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PREVENTION OF RHEUMATIC FEVER

Second Report of the Expert Committee on Rheumatic Diseases

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EXPERT COMMITTEE ON RHEUMATIC DISEASES

Second Session

Geneva, 1-5 October 1956

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PREVENTION OF RHEUMATIC FEVER

Second Report
of the Expert Committee on Rheumatic Diseases *

The Expert Committee on Rheumatic Diseases held its second session in Geneva from 1 to 5 October 1956. Dr P. Dorolle, Deputy Director-General of the World Health Organization, opened the meeting on behalf of the Director-General. Dr David D. Rutstein was elected Chairman; Professor C. Bruce Perry, Vice-Chairman; and Dr Maclyn McCarty, Rapporteur. The provisional agenda was adopted with slight modifications.

1. INTRODUCTION

The first report of the Committee 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] Since that time evidence of rheumatic fever prevention has continued to accumulate to a point where it is now possible to justify extending prevention efforts, particularly in those countries where the disease presents a serious health problem.

The second session of the Committee was called to review the evidence on prevention of rheumatic fever and to make practical recommendations of world-wide applicability which might serve as a guide to the development of national and local prevention programmes.

The report, which summarizes the deliberations of the Committee at this session, is mainly concerned with methods of assessing the importance

* The Executive Board, at its nineteenth session, adopted the following resolution:
The Executive Board
1. NOTES the second report of the Expert Committee on Rheumatic Diseases;
2. THANKS the members of the Committee for their work; and
3. AUTHORIZES publication of the report.
(Resolution EB19.R12, *Off. Rec. Wld Hlth Org.*, 1957, **76**, 4)

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

of rheumatic fever and rheumatic heart disease in particular geographic areas, the scientific evidence justifying a preventive programme in any area where these present a serious health problem, and the details of the practical application of available knowledge in the prevention of rheumatic fever.

The following definitions are given to clarify the terms used in the report.

By " rheumatic fever " is meant the disease syndrome which may be difficult to diagnose and which may have one or more of the following major manifestations : acute migratory polyarthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum (see Annex 1, page 21). The importance of rheumatic fever so defined is its liability to give rise to permanent heart disease.

By " chronic rheumatic heart disease " is meant that form of heart disease which may follow rheumatic fever. In general it is characterized by the occurrence of disease of the valves, particularly of the mitral and less commonly the aortic, together with varying degrees of myocardial and pericardial disease.

2. IMPORTANCE OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Despite a decrease in mortality in certain countries which, though not very precisely documented, has certainly occurred during the last few decades, rheumatic fever and rheumatic heart disease are still an important cause of morbidity and mortality among children and young adults in many parts of the world.

Exact statistics on the prevalence of rheumatic fever and rheumatic heart disease are not obtainable ; the following paragraphs summarize the information that can be gained from four sources—namely, mortality statistics, statutory reporting or notification, surveys of well persons, and statistics of hospital admissions. These statistics are all, with the exception of the surveys, based on diagnoses made by individual medical practitioners, who may not always be experienced in rheumatic fever and rheumatic heart disease. This introduces an uncertainty into most of the figures.

Mortality statistics

Because there may often be an interval of many years between the inception of rheumatic fever and death from chronic heart disease, interpretation of mortality statistics is very difficult. Some further difficulties,

arising from the methods of recording causes of death, are discussed in Annex 2 (page 26), and it is clear that the deaths recorded in accordance with the International Lists of Diseases and Causes of Death [1] as due simply to " rheumatic fever " or " chronic rheumatic heart disease " do not by any means include all the deaths really attributable to these causes. In persons under the age of 35, however, rheumatic heart disease, apart from congenital defects, is believed to be the only significant cardiovascular cause of death. Table 1 summarizes the mortality statistics from 20 coun-

TABLE I. DEATHS FROM CARDIOVASCULAR DISEASES IN PERSONS AGED LESS THAN 35 YEARS

Countries (year)	Deaths due to cardiovascular diseases (excluding congenital malformations)		Deaths recorded as due to rheumatic fever or chronic rheumatic heart disease expressed as percentage of all deaths from cardiovascular diseases
	As percentage of all causes	Death rate per 1000 living	
Norway (1952)	1.9	0.03	21.7
Denmark (1953).	2.2	0.04	24.8
Germany, Federal Republic (1953)	3.1	0.08	5.1
Netherlands (1953)	3.1	0.05	39.2
Switzerland (1953)	3.2	0.06	19.4
Canada [1] (1953).	3.4	0.09	42.6
Japan (1952)	3.4	0.15	13.9
Israel [2] (1952).	3.8	0.13	52.1
Austria (1953)	3.9	0.10	35.8
Italy (1952)	4.0	0.14	30.4
Sweden (1952)	4.1	0.06	15.0
New Zealand [3] (1951)	4.2	0.09	30.7
France (1953).	4.4	0.11	15.2
Australia [4] (1953)	4.6	0.09	27.8
Finland (1952)	5.0	0.13	15.6
Ireland (1952).	5.0	0.14	34.4
United States of America (1952)	5.2	0.12	30.0
England and Wales (1953) . . .	5.6	0.09	46.0
Northern Ireland (1953)	6.1	0.14	49.1
Scotland (1953).	6.4	0.13	46.3

