

**REGIONAL OFFICE FOR THE WESTERN PACIFIC**  
**of the**  
**World Health Organization**  
**Manila**



**REPORT ON THE**  
**FIRST REGIONAL SEMINAR ON THE PREVENTION AND CONTROL**  
**OF CARDIOVASCULAR DISEASES DUE TO INFECTIONS**  
**PARTICULARLY RHEUMATIC HEART DISEASE**

**Manila, Philippines, 5-12 November 1968**

FIRST REGIONAL SEMINAR ON THE PREVENTION AND CONTROL  
OF CARDIOVASCULAR DISEASES DUE TO INFECTIONS  
PARTICULARLY RHEUMATIC HEART DISEASE

Sponsored by the

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Manila, Philippines

5-12 November 1968

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NOTE

The views expressed in this report are those of the advisers and participants at the seminar and do not necessarily reflect the policy of the World Health Organization.

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## PREFACE

The First Regional Seminar on the Prevention and Control of Cardiovascular Diseases due to Infections, Particularly Rheumatic Heart Disease, organized by the WHO Western Pacific Regional Office, was held in the WHO Building, Manila, from 5 to 12 November 1968.

Sixteen participants from sixteen countries attended, one of them sponsored by the South Pacific Commission. Consultants, participants, observers and members of the WHO Secretariat are listed in Annex 1. A summary of objectives and the agenda of the seminar appear in Annex 2. The seminar was conducted in the form of plenary sessions, of which there were twelve.

The Director of the WHO Regional Office for the Western Pacific, Dr Francisco J. Dy, opened the meeting. In welcoming the consultants, participants and observers, Dr Dy emphasized the increasing importance of cardiovascular diseases and pointed out in particular that the preventability of rheumatic heart disease by control of streptococcal infection made it a problem of public health concern. He expressed his satisfaction that governments in the Region had recognized the problems associated with rheumatic heart diseases to be important enough to make the seminar possible.

Dr G.H. Stollerman, Director of the Seminar, was elected Chairman. Daily rapporteurs in English and French were nominated by the Chairman.

The Director took the floor after Dr Dy and outlined the aims of the seminar.

The closing ceremony of the Seminar took place on 12 November 1968.

The Director summarized the work done and thanked the participants for their active interest and participation in the Seminar.

The Director of Health Services, on behalf of the Regional Director, made a short statement on the situation of cardiovascular diseases and related programmes in the Region and declared the Seminar closed.

## I. INTRODUCTION

Rheumatic fever and rheumatic heart disease pose a problem to the health of the individual which is as serious in the Western Pacific Region as it is in other parts of the world. The extent of the problem, however, and its epidemiological aspects are not well defined in most countries of the Region and some of the specific clinical features of the disease may require further study and definition.

It appears, however, that in a number of the developing countries of the Region, socio-economic conditions exist which predispose to a high prevalence and incidence of rheumatic heart disease. Because of this situation, and in view of the preventability of rheumatic heart disease, WHO considered it appropriate to attempt to clarify the problem by bringing together experts in this field who would exchange their own experiences, explore possibilities for the collection of data, formulate preventive measures suitable for the Region and suggest guidelines for the implementation of control programmes. Although rheumatic fever is currently the most important, it was also considered appropriate to identify other preventable causes of heart disease due to infectious agents and to formulate programmes which might be applicable to their prevention and control.

In addition, the increasing importance of hypertensive cardiovascular disease and of ischaemic heart disease prompted consideration, in a preliminary way, of any particular preventable causes of arterial hypertension and of coronary artery disease, respectively, which might be uncovered in the course of the seminar.

## II. RHEUMATIC FEVER

### 1. Size and Nature of the Problem

#### 1.1 Global situation and trends in the Region

Dr Stollerman outlined global trends on the occurrence of rheumatic fever and rheumatic heart disease. He stressed that the two important quantitative factors determining the attack rate of rheumatic fever were: (1) duration of carriage of streptococci after a bout of pharyngitis. Failure of treatment to eradicate streptococci during three - five weeks of convalescence gave a higher attack rate; (2) the magnitude of the immune response as measured by ASO titre. A strong immune response corresponded with an attack rate as high as 10%. Dr Stollerman cited investigations in the United States of America which provided clear cut evidence that serious epidemics of streptococcal infections could be prevented by eliminating the infectious agent in populations living under conditions conducive to their rapid transmission from person to person (under crowded conditions, for example). Furthermore, he described the remarkable efficiency with which second attacks of rheumatic

fever could be prevented by the use of continued penicillin prophylaxis following first attacks. Data were presented which indicated in general that deaths from acute rheumatic fever had been on the decline during the past several decades but that in the case of rheumatic heart disease mortality statistics indicated that a plateau had been reached and a constant level persisted.

The size and nature of the problem in countries of the Western Pacific Region was considered in presentations made by Dr Reader and by the participants. Dr Reader cited the observations made by a team of consultants who visited Malaysia, Singapore, Cambodia, Hong Kong and the Philippines prior to the meeting. He also commented briefly on the situation in Australia and New Guinea. In all countries it was quite apparent there was a significant amount of rheumatic fever and particularly rheumatic heart disease. There was a tendency for clinicians to believe that the problem was serious but for public health administrators to minimize its importance. It was evident that a better definition of the situation was greatly needed and that representative surveys would be useful in providing necessary information.

Sir Kempson Maddox reviewed diagnostic criteria for rheumatic fever (Annex 4). He referred to a report of a mission carried out by Dr E. Kratkova and himself in November 1965 for WHO<sup>1</sup>. On the basis of replies received to a questionnaire and numerous interviews, it had been concluded that the rheumatic fever problem in the Philippines, Ceylon and Israel was considerable at that time.

Each of the participants summarized the size and nature of the problem in their countries as seen from their individual vantage points.

Dr Limson presented data indicating that the severity of streptococcal infection and the magnitude of the immune response to streptococci as measured by ASO in a tropical setting like the Philippines were factors influencing a high rheumatic disease incidence, similar to that in temperate countries.

## 1.2 Conclusions from the reports of the participants

(1) Reports from all countries of the Region revealed a wide range in the magnitude of the problem from those which considered the problem under good control, such as among the European population of Australia and New Zealand, to those who recognized a severe and intense problem, such as the representatives of the Philippines and the consultants reporting on Hong Kong and Singapore.

(2) There appeared to be a direct relationship between the magnitude of the problem and the socio-economic status and overcrowded conditions and large families. There seemed to be no predisposition to acute rheumatic fever or rheumatic heart disease by ethnic groups other than that influenced by the above conditions.

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<sup>1</sup>Unpublished document, CVD/RF/66.3 - Diagnostic Criteria of Rheumatic Fever and Rheumatic Heart Disease.



(3) The notification of rheumatic fever cases was either non-existent or ineffective. Information on streptococcal disease prevalence was available from Manila and the institution of a notification programme for Fiji was noteworthy. An extensive and detailed report of heart disease in schoolchildren from Osaka, Japan was made available.

(4) Most statistics presented were from hospital admissions and in most cases the figures available were not necessarily representative of the entire community.

(5) There was no uniform plan for case detection and notification in any of the countries represented at the seminar.

(6) Autopsy figures were largely unavailable.

(7) A number of countries consisted of many scattered islands which made control and analysis of data difficult.

(8) Difficulties existed with respect to inaccurate diagnosis, the reluctance of the parents of patients to be brought for medical advice and unregistered treatment by medical practitioners.

## 2. Resources Necessary for Preventive Measures

### 2.1 General principles

#### 2.1.1 Organization of medical care (see Annex 5)

The degree of organization must be matched to the severity of the problem.

