur and should be carefully watched. Questionable murmurs which are intermittently present or which, after a period of observation cannot be clearly classified as significant, are rarely of any import.

² A *significant organic apical systolic murmur* is frequently accompanied by a low-pitched, short *mid-diastolic murmur* which is sharply localized to the chest wall over the apex of the heart and often heard best with a patient in the left lateral position with the breath held in expiration. This murmur, rarely present in the absence of an apical systolic murmur, confirms the significant nature of the latter. It must be differentiated from the long, low-pitched, crescendo, apical presystolic murmur followed by an accentuated mitral first sound which is indicative of mitral stenosis but not of acute carditis.

³ The development of a *basal diastolic murmur* of aortic insufficiency is also indicative of carditis. It is an early, short, diminuendo murmur usually heard only or heard best along the left sternal border in deep expiration. It has great diagnostic value, even though it may be difficult to hear and present only intermittently.

III. *Chorea*

This must be differentiated from habit spasm, athetosis and cerebellar ataxia. Movements must be characteristic, involuntary and of moderate severity if chorea is to be used as a major manifestation.

IV. *Subcutaneous Nodules*

Subcutaneous nodules are shot-like, hard bodies seen or felt over the extensor surface of certain joints, particularly elbows, knees and wrists, in the occipital region, or over the spinous processes of the thoracic and lumbar vertebrae.

V. *Erythema Marginatum*

This recurrent, pink, characteristic rash of rheumatic fever, in which the color gradually fades away from its sharp scalloped edge, is found mainly over the trunk, sometimes on the extremities, but not on the face. It is transient, is brought out by heat and migrates from place to place.

MINOR DIAGNOSTIC CRITERIA

I. *Fever*

A significant rise in temperature is a common symptom, but, because it occurs in so many illnesses, it has little differential diagnostic value. In order to be included, the elevation in temperature must clearly exceed the normal diurnal fluctuation in which there is great individual variation.

II. *Arthralgia*

Pain clearly located without objective findings is only a minor criterion for diagnosis. The pain must be in the joint, not in the muscles or other periarticular tissues, and must be distinguished from the nocturnal pain in the extremities occurring in normal children. Arthralgia must not be used as a minor criterion when polyarthritis is included as a major criterion.

III. *Prolonged P-R Interval in the Electrocardiogram*

Prolongation of the P-R interval may be nonspecific; it is considered a minor criterion and is not diagnostic of carditis. It cannot be used if carditis is already included as a major manifestation.

IV. *Increased Erythrocyte Sedimentation Rate, Leukocytosis, or Presence of C-reactive Protein*

Elevation in one or more of these nonspecific tests may be considered as a single minor criterion. Particularly to be deplored is the tendency to use any of these tests as a major criterion or as diagnostic of rheumatic fever. There are many other nonspecific tests, but these three are most commonly used.

V. *Evidence of Preceding Beta-Hemolytic Streptococcal Infection*

This must be documented by (1) a history of scarlet fever or by a typical clinical picture of other streptococcal infection, preceding the onset of rheumatic fever by one week to one month, the nature of the infection being confirmed by a history of immediate contact with other individuals having typical streptococcal infection or by positive culture of the nose or throat in which β -hemolytic streptococcus predominates or (2) an elevated or rising antistreptolysin-O titer.

VI. *Previous History of Rheumatic Fever or the Presence of Inactive Rheumatic Heart Disease*

The existence of either of these may be used as a minor criterion to aid in deciding the rheumatic nature of the illness in question. For this use, the previous history must be documented by the same objective criteria as are set forth in this statement or by the presence of inactive rheumatic heart disease.

OTHER MANIFESTATIONS

These include systemic manifestations, such as loss of weight, easy fatigability, elevated sleeping pulse rate (tachycardia out of proportion to fever), malaise, sweating, pallor or anemia and local manifestations such as epistaxis, erythema nodosum, precordial pain, abdominal pain, headache and vomiting. These, as well as a family history of rheumatic fever, provide additional evidence of the presence of rheumatic fever, but are not to be included as diagnostic criteria.

Combinations of these diagnostic criteria that occur in the presence of other illnesses must be ruled out before a definitive diagnosis is made. One combination in particular, polyarthritis, fever and elevated sedimentation rate, is the weakest of all combinations of major and minor criteria. Diseases to be ruled out include rheumatoid arthritis, gonococcal arthritis, lupus erythematosus disseminatus, subacute bacterial endocarditis, non-specific pericarditis with effusion, leukemia, sickle cell anemia, serum sickness (including manifestations of penicillin sensitivity), tuberculosis, poliomyelitis, undulant fever and septicemias, particularly meningococemia.

Annex 2

CONTINUOUS STREPTOCOCCAL PROPHYLAXIS SCHEDULE

Mode of administration	Penicillin		Sulfadiazine
Intramuscular	Dibenzyl penicillin	1 200 000 IU once a month for children, every 3 weeks for adults	
Oral	Penicillin G (benzyl penicillin)	200 000 IU twice a day	0.5 g a day for children, 1 g a day for adolescents and adults
	Penicillin V (phenoxymethyl penicillin)	100-125 mg twice a day	

Annex 3

TREATMENT OF STREPTOCOCCAL INFECTION

Mode of administration	Penicillin		Erythromycin
Intramuscular	Dibenzyl penicillin	1 200 000 IU in a single injection (600 000 and 900 000 IU in children)	
	Crystalline penicillin G, procaine penicillin and dibenzyl penicillin	1 200 000 IU in a single injection (600 000-900 000 IU in children)	
Oral	Penicillin G (benzyl penicillin)	200 000 IU 3 or 4 times a day for 7 to 10 days	250 mg four times a day for 7 to 10 days (40 mg/kg/day in children)
	Penicillin V (phenoxymethyl penicillin) or phenoxethyl penicillin (phenethicillin)	100-125 mg 4 times a day for 7 to 10 days	

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