[1] Excluding Yukon and North-West Territories
[2] Jewish population only
[3] Excluding Maoris
[4] Excluding full-blood aborigines

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[1] World Health Organization (1948-49) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, Geneva, 2 vols. A new edition of this Manual, incorporating the Seventh Revision of the International Lists of Diseases and Causes of Death, will be published early in 1957.

tries on this basis. In most of them cardiovascular diseases (excluding congenital defects) account for 3-5% of all deaths under the age of 35. These figures are an underestimate of the total mortality attributable to rheumatic heart disease, since many patients survive to more than 35 years of age.

The simple figures for mortality from rheumatic fever and rheumatic heart disease, even though they show that these conditions account for a substantial proportion of the deaths in children and young adults, do not fully indicate the magnitude of the problem ; for not only do many of the deaths occur at young ages, so that the loss in terms of working life is particularly great, but the non-fatal attacks often lead to long-continued disability, with the risk of recurrence of severe illness.

Compulsory notification

Statutory reporting of rheumatic fever and rheumatic heart disease has been attempted in a number of countries but has not proved very satisfactory in most, because of the difficulties of ensuring complete recording. At times, for the purpose of a special study, it may be desirable to require statutory reporting of the two diseases, as part of a more complete method of evaluation which would include consultative services for verification of diagnosis and special supervision to obtain compliance with the requirement.

As an example of the results obtainable in a special study, the experience in England and Wales may be cited, where for the last few years notification of new cases of the disease in children up to 15 years of age has been required in seven areas with a total population in this age-group of about 500 000. All the patients are seen by an expert cardiologist before the notification is confirmed so that the figure obtained is certainly not exaggerated by false diagnosis ; the number of missed cases is not known. Over the years 1951 to 1954, the number of cases reported annually has varied between 2.6 and 2.9, with a mean of 2.7, per 10 000 of the age-group 0-15.

Surveys

A great number of surveys of well persons have been carried out in the USA, as well as a few in some other countries. Interpretation of the results is difficult because of the varying standards used in the surveys, but in general about 1-2% of children in schools in the USA and in Italy have been found to have heart lesions indicating a previous rheumatic attack. Similar rates were found among men drafted into the US armed forces.

Hospital admissions

The frequency with which patients are admitted to hospital with acute rheumatism, or with chronic rheumatic heart disease, cannot give a precise indication of the frequency of the disease in a population because of the varying factors determining admission to different hospitals. Nevertheless, hospital admission statistics can give a rapid indication of the likelihood that the disease is a serious problem in any country. Figures of between 1% and 2% have been recorded from places as diverse as the northern USA, Finland, Italy, Netherlands West Indies, Puerto Rico, Ceylon, India and Australia.

Rheumatic heart disease in tropical countries

Almost all the extensive studies on rheumatic fever and rheumatic heart disease have been reported from temperate countries, but hospital statistics make it clear that the disease exists also in the tropics. Most of the discussion in the report necessarily deals with the situation in temperate countries ; further research is needed to determine its applicability in the tropics.

Methods of obtaining further information

The most accessible index of the magnitude of the problem of rheumatic fever and rheumatic heart disease is the number of patients suffering from the diseases to be found in hospital wards and out-patient departments, wherever these exist.

Examination of hospital records, together with mortality statistics, may indicate that the disease is so prevalent as to justify special control measures. The details of any control programme must depend on the local and national health services of the individual country and must be related to the demands on these services in respect of other health problems.

In some special circumstances it may be desirable to obtain more accurate information on prevalence, to facilitate planning of control measures. Since the necessary surveys are expensive to perform, however, it should first be considered whether the available funds are not better conserved for the treatment and prophylaxis of recurrences in patients known to have the disease.

There seems little doubt that the best method of obtaining further information is by a properly designed pilot survey of the population. The advantages of the survey method are that it :

(1) requires the collaboration of relatively few people in comparison with, for example, notification ;

(2) can achieve a constant standard of diagnosis ;

(3) can yield results in a reasonably short period of time ;

(4) gives information in direct relation to the actual situation in the population—unlike mortality statistics, which relate in part to the situation of some years previously ; and,

(5) lastly, discovers patients with active disease who can be helped by treatment and prophylaxis.