1. Existing medical services may be sufficient but it is necessary to ensure that they are readily available to all in the community with or without financial aid from the government.

2. If the magnitude of the problem is so great that a preventive programme organized at public health level is necessary, it may involve either a secondary and/or primary preventive programme but in any case will require:

(a) Data collection - This would confirm the need for the programme, indicate its extent and provide information as to its effectiveness. It should reflect the situation in the whole community and should indicate the incidence of new disease as well as prevalence of chronic stages. A secondary preventive programme will require:

(1) adequate case-finding of asymptomatic patients and clinical and bacteriological diagnostic facilities for diagnosing symptomatic cases of rheumatic fever and rheumatic heart disease;

(2) an organization for the supervision and continuing care of patients in the programme;

(3) availability of antibacterial drugs for all.

Should the situation require and permit a primary preventive programme, the main requirements would be a bacteriology service capable of rapid and reliable diagnosis of streptococcal infection which is freely available to the practising doctors.

#### 2.1.2 Problems of clinical diagnosis (Annex 4)

The value of the (revised) Jones criteria was emphasized and the classical diagnostic features reviewed. Reference was made to the importance of differentiating such conditions as Still's disease, osteomyelitis, poliomyelitis, Henoch's purpura and acute appendicitis, etc. Special attention was paid to the criteria of cardiac involvement in the acute phase and the differentiation of chronic rheumatic heart disease from congenital heart disease and from normal hearts with innocent murmurs. The special problems of recognizing SBE and recurrent rheumatic carditis were reviewed.

Sub-clinical, occult and chronic forms of the disease and also the incidence of acute rheumatic fever in adults were referred to and a series of fifteen such patients in one hospital in Sydney were discussed.

#### 2.1.3 Diagnosis of streptococcal infections (Annex 6)

Bacteriological diagnosis is essential for the optimal control of rheumatic heart disease. The laboratory must be capable of identification of Group A streptococci and determination of streptococcal antibody titres. Sequential serological studies were desirable. The more detailed study of streptococcal types was discussed but it was acknowledged that these were not essential if only diagnosis and treatment were involved.

Certain technical requirements were essential, e.g., the use of sheep's blood for agar plates, high quality and potency of reagents and maintenance of standard strains of streptococci for evaluating laboratory methods. Access to a reference laboratory, adequate training and proficiency of technical staff were other requisites mentioned.

In conclusion, the advisability of using simple methods and achieving a high standard in them, rather than attempting more sophisticated studies, was emphasized.

#### 2.2 Resources within the Region

2.2.1 In the report of the consultants, it was stated that in countries visited there were no organized community programmes for secondary and primary prevention. However, resources for such programmes were adequate in all these countries except that bacteriological services where present were not adequately utilized for the needs of the community.

There is good professional awareness of the needs and techniques for prevention and there are organized health services which are suitable for implementing a secondary preventive programme. Where prophylaxis is carried out, it is done on an individual basis and there are several aspects which prejudice the continuation of such a programme including the cost or lack of drugs and the fear of untoward reactions.

There is a general lack of enthusiasm for a systematic preventive programme because the public health authorities do not consider this as of high priority. There is a need in these countries, however, for implementing such a programme because the majority of the population is young and at high risk and patients tend to suffer from a severe form of the disease.

2.2.2 In the general discussion which followed, the following points emerged:

(1) In the early stages of an epidemic, the response to penicillin of a few cases provides a good indication as to whether the streptococcus was responsible.

(2) Of the various clinical manifestations of pharyngitis, fever, leucocytosis and cervical adenitis were those most commonly associated with a streptococcal aetiology.

(3) The cost in Manila of setting up a bacteriological service for laboratory diagnosis of streptococcal infections was reported as \$US 10 000 and the monthly running costs \$US 100 to 200.

(4) "Mail in" bacteriological diagnosis of throat swabs was not prejudiced by tropical conditions.

(5) Over-diagnosis of rheumatic fever tended to occur in Australia when polyarthritis occurred without carditis.

(6) The WHO Regional Office for the Western Pacific would assist Member countries with bacteriological or serological studies if requested by the government concerned.

(7) Cases of acute rheumatic carditis without other manifestations of acute rheumatism were usually asymptomatic and thus identified in its chronic stage of inactive rheumatic heart disease only by case-finding methods.

### 3. Formulation of Preventive Programmes

#### 3.1 Data collection

The formulation of a preventive programme for rheumatic fever with special reference to data collection was the subject for discussion.

Dr Reader introduced the subject emphasizing that plans for primary and secondary preventive programmes should be associated with adequate data collection.

Dr Stollerman then outlined the various methods of data collection relevant to assessing the problem of rheumatic heart disease (see Annex 1), and emphasized that existent health services should be utilized when possible. A discussion on the feasibility of surveys in schoolchildren in the various countries ensued. In Australia where education is compulsory, most children were examined routinely by school medical officers. A survey of schoolchildren was made in Sydney in 1958 and children found to have a cardiac murmur were referred to a panel of consultants for evaluation. In other countries, such as Fiji, trained nurses examine children and doubtful cases are referred to the doctor. In some countries, including Malaysia, not all children attend school. In the Philippines, many children are now examined while attending school. In Japan, a large prospective study of 250 000 schoolchildren is in operation at Osaka. In China (Taiwan), where there is compulsory education, a good school health service is available. Fiji is the only country of the Region in which notification of rheumatic fever has been established. Therefore, school surveys in that country would be very fruitful.

A discussion of the detection of cardiac defects by tape recording of heart sounds was then introduced by Dr Stollerman. This method could be a useful epidemiological tool in some regions with a high prevalence of heart disease. Dr Fejfar mentioned other ways of combining a computer tape recording with computer analyzer for detection of cardiac defects.

The routine examination of women during pregnancy was then discussed as existing medical services could usually be utilized. However, in some countries, prenatal care was carried out by nurses and only where medical personnel was available is this method suitable for case detection.

The possibility of using mass X-ray programme was discussed as a method for the detection of cardiac abnormality. It was generally agreed that additional diagnostic procedures would be necessary to distinguish rheumatic from other causes of cardiomegaly and on the other hand many cases of rheumatic heart disease without cardiac enlargement would be overlooked.

The routine examination of military recruits or for industrial employment was then discussed, but it was felt that the results of such examinations were limited, as were surveys based on the examination of various groups such as university students, people seeking life insurance and migrants.

The usefulness of morbidity statistics was considered. Hospital statistics were generally regarded as being of doubtful value except in small areas where all patients are treated at one centre.

Two methods of obtaining morbidity statistics were described: (a) a cross-sectional method in which everyone at a certain time is examined, and (b) the true morbidity survey in which a prospective survey of illness is made over a set period. This is a good method but is limited by the availability of trained personnel, accuracy of diagnosis, etc.

Mortality data involving the inaccuracies of death certification were regarded as of limited value for the purposes of the meeting and autopsies too infrequent to provide information relevant to total incidence. The important subject of future survey programmes was then discussed with enthusiasm by participants and consultants.

### 3.2 Education

Dr Fejfar emphasized the prime importance and inherent difficulties of education in any preventive programme. He outlined the various aspects of such a programme including the distribution of documents, the holding of conferences and the education of the public, and then described the fellowship and research training programmes and the WHO biomedical research information service.

Participants emphasized that WHO publications in the field of cardiovascular diseases are not well enough known in the countries of the Region. They suggested a wider distribution, translation into certain local languages and distribution to members of the seminar and to press and the public. To this end a bibliography of WHO documents was distributed to members of the seminar.