The difficulties of the survey method are that, being complex, it has to be planned and carried out by experienced and well-trained physicians, statisticians and nurses, working together with good administrative personnel. It is therefore expensive, needs to be carefully planned and coordinated, and can be recommended only as a research procedure.

3. RELATIONSHIP OF STREPTOCOCCAL INFECTION TO RHEUMATIC FEVER [1]

Infection with Group A haemolytic streptococci is now recognized as the only established inciting factor in acute rheumatic fever. The evidence which proves the relationship between the two is derived from many sources. Clinical observations that rheumatic fever is often preceded by streptococcal sore throat or scarlet fever have been substantiated and carried further by epidemiological studies. Conclusive laboratory evidence was subsequently provided by serological investigation which showed that an immune response to streptococcal antigens occurs with great regularity in patients with rheumatic fever. Further support was later provided by the demonstration that the prophylactic use of antibacterial drugs prevents recurrences of rheumatic fever and that antibiotic treatment of streptococcal sore throat can prevent first attacks of the disease.

The possibility that other infections or injuries may also act as inciting agents in rheumatic fever has long been considered, but there remains no clearly documented evidence that any of these can initiate the disease without the intervention of an associated streptococcal infection. In any event, if attacks can be induced by agents other than Group A streptococci, such attacks must be very rare. Therefore, the practical problem of rheumatic fever prevention remains one of the prevention and treatment of streptococcal infection.

[1] The Seminar on the Epidemiology and Prevention of Rheumatic Fever, organized by the International Children's Centre, Paris, in September 1956, was attended by most members of this Committee. The subjects covered by sections 3 and 4 of this report were discussed at length on that occasion, and fuller details than are given here may be found in the report of the ICC Seminar which is to be published in 1957 in the *Revue du Rhumatisme et des Maladies ostéo-articulaires*.

It is of great importance to know what proportion of streptococcal infections are followed by rheumatic fever. On the basis of extensive studies in a large military population, the view has been widely disseminated that 3% of acute streptococcal infections of the respiratory tract are followed by rheumatic fever. Although rates as high as this, or even higher, have been encountered in other epidemics in military camps and in schools, these have generally been reported because they seemed excessively high, and it is unlikely that they can be used to estimate the risk in ordinary civilian experience. Indeed, in the limited studies which have been reported in the civilian population, rheumatic fever appears to have been much less common than in military experience. The figures from these studies give no more than a general indication of the risk that a streptococcal infection will be followed by rheumatic fever, although they suggest that it may be substantially lower than 3%. It will be difficult to obtain precise data on this point, but it is evident that the effort should be made.

While the streptococcus must be considered as the specific inciting agent in rheumatic fever, there are obviously other factors which participate in the pathogenesis of the disease, since not all patients with recognized streptococcal infections develop rheumatic fever. Environmental conditions such as poverty and overcrowding have not been adequately assessed, and it remains possible that their influence is primarily on the incidence of streptococcal disease. The role of heredity, nutrition and other host factors is likewise poorly defined, and much further work will be needed before their true significance in the disease can be established.

The striking aspect of the pathogenesis of rheumatic fever is that the initiating streptococcal infection is capable of inducing a disease process which first appears after the usual manifestations of the bacterial infection have subsided and which may be perpetuated in the absence of the infecting streptococci. One of the most important problems in the ultimate understanding of the disease is to determine the mechanism of this delayed effect. This will almost certainly involve the accumulation of further basic knowledge concerning the biology of Group A streptococci and the host response to the organism.

4. BASIC DATA ON RHEUMATIC FEVER PREVENTION BY CONTROL OF STREPTOCOCCAL INFECTION

The prevention of rheumatic fever by control of beta haemolytic streptococcal infection has been accomplished : (*a*) through the prevention of recurrent attacks in rheumatic patients by continuous prophylaxis ; (*b*) by adequate penicillin treatment of superimposed streptococcal infection occurring in rheumatic patients ; (*c*) by adequate penicillin treatment of

streptococcal infection occurring in non-rheumatic patients ; (*d*) by prevention of streptococcal infection through administration of sulfonamides or penicillin to all members of closed population groups, such as schools, camps and institutions.

Prophylaxis of recurrent attacks of rheumatic fever in known rheumatic patients

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

The effectiveness of sulfonamides in the prevention of rheumatic recurrences in the large majority of cases 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 and the disadvantage of toxic manifestations, such as skin eruptions or blood disorders, particularly agranulocytosis. These are, however, infrequent and their danger may be reduced by establishing prophylaxis during the acute disease, when the patient is under frequent medical supervision, since these complications rarely occur after more than eight weeks of prophylaxis. Another disadvantage is the possible development of resistant micro-organisms in the throat—although this has not created serious difficulties.