The value of the working papers for meetings of the WHO Expert Committee was expressed.

Dr Fejfar outlined the Australian practice of actively undertaking community education. A public health relations officer and a full-time director are in constant contact with the press.

The role of the International Society of Cardiology in increasing professional knowledge was discussed. Newsletters of the Society would be published more frequently and the content would include current topics on advances in cardiology. The Society would also issue a series of monographs and the first on "cardiomyopathy" would be published by the end of 1968. The Asian Pacific Society of Cardiology is sending to each national society in Asia copies of "Modern Concepts of Cardiovascular Disease" and "Excepta Medica". The programme of the coming 1970 World Congress of Cardiology would be oriented to present advances in cardiology. The Society and WHO co-operate closely in all aspects of cardiovascular diseases.

The activities of the National Heart Foundation of Australia were described. Most states have organizations for post-graduate education and for providing information to the general public. Heart disease had only recently been regarded as a matter for the attention of public health authorities. The Foundation had been particularly active

in the field of ischaemic heart disease. About one-sixth of its annual budget is provided for education activities. The Foundation employs traditional methods of professional education including monthly revisionary pamphlets on cardiovascular topics. When a special problem arises, a document is specially prepared, such as on diet and coronary heart disease.

Community education was a more difficult problem but good co-operation of the mass media had been obtained. A week of intensive education in ischaemic heart disease had been very successful and made a great impact on the community. The Foundation also produces pamphlets for laymen. Fellowships in cardiology are provided. Rehabilitation activity is supported. Copies of written materials would gladly be made available if requested. A cordial relationship exists between the Foundation and the Government. The initial financing of the Foundation was the result of an appeal to the public for funds to which the Government contributed.

The WHO Expert Committee Report on "Prevention of Rheumatic Fever" was commended.<sup>1</sup> The value of secondary preventive clinics in disseminating information to the public was stressed.

Participants made further comments on the situation in their own countries. These are summarized below.

In Brunei, medicine is not yet universally accepted and communications were difficult. Many areas are only readily accessible by helicopter. Education of the community is thus difficult.

There is no definite programme at present in China (Taiwan).

In Fiji, rheumatic fever is well taught to medical students and health nurses. Seminars are held and rheumatic fever was discussed; press releases and radio talks are given.

Participants from the South Pacific area stated that the isolation of small islands is a serious problem. Regular overseas contacts with other workers is needed.

Problems in French Polynesia are similar. Medical officers suffer from isolation. There is a monthly meeting of physicians which might be used to spread information. Nurses are locally trained and are, therefore, particularly trusted and listened to by the local population and, for this reason, would be especially suitable for educating the public. Mass media varied in effectiveness depending on the economic status of the public who were to be reached. The lower levels, which are important, are best reached by visual means. Translation is a problem.

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<sup>1</sup>Wld Hlth Org. techn. Rep. Ser. (1956), 126.

In the Gilbert and Ellice Islands, there is at present no relevant education programme.

There is no organization for publicity on the subject of rheumatic heart disease in Korea. The Government and the medical associations should be encouraged to co-operate in the field of medical education.

In Malaysia, educational facilities exist for educating the public about medical problems but there should be more information on rheumatic fever.

Rheumatic fever is not apparently a problem in Nauru and there is no organization to deal with publicity. Remoteness did not necessarily limit the flow of ideas but seminars such as the present one were useful. Education of the public in medical matters is difficult. There is only one local weekly newspapers but radio can be used. There is no television. Health talks could be successful if they were held under the auspices of the churches. No medical newsletter is at present circulated. Help from WHO is needed.

There is no particular problem in New Caledonia. Physicians are trained in France. Nurses are of two kinds: (a) French-trained, and (b) locally-trained. The latter have little cardiological training. Nurses are taught by practical demonstration during their work. Doctors receive bulletins of the French Cardiovascular Society and also other French publications. Medical societies exist and sometimes publish articles on heart diseases. Newspapers would not be of much help. Television is the best medium. Tuberculosis and leprosy are given priority. More emphasis on rheumatic fever is required. Cartoons and films for television or cinemas would be helpful if WHO could supply these.

In New Zealand, health education is carried out also by nurses. A similar problem to rheumatic fever, namely, deafness secondary to otitis, had been effectively solved with the help of health education. Rheumatic fever is being dealt with in the same way. The importance of the education of Maoris was emphasized. The public generally is keen to learn.

There is no special organization for education in rheumatic heart disease in the Philippines. A little had been done by the universities and the Philippine Heart Association in the field of medical education. An occasional television programme had been prepared and shown. The prevalence of more important problems, e.g., tuberculosis and cancer, tend to inhibit education on cardiological subjects. The Philippine Heart Association had made attempts to advise mothers on the prevention of rheumatic fever. The public are clearly interested in cardiovascular disease and support from the Government for education should be considerably increased.

There is no preventive programme in Tonga. Newspapers and radios are available for education, but there is a shortage of people to carry out the work.

In Viet-Nam there is no cardiovascular society and publications on cardiovascular diseases are few. Prevention should be emphasized in the teaching of students and the Government should be asked to undertake education of the general population. More WHO publications are needed.

The importance of training in developing laboratory resources was mentioned. At an early stage, a person who is knowledgeable in laboratory technology should be brought into discussions and planning. An account was given of the way the Communicable Diseases Section of the Public Health Department in the United States of America undertook health education after consulting with local authorities. The importance of follow-up training was emphasized. Films are of value in teaching technicians and are available through the WHO International Typing Centre in Prague.

A regional reference laboratory should be designated in the Western Pacific which would be responsible for training technicians, introducing new techniques, supplying reagents, etc. Laboratory manuals are already available.

### 3.3 Secondary prevention programmes

Dr Stollerman made a preliminary statement giving his reasons for placing secondary protection before primary protection. He emphasized that young subjects with rheumatic heart disease must be protected against further attacks because they are most vulnerable and have the most to gain from prophylaxis. He stated that following an attack of rheumatic fever, a patient is ten times more likely to have a further streptococcal illness than a non-rheumatic subject. He also emphasized that rheumatic fever patients with heart disease were far more likely to develop a recurrence following a streptococcal infection than those without heart disease. He felt, therefore, that there was a moral obligation on the community to prevent recurrences of streptococcal infection. Dr Stollerman indicated that primary prevention is a more difficult problem. From reports of the other members it did not appear that epidemic streptococcal infections were very common in the Region and it also emerged that there did not appear to be a seasonal incidence as regards these infections.

#### 3.3.1 Case-finding and registers

The question of the desirability of case registers was discussed. Most doctors appeared to object to form-filling. Dr Walsh stated that rheumatic fever had been a notifiable disease in all Australian states but had now been abandoned in all except Queensland. It was stated that it is difficult to legislate doctors into conformity - most of them were conscientious as regards patient care and would object to form-filling unless it was necessary for the patient's welfare. A means of notification was discussed whereby the drugs for chemoprophylaxis could be obtained free by means of a special prescription form. This form would contain relevant details as regards patient and could, therefore, be used for compiling registers. As regards this, Dr Wong stated that in Malaysia, the Government paid a special grant to tuberculosis patients and, therefore, the patients themselves insisted on notification.



Dr Stollerman was in favour of notification which he stated is mandatory in many states of the United States. Failure to notify rheumatic fever would not, of course, be viewed with the same seriousness as a similar failure in an infectious disease such as diphtheria or smallpox. He also made the point that notification gives the disease a certain public health stature and that this is helpful psychologically as a reminder to physicians of its preventable nature. He also stated that once diagnosed, a case should have recourse to a definite prevention programme if registration is mandatory.

### 3.3.2 Chemoprophylaxis

Discussion as regards specific chemoprophylaxis for patients who have had rheumatic fever brought out the following points:

(1) Penicillin V for oral use in Group A streptococcal prophylaxis has no significant advantage over penicillin G which is considerably cheaper. Superior absorption from the G-I tract has been claimed for penicillin V but this was judged to be of no importance as the Group A haemolytic streptococcus is so extremely sensitive to penicillin that high blood levels are not required.

(2) In using sulphonamides, sulphadiazine is suitable and those more expensive sulfonamide preparations with greater urinary solubility need not be used as there is no danger of nephrotoxicity from the small doses of sulfadiazine needed to prevent Group A streptococcal infection.

(3) In the treatment of a streptococcal sore throat, 1.2 million units of benzathine penicillin G intramuscularly in an adult or 600 000 units of a similar preparation in a child is optimum treatment. Mixed types of penicillins which do not contain this amount of benzathine penicillin G and which substitute shorter acting penicillin salts need not be used as the period of cover may not be long enough and high immediate levels are not required.

(4) As regards the choice between oral or intramuscular penicillin, it was suggested that:

- (a) Where the streptococcal challenge is greatest, intramuscular benzathine penicillin G should be used.
- (b) Where the host is at greatest risk, that is, in those with established rheumatic heart disease, intramuscular benzathine penicillin G should be used also.
- (c) Oral penicillin G in daily doses of approximately one million units must be given ten days to be maximally effective. Fidelity of patients to the full ten-day regimen is rare. However, in areas of less serious streptococcal disease and in less susceptible hosts, oral penicillin has been satisfactory. Sulfonamides should not be used to treat an established streptococcal infection. They do not result in bacteriologic cure and, therefore, do not prevent rheumatic fever when used therapeutically.

It was estimated that the cost of penicillin prophylaxis, in fact, was very low - for example, in the United States of America, it was estimated that oral prophylaxis costs approximately 30 cents a month as against 75 cents for intramuscular cover when drugs are purchased in large quantities for health agencies at wholesale prices.

Sulphadiazine was also generally accepted as a reliable drug for chemoprophylaxis.

Dr Mulet raised the question of anaphylactic shock following penicillin injections. Dr Stollerman quoted a large series in the United States of America where approximately 400 000 military personnel received benzathine penicillin G injections. They were followed up for nine weeks after the injection and there was only a .8% reaction rate. There were no fatalities. The relative stability of benzathine penicillin G was emphasized and the risk of fatal anaphylaxis weighed against that of rheumatic recurrences in the young rheumatic cardiac. The allergenic properties of less stable penicillin G salts were pointed out and the fact that breakdown products of penicillin G (penicilloic and penicillenic acid derivatives) were the causing allergy was emphasized. Participants were warned against solutions of penicillin G stored too long and insufficiently refrigerated.

Duration of prophylaxis was also discussed. It was emphasized that no arbitrary age could be set but that one must individualize the risk of discontinuing prophylaxis by such factors as: (a) the presence or absence of heart disease; (b) exposure to children and to streptococcal infections; (c) time elapsed since last attack, etc.

### 3.3.3 Follow-up measures

The following aids were stressed in securing help to follow patients receiving continuous chemoprophylaxis:

(1) Education and proper use of allied health personnel - public health nurses, school nurses, teachers, parent-teachers organizations, clerical help.

(2) Rural health units or teams, particularly in the Philippines.

(3) Provision of free chemoprophylaxis with a distribution system that required patients appear for renewal of prescriptions and where a registration would reveal those who are delinquent.

### 3.3.4 Laboratory support

Laboratory support was considered less essential for secondary prevention programmes than for primary programmes. Patients receiving continuous prophylaxis have less need for identification of streptococcal infection than do patients who are not rheumatic and who present to physicians for treatment of sore throat.

However, the use of ASO titres to aid in the diagnosis of rheumatic recurrence was very helpful and it was also considered quite useful, if not essential to have throat cultures available when breakthrough of streptococcal infections require diagnosis by cultures of a sore throat in rheumatic patients receiving continuous prophylaxis.

It was apparent that laboratory services were very limited in many areas where the problem of rheumatic fever was most severe.

### 3.4 Primary prevention programmes

#### 3.4.1 Control of epidemics

The availability of mass prophylaxis to terminate streptococcal epidemics in limited populations was re-emphasized. Although none of the countries could identify epidemic conditions, it was considered worthwhile to review the effectiveness of giving all members of a population an injection of benzathine penicillin G, 1.2 million units. The prolonged protection - five to six weeks afforded by a single dose, plus its effectiveness in eradicating organisms from the throat of both carriers and symptomatic cases was emphasized. Penicillin by mouth in daily divided doses of 1 million units for ten days is also useful but less effective.

The need to identify epidemic pharyngitis as due to Group A streptococci was emphasized. For this, throat cultures are essential. However, failure of exudative pharyngitis to respond to penicillin signals viral rather than streptococcal pharyngitis. Prompt and invariable response clinically suggests streptococcal etiology but is sometimes misleading when brief viral infections abate coincidentally after penicillin treatment.

#### 3.4.2 Treatment of sporadic sore throat - individual prophylaxis

From a review of all countries represented, it seemed that the problem was more one of identifying the etiology of a steady, consistent, incidence of sore throat and acute rheumatic fever rather than a seasonal outbreak of the former or cluster of the latter.

The value of one good laboratory in an area to define the magnitude of the streptococcus problems and to sample the population was emphasized and demonstrated by Dr Benjamin's laboratory at the University of the East which has yielded such valuable data for Manila.

Dr Moody reviewed ways in which laboratory support for streptococcal disease diagnosis was implemented in the United States of America including a regional reference laboratory, local state health department laboratories, local hospital and clinic laboratories and mail-in of cultures for rural areas.

Education and training of allied health personnel and of parents and teachers to the need for proper diagnosis and treatment of sore throat was reviewed. The case of training relatively unskilled help to swab throats and inoculate blood agar plates was discussed.

Even in the absence of laboratory facilities, sore throats should be treated as streptococcal by clinicians if the incidence of rheumatic fever in the community is high. The intensity of the treatment should be geared to the magnitude of the rheumatic fever problem. Where much mild streptococcal disease exists in high socio-economic groups, rheumatic fever occurs so rarely that less stringent treatment for less than ten days and with antibiotics other than penicillin is associated with little rheumatic fever. Such measures, however, cannot be recommended for low socio-economic populations in very crowded areas where the problem is severe. Here, single injections of benzathine penicillin G should be used. Mixtures of different penicillin salts are not needed for Group A streptococcal infections.

The excellent opportunity to study the problem of primary prevention control in the Region was emphasized, especially in certain areas of crowding and rapid industrialization.