Prophylaxis with penicillin by mouth (100 000-200 000 units of benzylpenicillin (penicillin G) twice a day) or by injection (1 200 000 units of benzathine penicillin intramuscularly once a month) has proved somewhat more effective than prophylaxis with sulfonamides. Toxic manifestations, which are less severe, consist of allergic reactions such as urticaria, oedema and joint inflammation, and are of little importance in children.

Oral penicillin has the advantage of ease of administration but, as is the case with sulfonamide drugs, has the disadvantage of requiring careful supervision to be sure of continuous prophylaxis. It is also expensive. Intramuscular benzathine penicillin assures continuous protection and is less expensive, but has the disadvantage of requiring repeated injections, which are painful and which may be followed by local or general reactions.

As yet, no strain of penicillin-resistant beta haemolytic streptococcus resulting from continuous drug prophylaxis has been reported. However, continuous penicillin administration has resulted in the development of 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 be noted. During prophylaxis the *Streptococcus viridans* of 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. However, strains of Group D streptococci (enterococci) have become resistant to high levels.

Broad-spectrum antibiotics, especially chlortetracycline (0.25 g per day), seem to be effective in continuous prophylaxis but less effective than penicillin and sulfonamides. The high cost, the possibility of resistant organisms, and the occurrence of digestive upsets and fungus infections not found after sulfonamides or penicillin, limit their use in continuous prophylaxis.

Treatment of superimposed streptococcal infection in rheumatic patients

When prophylactic treatment is not regularly followed, or if prophylaxis is unsuccessful, superimposed streptococcal infection may develop. In such cases, the risk of rheumatic recurrence is very high but may be lowered by adequate treatment of the streptococcal infection with penicillin.

It is very 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 eradicate streptococci from the upper respiratory tract. When penicillin is available, therefore, sulfonamides should never be used for the treatment of streptococcal infections, despite the fact that they have been found effective in the prevention of such infections.

Penicillin has been effective in the prevention of rheumatic fever by the treatment of streptococcal infection, when employed in the following dosage : (*a*) benzylpenicillin (penicillin G), by mouth, 200 000 units three times a day for ten days ; (*b*) in adults, penicillin in oil with aluminium monostearate (PAM), three injections of 600 000 units the first, fourth and seventh days ; (*c*) benzathine penicillin, one injection of 1 200 000 units.

The tetracyclines have been used instead of penicillin in the treatment of streptococcal infection in penicillin-sensitive patients, but their ability to eradicate streptococci is much lower.

Prevention of first attacks of rheumatic fever

Prevention of the first attack of rheumatic fever has been achieved by early treatment of the streptococcal pharyngitis or tonsillitis with therapeutic dosage of penicillin for at least 7 to 10 days in young adults in military populations. Such prophylaxis was achieved with penicillin in

oil containing aluminium monostearate, or with injectable benzathine penicillin, during epidemics of streptococcal infection. The results were good, the incidence of rheumatic fever being greatly reduced as compared with the controls. The results obtained with chlortetracycline and oxytetracycline were less satisfactory than those with penicillin. Sulfonamides were totally ineffective.

Prevention of streptococcal infections

Although the preceding sections have dealt with the prevention of the rheumatic complications of streptococcal infections, the ideal approach to the prevention of rheumatic fever would be through the control of streptococcal infection. It may be said directly that there is no method for preventing infections in the population at large. However, in small closed or semi-closed communities, such as schools, children's homes, etc., there are methods which can probably terminate epidemics and can therefore protect some of the members of the community from infection.

Possible methods for the control of streptococcal infections may be considered under three categories : (1) protection of the susceptibles by mass chemoprophylaxis ; (2) isolation and treatment of the persons transferring the infection ; (3) control of the environmental pathways by which infection spreads from person to person.

Chemoprophylaxis

Extensive investigations indicate that even very large epidemics of streptococcal infection have been terminated by the administration of sulfonamides or penicillin by mouth to all the members of the community. Penicillin is the agent of choice but it must be given for 10 or more days.

Isolation of carriers

Certain circumstances may make mass chemoprophylaxis impossible. If bacteriological facilities are available, an attempt may be made to control outbreaks by seeking carriers who may be disseminating the infection. In such cases, it is particularly important to seek nasal carriers, since they are far more important sources of infection than throat carriers. Search should also be made for persons with otorrhoea or infected skin lesions. All such sources of infection may ordinarily be eradicated by therapeutic doses of penicillin.

Environmental control

Despite the fact that, in environments where streptococcal infection is spreading, the streptococci can often be recovered in very large numbers

from the air dust, there is no clear-cut evidence that currently available methods of air disinfection or dust control will prevent the spread of the infection.