### III. SUB-ACUTE BACTERIAL ENDOCARDITIS (SBE)

#### 1. Introduction

##### 1.1 Natural history of SBE (Annex 7)

Dr Stollerman referred to alteration in the natural history of sub-acute bacterial endocarditis due to irregular and inadequate administration of antibiotics to sufferers in the earlier stages of the disease which temporarily suppresses the infection and frequently interferes with likelihood of isolation of the micro-organism from the blood. Infection tended to occur in situations where, as the result of rheumatic or congenital heart disease, a strong jet of blood was present in areas of the heart. In 85% of cases infection was due to Streptococcus viridans arising from the oral cavity, and this organism was usually sensitive to penicillin. He also referred to the L-form of S. faecalis emerging after long exposure to penicillin and proving resistant to antibiotics, resulting in valve abscesses and thus congestive heart failure. He drew attention to the new spectrum of organisms now appearing in the blood of patients following cardiac surgery including monilia infections which are quite resistant to antibiotics in common use. He emphasized that patients with rheumatic heart disease on chemoprophylaxis as part of a secondary preventive programme were not necessarily protected from sub-acute bacterial endocarditis in such individuals had been reported. He felt that both sub-acute bacterial endocarditis vasculitis and glomerulonephritis rarely occur nowadays and recently drug fever have become rare. He referred to a single spike of fever as embolization and not representing a relapse requiring a change of treatment.

## 1.2 Diagnosis and treatment

Sir Kempson Maddox spoke on diagnosis and treatment of sub-acute bacterial endocarditis and referred to its frequency following dental treatment and genito-urinary instrumentation. In his experience, it was infrequent following pregnancy, road accident, bronchoscopy and cardiac catheterization. He agreed with Dr Stollerman that the clinical picture has changed considerably as a result of premature and inadequate administration of antibiotic prior to admission to hospital. However, treatment should be commenced as soon as possible by using the antibiotic indicated as a result of laboratory study. If blood cultures remain negative after 72 hours, treatment should be started with intramuscular penicillin in high dosage combined with streptomycin with two daily injections. If reduction in fever and toxæmia has failed in the next three days, ampicillin, or cephaloridine should be substituted and vancomycin and kanamycin should be reserved for the highly resistant situations.

Tests for inhibiting growth of the infecting organisms by the patient's own serum should be done twice weekly as well as full blood counts.

Treatment even after clinical improvement should be continued for at least four weeks and be supervised in the hospital for at least ten days.

In differential diagnosis the main difficulty is to distinguish SBE from relapses of rheumatic carditis. Common to both are cardiac enlargement, CHF, and fever and arthralgia and sometimes generalized rashes and anaemia. In the case of rheumatic relapse, reliance should be placed on a history of recent sore throat, migratory polyarthritides, specific rheumatic rashes, nodules, absence of splenomegaly but chiefly a rise in ASO titre.

Other conditions requiring differentiation are similar to those which mimic acute rheumatic fever, e.g. serum sickness, sickle-cell anaemia, acute leukemia, brucellosis, meningococcaemia, etc.

In discussion, the question of differentiation from other tropical fevers as malaria, typhus, etc. was brought up, but this would not appear to be of any urgent import.

## 1.3 Preventive measures (Annex 8)

Dr Limson briefly outlined the preventive measures. Specific steps included indoctrination of the patient with regard to suitable antibiotic prophylaxis before undergoing dental, urological and other surgical procedures. He emphasized the importance of the education of the four groups of individuals more or less directly involved: dentists, ENT specialists, urologists, obstetricians and gynaecologists. Where the patient happens to be a minor, it is important that the parents or the guardian, as the case may be, should be duly informed of the importance of prophylactic measures.

## 2. Discussion by Participants

The experience in the Region was reviewed. There was an impression from several countries (Malaysia, Philippines, Fiji and China (Taiwan)) that the incidence of positive cultures was low in suspected cases of SBE. Dr Limson and Dr Stollerman, however, indicated that in their studies up to 80% of cultures were positive in the first three samples of blood taken in patients with clinical diagnosis of SBE.

Two suggestions were made to explain this:

- (a) That many fevers, many causes of splenomegaly and anaemias may confuse the picture of SBE in the area.
- (b) That technique of blood culture may be inadequate especially if penicillin is not used in cultures.

A review of methods of blood culture suggested improvement of diagnosis by use of (a) vacuum flasks containing medium for direct inoculation; (b) anaerobic cultures and (c) better proximity of patient to laboratory with direct supervision of the culture by a physician.

Recommendations for prophylaxis of SBE should bear in mind that in some countries, e.g., Malaysia, dental nurses cannot give injections and oral prophylaxis may be necessary.

From Dr Limson's data in the Philippines, it appeared that the usual oral flora are most common causes of SBE but that infections acquired in the hospital show a higher incidence of more unusual and resistant organisms. The data in China (Taiwan) were similar.

## IV. MISCELLANEOUS DISEASES OF THE HEART

### 1. Diphtheria

Clinical impressions of frequency were unreliable but notification figures from the Region indicate that it is present in all countries and there is a significant mortality in all countries.

Several speakers emphasized the danger of missed diagnosis in countries such as Australia and French Polynesia where, as it is not common, clinicians tend to overlook the possibility of its occurrence. Diagnosis is usually made without difficulty in those countries where it is common such as Viet-Nam. However, there was a danger of overlooking those cases which presented with myocarditis without pharyngeal or neurological manifestations, particularly if heart block is also absent. The toxin attacks Purkinje system first and myocardium subsequently. Thus, heart block is an early manifestation and myocarditis occurs later. For the same reason, recovery from heart block is not infrequent while recovery from myocarditis with cardiac dilatation is rare. The possibility of wrongly attributing the condition to viral myocarditis and other conditions causing myocarditis such as beri-beri, rheumatic carditis and anaemia was stressed.

Immunization against diphtheria is not compulsory in all countries and even where it is, it is not universally practised.

The importance of throat swabs and also nasal swabs in the investigation of difficult cases of myocarditis was emphasized.

The control of diphtheritic myocarditis depends primarily on the public health measures for the control of diphtheria. However, it was stressed that physicians both in countries where it is common and also where it is rare, should bear the diagnosis in mind in cases of myocarditis.

## 2. Viral Myocarditis

The lack of satisfactory laboratory means of diagnosis of most forms of viral myocarditis was stressed although coxsackie infections could be identified in this way. The occurrence of epidemics due to this organism was mentioned. The absence of organic murmurs was mentioned as useful in distinguishing viral from rheumatic myocarditis. It was emphasized that the condition arises at all ages even in newborn.

There was general agreement that there was insufficient data to show whether it represented a significant public health problem.

## 3. Rubella

While it was unknown how common congenital heart defects resulting from rubella in pregnancy were in the Region, the incidence appeared to vary greatly from one country to another. In four countries, it is a notifiable disease. In Australia, 2000 to 2500 cases were notified annually. The haemagglutination test is a sensitive and reliable index of immunity and could provide a means of determining the frequency of the condition in the community. It was indicated that WHO could assist in sending of blood samples for this type of investigation.

The finding of arteritis in renal, pulmonary and other vessels in patients dying with the rubella syndrome was mentioned and the possibility that these could be responsible for cardiovascular disease in surviving patients in later life was referred to.

The possibility of effective prevention by vaccination with attenuated virus was discussed. Such a vaccine will be available shortly. Its use will lead to some problems where there is a possibility of pregnancy at the time of, or its onset within six weeks of, vaccination and the advisability of using it in women of child-bearing age needed careful consideration before its use in a preventive programme.

#### 4. Syphilis

Although there was an appreciable prevalence of cardiovascular syphilis in some countries of the Region, the numbers appeared to be decreasing. Primary and secondary syphilis, though less common than formerly, appeared to be on the increase recently. Public health authorities in all countries appeared to be active in the control of this problem; and the fact that it is extremely sensitive to penicillin facilitated its control.

#### 5. Acute Endocarditis

Acute endocarditis was not discussed.

#### 6. Typhus

Scrub typhus is endemic in a number of countries in the Region but cardiac complications were not well documented, and appeared to be uncommon. Diagnosis was usually made in the routine investigation of patients with fever and laboratory tests for this and other rickettsial infections were available and chloromycetin was an effective therapeutic agent.