5. PRACTICAL APPLICATION OF AVAILABLE KNOWLEDGE IN RHEUMATIC FEVER PREVENTION

It is clear from the foregoing section that if known rheumatic subjects are not allowed to develop infection with the haemolytic streptococcus they will not develop relapses of rheumatic fever. Furthermore, attacks of rheumatic fever may be prevented if all infections with the haemolytic streptococcus are recognized and treated promptly and effectively so that the micro-organism is eradicated with as little delay as possible.

In any individual country the form of programme developed to prevent rheumatic fever must depend on the relative importance of this problem in comparison with the other health problems confronting the country. In all circumstances, however, it is desirable that everything possible should be done to protect individual cases as they are recognized. For this reason it is essential :

(1) that some form of efficient prophylaxis should be instituted for all persons known to have rheumatic fever or to have chronic rheumatic heart disease ;

(2) to ensure that all recognized cases of acute haemolytic streptococcal infection should be given adequate treatment with penicillin.

Diagnostic criteria

Unfortunately there is no specific diagnostic symptom, sign or laboratory investigation which establishes the diagnosis of rheumatic fever. Nevertheless, before submitting a patient to a prolonged period of prophylactic treatment it is essential that the diagnosis of rheumatic fever should be made as precisely as possible. The most useful criteria on which to base such a diagnosis are those formulated by T. Duckett Jones and subsequently modified. These recommendations are reproduced as Annex 1 to this report (see page 21).

It is also necessary to define and clarify the practical recognition of beta haemolytic streptococcal infection.

Recognition of beta haemolytic streptococcal infection for prevention of rheumatic fever

For the purpose of a practical rheumatic fever prevention programme, a beta haemolytic streptococcal infection is defined in terms of those

clinical, epidemiological and laboratory features which are easily recognized by a practising physician. Many streptococcal infections which may precipitate 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 and elevated temperature, and associated with enlarged, tender lymph-nodes at the angle of the jaw, leucocytosis or a positive throat culture ;

(3) complications of upper respiratory disease or syndromes which are frequently due to the streptococcus, such as otitis media, mastoiditis and erysipelas ;

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

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

Certain laboratory examinations are useful in assisting the physician in differentiating streptococcal disease from other varieties of upper respiratory infection. The measurement of the white blood count is probably the simplest because it is unusual to get 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 acute streptococcal infection, the carrier state and the total absence of streptococci. However, this is not possible because the results of a throat culture depend upon many factors which are difficult to control.

The best available technique represents an attempt to reduce these uncertainties. It 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 blood-agar plate before drying of the swab can occur, the careful streaking with a platinum loop to ensure adequate distribution of the organisms, and the use of a suitable nutrient agar base to which blood has been added. 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.[1]

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

(1) Throat cultures obtained from the great majority of patients with acute streptococcal sore throat will show a heavy predominance of Group A haemolytic streptococci.

(2) Throat cultures from carriers will only show comparable numbers of organisms in a small proportion of instances.

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.

In summary, it is possible for the practising physician to recognize certain disease syndromes that are manifestations of beta haemolytic streptococcal infection for the purpose of adequate penicillin treatment, in the hope that initial and recurrent attacks of rheumatic fever may be prevented. When throat cultures are used as an aid in diagnosis, it is essential that a satisfactory technique be followed.

Prevention of rheumatic fever recurrences

In the prevention of recurrences, the technique of control depends upon whether the patient is exposed to an excessive risk of infection with the beta haemolytic streptococcus or whether such exposure is casual.

Excessive exposure

In the case of excessive exposure, as occurs in the wards of hospitals or in semi-closed communities such as institutions and camps where streptococcal infection may be epidemic, control is simple and straightforward.

The physician being aware of the need for the protection of precisely diagnosed rheumatic patients will, at the time of admission of the patient to the hospital or institution, particularly in the medical, surgical or paediatric wards, prescribe penicillin in a form and dosage to provide relatively

[1] The methods for obtaining and interpreting throat cultures are discussed in detail in : American Public Health Association (1955) *Diagnostic procedures and reagents for public health laboratories in bacteriology, mycology, parasitology and immunology*, 4th ed., New York.

high and constant blood levels throughout the period of exposure. A possible schedule might be double the dosage recommended for continuous prophylaxis in Annex 3 (see page 27).

Nurses, social workers and other personnel in hospitals and institutions should be instructed in their particular responsibilities in the protection of rheumatic fever patients in their charge. They must know of the danger to the rheumatic patient presented by the streptococcal infection, the desirability of avoiding contact of the patient with known infection, and the possibility of the prevention of rheumatic recurrences through prophylaxis. They must know the typical symptoms of streptococcal infection, and when they believe it to be present they should immediately refer the patient to a physician.