#### 7. Tuberculous Pericarditis

The incidence of tuberculous infections in many countries in the Region is high and thus tuberculous pericarditis is not uncommon. However, its prevention depends on public health measures and all countries active programmes in the field. In the meantime, early diagnosis and treatment was urgent.

#### 8. Cor Pulmonale

This was a common and serious form of heart disease in the Region. It usually accompanied obstructive lung disease the result of chronic bronchitis, tuberculosis, asthma, etc. Smoking of tobacco and opium were referred to as predisposing factors. Overcrowding and environmental conditions conducive to high incidence of intercurrent respiratory infections appeared to be significant factors.

There was general agreement that this was a serious problem in the Region, with implications for preventive measures and that it should be considered in depth in some further discussion.



### 9. "Black Foot Disease"

The occurrence of 800 cases of this disease in the past ten years was reported from China (Taiwan). Investigations had indicated that it was associated with drinking deep well water which contained relatively high levels of arsenic, of the order of 0.15 to 1.0 ppm (normal up to 0.05 ppm). A survey had shown a prevalence of 8.9 per 1000 of population. It occurred at all ages (range 2 years to 82 years). The clinical feature was gangrene of the extremities of insidious onset and other features of peripheral vascular disease were present. It was frequently associated with arsenical dermatitis and neoplastic change but central nervous involvement was uncommon.

Since public health measures had prevented the drinking of the infected water, the condition is diminishing.

### V. PREVENTABLE ARTERIAL HYPERTENSION

The subject was introduced by reference to the problems of definition of hypertension and the pitfalls of casual readings. It was generally agreed that levels above 160/95 were abnormal. Two aspects of prevention, that of the hypertension itself and that of prevention of complications were emphasized. Of the various primary causes of hypertension, glomerulonephritis and pyelonephritis were the main conditions that offered an opportunity for primary prevention. The discussions made it clear that there was very little statistical information on the incidence of hypertension or on its various causative factors in the Region. However, the following comments were made by the participants:

As in other western countries, hypertension is a common cause of cardiovascular disease in Australia but the mortality from its complications is falling. Acute glomerulonephritis and pyelonephritis are common in children.

In Brunei, it is difficult to assess the extent of the problem but it appears to be common and gout is also common among Malays. Toxaemia is uncommon.

Hypertension is common in China (Taiwan) but the incidence varies in different areas, being as high as 20% in one fishing community and only 2.7% in an urban community. Cerebral vascular disease had been the main cause of death since 1963. In a series of patients with juvenile hypertension, 80% was considered to be primary, 14% secondary to renal disease and 2% attributed to other conditions.

In Fiji, hypertension is common among Indians, but uncommon in Fijians and acute glomerulonephritis shows a similar pattern.

French Polynesia - one-third of all cardiovascular admissions to hospital are due to hypertension. Diabetes, obesity and gout are frequently associated. Glomerulonephritis is not often diagnosed but may be under estimated. Toxaemia is rare.

Hypertension does occur in the Gilbert and Ellice Islands but usually in the elderly and complications are rare.

In Japan, ischaemic heart disease is infrequent but hypertension is common and cerebrovascular disease is one of the commonest causes of death.

Neither hypertension nor toxaemia is common in Nauru.

In New Caledonia, hypertension is frequent after the age of 30 and diabetes and hypercholesterolemia are often associated. There are few cases of toxaemia and renal disease is not common.

In New Zealand, the problems in Europeans resemble those in other western countries. There is a surprisingly high incidence in Maoris and hypertension is frequently associated with a gouty diathesis. While the mortality from hypertension in Europeans is falling, this is not so in Maoris.

Hypertension is an important cause of cardiovascular disease in the Philippines but investigation of the cause is difficult because of lack of facilities. A study had shown that blood pressures in a Filipino population were 5 mms. of Hg. lower than in comparable subjects in the United States of America.

In Samoa there are few hospital admissions for hypertension and those are mostly men. The condition is often associated with obesity or diabetes. Toxaemia is not seen.

Hypertension is not common in Tonga and is often associated with chronic nephritis and diabetes. Toxaemia of pregnancy is rare.

Hypertension is frequent in Viet-Nam and is frequently associated with nephritis. Toxaemia is common in women.

A general discussion followed on the control of various forms of nephritis.

The common association between acute glomerulonephritis and streptococcal pyoderma was emphasized. For diagnosis it was recommended that a swab be taken for bacteriological examination after simple removal of scabs by clean gauze and warm water. Treatment of the skin lesion depends on local cleanliness and hygiene but in severe infections, systemic penicillin treatment was indicated. The pathogenesis of acute glomerulonephritis was discussed and although this differed in some respects from rheumatic fever, it was generally agreed that measures for controlling streptococcal infection were equally necessary in the two conditions.

It was agreed that prevention or early treatment of urinary tract infections offered a most effective means of preventing one form at least, hypertension. Professional education, for nurses as well as doctors, was an important measure, particularly to emphasize the dangers of catheterization as an important cause of pyelonephritis and also to stress the importance of adequate treatment. The value of simple urinalysis in detecting cases of nephritis was stressed and it was suggested that this may have a place in case-finding in some situations.

## VI. ISCHAEMIC HEART DISEASE

### 1. Prevention of Ischaemic Heart Disease

This subject was introduced by Dr Fejfar, who gave the conference available information on the overall frequency of ischaemic heart disease. Mortality from arteriosclerotic and degenerative heart disease in 1964 in twenty-three countries accounted, on average, for 53% of deaths among all types of heart disease. Marked differences in the death rates among the countries exist, particularly in younger age groups. Those countries with the lowest mortality rates in 1965 experienced the greatest increase since then, particularly in the lower age groups, whereas in the United States of America, there had been no age specific increase. All countries showed a distinct sex difference (less in females), decreasing with age. Greater reported differences sometimes exist between population groups within a country of high incidence than between countries. Morbidity statistics are generally unavailable. The prognostic influence of several so-called risk factors has been well established, but only a few studies on primary or secondary prevention have shown altered incidence of ischaemic heart disease by control of these factors. Encouraging results have followed attempts at decreasing caloric intake and alteration of the types of fat consumed, but there is need for further confirmation. The pilot study in the United States of America of such modification of diet has shown that a double-blind investigation on a larger scale is feasible. A further inquiry as to the value in primary prevention of clofibrate ("Atromid S") covering 5000 individuals is in progress with WHO support, but 15 000 subjects will be required altogether. It remains to be proved whether lowering of blood pressure will change the natural history of ischaemic heart disease. In the WHO study of autopsies in Europe, it was found that myocardial infarction accounted for 12-16% of all deaths in the 30-45 age group. This raises the question of how soon active intervention by control of risk factors should begin. In a disease of multifactorial origin, controlled trials where more than one factor is modified are desirable, and it has yet to be determined whether the risk factors singly or together operate directly or indirectly. For example, arterial hypertension is usually associated with ischaemic heart disease in populations where blood cholesterol levels are above 200 mg per cent. Other influences such as the hardness of drinking water, altered balance of some minerals, emotional stress and habitual physical activity, tobacco, diabetes, gout, obesity, may be of importance.

Dr Fejfar then discussed treatment in respect to the prevention of complications following myocardial infarction such as the use of anti-coagulants, early ambulation, observation of electrical instability of the heart, etc. He referred to the all-important problem of cardiogenic shock, at present largely uninfluenced by treatment, the problem of deaths before admission to hospital, and the various criteria preferred for admission to an intensive care area. He spoke of future attention to these problems and to the increasing possibility of surgical intervention in the acute phase, and of the role of the community in the problem. Secondary prevention and rehabilitation are equally important considerations.

## 2. Magnitude of the Problem in the Region

### 2.1 Report by consultants

Dr Alimurong, employing his knowledge of the Philippines and of neighbouring countries, noted the lower incidence of ischaemic heart disease in Manila as compared to that of western countries, quoting a figure of 15.5% of all cardiovascular diseases in Filipinos admitted to hospitals in the city of Manila, and of 9.5% Chinese admitted to the Chinese General Hospital. He stated that in Japan, there were no occupational differences; the disease was more prevalent in urban communities and was increasing. According to his information, the incidence in Korea, China (Taiwan) and Malaysia was low.

Dr Reader gave his impressions of the situation in countries visited prior to the seminar. He had concluded that ischaemic heart disease was an increasing problem in Malaysia, Singapore and Hong Kong but extremely rare in Cambodia. He quoted from hospital admissions in Kuala Lumpur, a rate of 25% of all admissions for cardiovascular disease, 20% in Singapore and 10% in Hong Kong, while only 7 cases in ten years had been seen in Phnom-Penh by a physician of that city. A feature of the disease in Phnom-Penh was the absence of pain. In the countries visited, differences in incidence among ethnic groups were clearly apparent.

### 2.2 Discussion by seminar participants

Australia - Ischaemic heart disease was a major problem and the most common cause of death.

China (Taiwan) - Ischaemic heart disease is rare. Blood cholesterol levels were below 210 mg% in 90% of subjects in one survey. Ischaemic heart disease constituted only 9.5% of all cardiac admissions to the National University Hospital, and in 1958, 1.8% of total deaths in China (Taiwan).

Fiji - The incidence of ischaemic heart disease in the Indian population is high, e.g., 98 of last 100 admissions with this disease to the Memorial Hospital, Suva, were Indians. The infrequency in Fijians may be related to their more active life and predominantly fish diet.

French Polynesia - There were only 25 cases in five years at the Colonial Hospital in Papeete, i.e., 6 per 1000 hospital admissions. In routine electrocardiograms of all hospital admissions, only 5% showed an abnormality.

Japan - In Osaka, the incidence of myocardial infarction had increased from 9.9 per 100 000 of the population to 27.7 between 1950-1967.

New Caledonia - The incidence is low but increasing. It was responsible for 13% of hospital admissions in recent years. Europeans were the main victims.

New Guinea - Ischaemic heart disease was rarely seen either in clinical practice or in certain population surveys.

New Zealand - The situation in regard to the Europeans is similar to that of Australia, but there is a surprisingly high prevalence in Maori women. In Rarotonga, the incidence is higher than in Puka Puka, where physical activity is greater and contact with western civilization less.

Philippines - The epidemiology of ischaemic heart disease was not well studied and the increasing use of the electrocardiograph had given a false picture of the trend.

Singapore and Malaysia - Ischaemic heart disease occurs least frequently in Chinese and more common in Malays and Indians. It appears to increase with improved standards of living among these ethnic groups.

Tonga - Ischaemic heart disease is rare but increasing, e.g., was responsible for 0.12% of total deaths in 1964, 3.5% in 1965-66 and 5% in 1967.

South Viet-Nam - There have been few cases; the condition is not a problem, but it may be increasing now.

Brunei	)	
South Korea	)	In these countries ischaemic heart disease
Nauru	)	was very infrequent.
Western Samoa	)	

In general discussion, Dr Stollerman spoke of the opportunity for a study in depth of contrasting prevalence and incidence of risk factors in the Region but emphasized the necessity for control of the many variables involved. He felt that interested bodies should plan such investigations.

Dr Maddox felt that in collaboration with WHO, certain research groups such as the Research Committees of the Asian-Pacific Society of Cardiology and the International Society of Cardiology could become interested in this problem. He drew attention to the contrasting incidence of ischaemic heart disease in the same ethnic group located

in different areas of the Western Pacific. As a model for such investigations, the study now in progress in the New Guinea Highlands should be considered. He felt that any investigation should take note of thrombotic tendencies and of pain threshold in differing ethnic groups. It was premature to discuss primary prevention at this stage.

## VII. SUMMARY AND CONCLUSIONS

### 1. Rheumatic Fever (Agenda Item II)

#### 1.1 Size and nature of the problem in the Region (Agenda Item II - 1)

1.1.1 Reports from all countries of the Region revealed a wide range in the magnitude of the problem. Rheumatic fever appeared to be under good control in several populations such as the Europeans of Australia and New Zealand, but was severe and intense in such areas as the Philippines, Hong Kong and Singapore.

1.1.2 The consistent increase in the magnitude of the problem of rheumatic carditis under conditions of depressed socio-economic status and overcrowded living conditions was impressive.

1.1.3 All ethnic groups are vulnerable to rheumatic fever and when any such group is exposed to the above conditions, the attack rate of rheumatic fever is high.

#### 1.2 Resources necessary for preventive measures (Agenda Item II - 2)

1.2.1 In most areas of the Region, existing health services can accommodate at least a secondary preventive programme. Lack of specific formulation of the programme, lack of free chemotherapeutic agents, and lack of awareness of need by the professional and lay community are main obstacles to its implementation.

1.2.2 The following problems interfere with establishing a secondary prevention programme in this Region as elsewhere:

- (a) Despite the fact that rheumatic fever is recognized as a clinical problem, it is not accepted as a problem deserving high priority by public authorities.
- (b) Prophylaxis of rheumatic fever is often accepted in principle but not in practice.
- (c) In contrast to the great interest of clinicians in the advanced medical and surgical management of rheumatic heart disease, there is a lack of enthusiasm for initiating preventive measures against rheumatic fever.

- (d) There is a need for the education of practitioners to appreciate the significance of polyarthralgia and polyarthritis, particularly in children.
- (e) Chemoprophylaxis is often not instituted properly because of the cost of drugs, the patient's fear of penicillin injections, the physician's anxiety concerning anaphylaxis to penicillin, and the lack of awareness of the most appropriate chemotherapeutic agents for prevention of primary and secondary attacks.
- (f) A lack of public awareness of the need for continuous prophylaxis in the asymptomatic patient makes it difficult to sustain the prolonged co-operation essential to an effective preventive programme.
- (g) Although the laboratory facilities for the diagnosis of rheumatic fever and streptococcal infections exist in major medical centres, such facilities are not generally available to the community, particularly in areas where the problem seems to be most severe.

1.2.3 The situation for prevention of rheumatic fever is particularly suitable in the Region because:

- (a) There is a predominance of a young population in many countries.
- (b) Severe chronic rheumatic carditis exists in large numbers, particularly in urban and industrial centres.
- (c) Different ethnic groups with varied socio-economic conditions allow the identification and treatment of populations that are most seriously affected and are at greatest risk.
- (d) A marked contrast in the rheumatic fever problem is evident in many countries between rural and industrial areas which permits concentration on the problem in specific locations.
- (e) Frequent development and rapid progression of rheumatic heart disease in children is a feature of many areas of the Region. The effectiveness of prophylaxis, therefore, will be particularly evident and rewarding in such areas.

### 1.3 Formulation of preventive programmes

#### 1.3.1 Data collection (Agenda Item II - 3.1)

(a) As the problem appears to be more extensive in many areas than has been appreciated, and adequate data are lacking, it is important to define the extent of the problem more accurately.

(b) Under present circumstances, the most effective and feasible method of data collection for countries in the Region is by surveys based on school health services. Representative population samples will yield a great deal of information. Surveys based on maternal health services may also provide useful information but are less satisfactory than school surveys.