The hospital administrator, including the director of community hospital services, and the administrator in charge of the individual hospital, should, through an educational programme, be aware of the benefits of a preventive programme to the individual patient. He must know about the decrease in hospital cost resulting from a shortening of hospital stay of rheumatic patients through prevention of recurrences. He should, with the co-operation of the hospital staff, incorporate procedures in the hospital regulations for communicable disease which will guide the physician and others at the time of admission of a rheumatic patient. He should also ensure the availability of penicillin for all rheumatic patients, regardless of economic status, and, if the hospital be unable to provide an adequate supply, he will explore other possible sources of funds for this purpose.

A public health agency concerned with the control of streptococcal infection should, during epidemic periods, warn the medical profession and hospital administrators and assist them in the prevention of spread of streptococcal infection to rheumatic patients.

The rheumatic patient himself has a role in the programme. At the time of his first attack or when rheumatic heart disease is first diagnosed, he should be warned of the dangers of a superimposed beta haemolytic streptococcal infection and the effectiveness of penicillin in protecting him under conditions of intimate exposure.

Casual exposure

The prevention of recurrences in known rheumatic fever patients from streptococcal infection resulting from casual exposure under ordinary conditions of daily life, is much more difficult, as it is necessary to continue prophylaxis for long periods of time in individuals who usually feel perfectly well. In such circumstances prophylaxis can be successful only under the following conditions :

(1) Where the diagnosis of rheumatic fever is clearly established according to generally acceptable criteria. The diagnosis of rheumatic fever must never be made by exclusion, and prophylaxis must never be instituted in the absence of a clearly established diagnosis.

(2) Where the responsibility for continual medical supervision of the patient is accepted by the physician caring for the patient. It is unlikely that prophylaxis can be continued successfully if the physician does not accept and assume continuous responsibility, or if the patient changes frequently from physician to physician.

(3) Where the physician is convinced of the benefit of continuous prophylaxis, aware of its difficulties and conscious of its possible dangers. The continuous medical supervision of a patient receiving prophylaxis implies that the physician will recognize the symptoms and signs of a superimposed streptococcal infection, the supervention of a rheumatic recurrence, the development of rheumatic heart disease, and the appearance of toxic effects or intolerance of the drug.

(4) Where the patient and his family learn the benefits of continuous prophylaxis, and recognize warning signs requiring immediate attention by the physician. Prophylaxis of rheumatic fever is possible only if the patient and his family really desire it and if they co-operate with the physician by learning about the warning signals of streptococcal infection, rheumatic recurrence, and drug reactions.

(5) Where the public health services assist the physician to ensure continuous medical surveillance. For example, visits by a public health nurse or a social worker to the home of the patient should ensure that the physician's recommendations are carried out and should assist him in encouraging the patient to continue on the prophylactic regimen. She must also be able to observe and report warning signals in patients. In the local public health services, if it is possible to maintain a current list of patients with known rheumatic fever, it will be useful to the health administrator in ensuring that such patients are kept under continuous medical supervision and prophylaxis.

(6) Where proper governmental or voluntary community agencies accept responsibility for ensuring adequate supplies of prophylactic drugs to the rheumatic fever patient, regardless of economic status.

(7) Where prophylaxis is continued throughout the year despite the seasonal occurrence of streptococcal infection, because recurrences of rheumatic fever do occur during the summer. Moreover, it may be difficult to re-institute daily continuous prophylaxis after a period of interruption. The duration of prophylaxis cannot be precisely defined in the present state of knowledge, but a reasonable compromise would suggest that prophylaxis

at a dosage level such as that suggested in Annex 3 (see page 27) must be continued without interruption at least up to the age of 15 or during a period of five years following the end of the last recognizable attack, whichever is longer. Moreover, prophylaxis should be resumed in any patient exposed to unusual risk of infection, for example in a mother with a previous history of rheumatic fever or with rheumatic heart disease who may be exposed to streptococcal infection brought into the household by her children. There are some students of this disease who, after observing recurrences of rheumatic fever late in life, have recommended continuous life-time prophylaxis.

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 and the availability of the drugs, the ability of the patient or parent to accept responsibility for daily oral administration, and drug sensitivity. The physician must weigh these factors in the selection of the prophylactic agent for his particular patient.

To satisfy all these requirements, 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 so that the physician may be informed and be able to carry out his share of preventive responsibility. Similarly, other medical 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 and institutions such as hospitals, must also be informed. Finally, as in the case of excessive exposure, the patient himself must be aware of the dangers of streptococcal disease and the benefits of prophylaxis.

Treatment of superimposed streptococcal infection in a rheumatic patient

When the rheumatic patient is not under prophylaxis, or in the uncommon event of prophylaxis being unsuccessful, he may develop superimposed streptococcal infection. It is then very important that he be given immediate intensive treatment with large doses of penicillin for ten days (see Annex 3, page 27). Because of the great vulnerability of known rheumatic patients to recurrences after superimposed streptococcal infection, treatment should be instituted at the first suspicion of streptococcal disease—i.e., from the earliest appearance of a sore throat—without waiting for the development of conclusive evidence of streptococcal infection as one might do in the

case of normal individuals. Such treatment should be carefully supervised in order to eradicate all evidence of streptococcal disease from the upper respiratory tract of the individual. Sulfonamides, which are effective in the prevention of streptococcal infection, should never be used for the treatment of streptococcal infection where penicillin is available. Although sulfonamides may prevent septic complications, they will neither prevent the subsequent development of rheumatic fever nor eradicate the streptococci from the upper respiratory tract.

Prevention of first attacks

The evidence for the prevention of first attacks of rheumatic fever has been reported from studies in military establishments. There is practically no well-controlled published evidence documenting the prevention of first attacks of rheumatic fever in civilian population groups. Nevertheless, it should be possible in isolated cases of streptococcal infection in the community for the physician to institute effective treatment with penicillin and thus prevent rheumatic fever. This would appear to be a simple matter, and yet treatment is all too frequently terminated after two to four days when the classical symptoms of streptococcal infection have disappeared. Special attention must be given to the importance of prolonging treatment for ten days to ensure eradication of the streptococcus. With the availability of long-acting preparations for intramuscular injection of penicillin and compounds such as phenoxymethylpenicillin (penicillin V) for oral treatment, it should be possible for the practising physician to devise a treatment schedule for his particular patient which will ensure adequate blood levels for ten days (see Annex 3, page 27). Where streptococcal infection occurs in an individual in a low income group, it may be economic for appropriate community agencies to provide an adequate supply of penicillin for treatment, in order to avoid the expense of prolonged care of an attack of rheumatic fever.

At this time, the prevention of first attacks of rheumatic fever consists of the above procedures, supported by the streptococcus control activities of the public health agency, by the methods for control of the spread of streptococcal infection in closed communities mentioned on page 12, and by lay education to encourage patients who might have streptococcal infection to report to their physicians.

As yet no effective methods of early streptococcus case-finding on a community-wide basis have been developed for the purpose of preventing first attacks of rheumatic fever by adequate treatment of streptococcal infection with penicillin, and much well-controlled research is needed towards this end. Preliminary uncontrolled community studies in streptococcal case-finding have solved many of the practical problems which will

come up in the establishment of a controlled study, and seem to indicate that the school health service may serve as a useful screening device. Since the prevention of first attacks of rheumatic fever will eventually depend on the earliest recognition and adequate treatment of streptococcal disease, it is recommended that such studies, adapted to the special conditions of particular communities, be established using whatever agency gives greatest promise of effective streptococcal case-finding.

Thus, by effective use of community and medical facilities supported by the necessary educational programmes, it should be possible to prevent :

(1) most recurrences of rheumatic fever under conditions of intimate exposure to streptococcal infection ;

(2) many recurrences under conditions of casual exposure ; and

(3) occasional first attacks through effective treatment of recognized streptococcal infection.

But, finally, much research is immediately needed to yield information on methods by which more streptococcal infection may be recognized and treated early so that most first attacks of rheumatic fever may be prevented.

6. ADDITIONAL RECOMMENDATION

Standardization of antistreptolysin titration

The determination of the antistreptolysin titre is of considerable value in the diagnosis of those cases of rheumatic fever in which the demonstration of the occurrence of a preceding streptococcal infection is crucial. It is also useful in differentiating between recurrences and recrudescences of rheumatic fever. While in general it is desirable to compare the titres of sera taken on separate occasions, it will often be necessary for the results to be interpreted on the basis of a single absolute titre. For this reason, and because there are wide variations in the results now obtained in various parts of the world, it is essential that methods of standardization make it possible for the same values to be obtained in different laboratories. At the present time there is no generally recognized standard by which individual laboratories can assess their results. It is therefore recommended that WHO be asked to consider the setting up of an international standardization procedure.

Annex 1

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

Rheumatic fever is related to previous infection with Group A beta haemolytic 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 [2] 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 over-diagnosis and under-diagnosis. 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,

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[1] Taken from *Circulation*, 1956, **13**, 617, by kind permission of the American Heart Association.

[2] In 1944, the late Dr T. Duckett Jones published criteria for the diagnosis of rheumatic fever which have been generally accepted in the USA and in many parts of the world. Subsequently, Dr Jones guided the revision of his criteria for use in the United Kingdom/United States Cooperative 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 practising physician. These modified Jones criteria are based in great measure upon his suggestions.

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 section on " Other manifestations ", page 24). 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 judgement of the clinician. They are designed only to guide him towards 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

Carditis

Carditis, as evidenced by any one of the following :

Murmurs (see page 25). The presence of a significant apical systolic murmur, apical mid-diastolic murmur, or basal diastolic murmur 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 a history of rheumatic fever or rheumatic heart disease.

Increasing cardiac enlargement. Obviously increasing cardiac enlargement by X-ray.

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

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

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.

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.

Subcutaneous nodules

These 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.

Erythema marginatum

This recurrent, pink, characteristic rash of rheumatic fever, in which the colour 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

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.

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.

Prolonged P-R interval in the electrocardiogram

Prolongation of the P-R interval may be non-specific ; 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.

Increased erythrocyte sedimentation rate, presence of C-reactive protein, or leukocytosis

Elevation in one or more of these non-specific 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 non-specific tests, but these three are most commonly used.

Evidence of preceding beta haemolytic 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 beta haemolytic streptococcus predominates ; or (2) an elevated or rising antistreptolysin-O titre.

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 anaemia, 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.

There are combinations of these diagnostic criteria which occur in the presence of other illnesses which 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, leukaemia,

sickle-cell anaemia, serum sickness (including manifestations of penicillin sensitivity), tuberculosis, poliomyelitis, undulant fever, and septicaemias, particularly meningococcaemia.

Murmurs indicating carditis

Significant apical systolic murmur

A significant apical systolic murmur is long, filling most of the 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.

Apical mid-diastolic murmur

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 is 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 pre-systolic murmur followed by an accentuated mitral first sound, which is indicative of mitral stenosis but not of acute carditis.

Basal diastolic murmur

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 may be present only intermittently.

Annex 2

NOMENCLATURE

It was agreed to accept the nomenclature of " rheumatic fever " and " chronic rheumatic heart disease " used in the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.*[1] However, it appears desirable to call attention to the following inaccuracies that may arise when this classification is used in an attempt to assess the importance of rheumatic heart disease as a cause of death in any country or community.

All deaths registered as due to conditions listed as " 400 : Rheumatic fever without mention of heart involvement " and " 402.0 : Chorea without mention of heart involvement " should be included in assessing total deaths from rheumatic heart disease and from heart disease in general, since death from rheumatic fever and chorea never occurs without heart involvement.

The entry " 411 : Diseases of aortic valve specified as rheumatic ", which excludes diseases of the aortic valve not so specified (421.1), will exclude certain cases of rheumatic heart disease, especially in the age-groups under 35, since the majority of cases of aortic valve disease in these ages are in fact rheumatic in origin.

The entry " 430 : Acute and subacute endocarditis ", unless associated with rheumatic heart disease as a cause of death or disease, hides a certain amount of rheumatic heart disease, since a large proportion of cases of subacute endocarditis are grafted on to pre-existing rheumatic heart disease.

Therefore, in assessing the mortality from rheumatic heart disease, entries under 400, 402.0, 421.1 and 430 should be taken into account.

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[1] World Health Organization (1948-49) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, Geneva, 2 vols. A new edition of this Manual, incorporating the Seventh Revision of the International Lists of Diseases and Causes of Death, will be published early in 1957.

Annex 3

SUGGESTED DRUG DOSAGE SCHEDULES

CONTINUOUS PROPHYLAXIS

Mode of administration	Penicillin		Sulfadiazine [1]
Oral [2]	Benzylpenicillin (penicillin G)	200 000 units twice a day	Children : 0.5 g per day Adolescents and adults : 1.0 g per day
	Phenoxymethyl-penicillin (penicillin V)	100 000 units twice a day	
Intramuscular	Benzathine penicillin	1 200 000 units once a month *or* 600 000 units twice a month	—

[1] This is the sulfonamide that has been most used.

[2] The dosages suggested for oral penicillin are higher than have sometimes been used, but failures have occurred with lower doses.

TREATMENT OF STREPTOCOCCAL INFECTION

Mode of administration	Penicillin		Tetracyclines
Oral	Benzylpenicillin (penicillin G)	250 000 units three times a day for 10 days	0.5 g four times a day for 10 days
	Phenoxymethyl-penicillin (penicillin V)	Dosage approximately half that for benzylpenicillin (penicillin G)	
Intramuscular	Penicillin in oil with aluminium monostearate	300 000 - 600 000 units on the 1st, 4th and 7th day	—
	Benzathine penicillin	1 200 000 units in one injection	