(c) Such information should be obtained in all countries of the Region where the problem is already known to be serious and particularly where overcrowding and exposure to infection is increasing. From the information already available at the conference, it was agreed that such conditions exist in the Philippines, Hong Kong, Singapore, Malaysia, Brunei, Viet-Nam, Fiji, Cambodia, Taiwan, Korea and among the Maoris.

### 1.3.2 Education (Agenda Item II - 3.2)

(a) Effective education was considered an essential and integral part of preventive programmes of cardiovascular diseases.

(b) Prevention of cardiovascular disease in general and of rheumatic fever in particular, for both individual patient care and community programmes should be emphasized in medical curricula, post-graduate courses, and in the training of hospital interns, general practitioners, paediatricians, and other medical specialists. This training should emphasize the importance of data collection and accurate completion of death certificates.

(c) Prevention of cardiovascular diseases should be included in the educational programmes of nurses and other allied health workers.

(d) The general public should be informed on all aspects of the prevention of rheumatic fever through available media, e.g., instruction of the family by a physician, mass media, instruction in schools, etc. Printed material, films and other documentary materials exist in considerable amounts, can be adapted to local customs and habits, and can be made available on request to appropriate agencies, such as WHO, national heart associations, etc.

(e) Facilities for training and for exchange of health workers in the field of cardiology should be developed with the help of governmental and other organizations and agencies, particularly for areas in which the problem of rheumatic fever is serious.

(f) Relevant publications such as reports and guidelines issued by WHO and other organizations should be made widely available and, where appropriate, translated into local language.

(g) The Region is characterized by many countries widely separated and often isolated. Communication is, therefore, particularly difficult and regional organization of training facilities in the form of conferences, seminars and other methods of post-graduate education are very necessary. Particular emphasis in all areas should be given for training in laboratory methods as they apply to the control of cardiovascular diseases.



1.3.3 Secondary prevention programmes (Agenda Item II - 3.3)

The following guidelines for secondary prevention programmes in the Region were formulated:

(a) It should be considered the responsibility of the community to identify those who have had rheumatic fever and to see that a suitable chemoprophylactic regimen is initiated.

(b) Identification should involve a programme of case-finding through existing services such as routine health examinations and particularly through school examinations and maternal and child health facilities.

(c) Wherever possible, notification and registration of cases identified should be accomplished through appropriate health agencies.

(d) Rheumatic fever prevention clinics should be organized within existing medical facilities, especially teaching hospitals where they should serve as a model of medical management for the community.

(e) An appropriate form of continuous prophylaxis should be instituted. The selection of oral penicillin or sulphadiazine, or intramuscular benzathine penicillin G at monthly intervals, depends upon the particular kind of patient and the region or country involved. Intramuscular benzathine penicillin G, being most effective, is recommended for the patient at greatest risk, namely, the young rheumatic cardiac exposed to a high incidence of streptococcal infection.

(f) The duration of such prophylaxis should be continued as long as the risk of recurrent rheumatic fever justifies the therapy. Such risk should be defined for each individual in terms of (1) challenge of streptococcal infection, (2) the presence or absence of rheumatic heart disease, (3) the age of the patient, and (4) the time elapsed since the last attack.

(g) Chemotherapeutic agents should be provided by all possible means of public support including:

- (1) Government agencies
- (2) International agencies, such as UNICEF
- (3) Voluntary organizations such as heart associations and other community organizations
- (4) Donations by pharmaceutical firms

(h) The follow-up of patients in such programmes should be re-enforced by all possible means such as: (1) monitoring system for distribution of prophylactic agents, (2) utilization of allied health personnel who have close contact with patients such as school nurses, and public health nurses, (3) voluntary health agency personnel, and (4) surveillance of patients by allied health personnel attached to a registry.

(i) Educational programmes concerning the need for, and the basic principles of, continuous prophylaxis should be instituted for the medical profession, including medical students, for nurses, and for public health and education personnel, including teachers.

(j) The general public should be educated by distribution of appropriate literature, special features for mass media, and formal instruction of patients and their families.

(k) When applicable, ad hoc committees of those interested in rheumatic fever prevention should be organized to lend advice, support and leadership to the development of such a programme.

(l) The group recognized the importance of rehabilitation as part of a secondary prevention programme. In some cities with extensive slum areas, the establishment of special convalescent hospitals or areas of existing hospitals for severely affected children coming from unsatisfactory home conditions is highly desirable.

(m) Provision for basic laboratory facilities for identifying Group A streptococci and streptococcal antibodies should be a part of a secondary programme.

#### 1.3.4 Primary prevention programmes (Agenda Item II - 3.4)

The following proposals for guidelines suitable for all countries were made:

(a) Effective treatment of streptococcal pharyngitis can prevent first attacks of rheumatic fever. It should be the responsibility of the community, therefore, to identify the magnitude of the problem of streptococcal diseases in order to determine the type and extent of the primary prevention programmes that are needed.

(b) Mass prophylaxis: epidemic streptococcal pharyngitis should be terminated promptly by treatment of all individuals in the affected group by intramuscular injection of 1.2 million units of benzathine penicillin G. For very young children, 600 000 units of benzathine G may be considered instead.

(c) Active measures to institute a primary prevention programme should be undertaken when a high incidence of endemic streptococcal pharyngitis is made apparent by:

- (1) the appearance of many cases of acute rheumatic fever;
- (2) the appearance of cases of severe intractable rheumatic carditis in children.

(d) Because the diagnosis of streptococcal pharyngitis by clinical criteria alone is uncertain, laboratory support of the diagnosis by throat cultures and immunological tests for streptococcal infection should be provided wherever possible. Laboratory studies on a sample population with sore throat can provide the clinician with an excellent picture of the streptococcal disease problem in the population as a whole.

(e) In areas where rheumatic fever and rheumatic heart disease are common, bacteriological facilities for identification of streptococcal infection should be established where they do not now exist. For more remote areas, techniques for mail-in or other means of transportation of cultures to an area or regional laboratory should be considered. A streptococcal reference laboratory for areas within the Region should be established to improve standards of diagnosis and to provide training.

(f) Prevention of first attacks of rheumatic fever depends upon efficient eradication of the organism. This requires at least ten days of penicillinemia. A single injection of 600 000 units of benzathine penicillin G in children and 1.2 million units in adults, should be used in populations at great risk. The alternative of ten days of oral penicillin, while theoretically effective, is often not faithfully carried through. It is acceptable, therefore, only in areas where the risk of rheumatic fever is known to be small. For patients who are allergic to penicillin, ten days of erythromycin, 1 gm a day in divided doses, is recommended.

(g) Educational programmes should be intensified for all members of the medical and allied health profession concerning:

- (i) the difficulties of diagnosis of streptococcal infections without laboratory support;
- (ii) the relative effectiveness of different chemotherapeutic regimens for the bacteriologic cure necessary to prevent rheumatic fever;
- (iii) adequate laboratory diagnosis of streptococcal infections.

(h) Public health and other appropriate governmental and social agencies should be alerted to the need for good diagnostic and therapeutic measures against streptococcal infection in areas of intense crowding and depressed socio-economic conditions. These authorities should be made aware that the trend toward increasing industrialization and population concentration will increase the risk of rheumatic fever in the future unless provisions are made to implement adequate control measures.

## 2. Sub-Acute Bacterial Endocarditis (SBE) (Agenda Item III)

2.1 Patients with chronic rheumatic or congenital heart disease should maintain a high standard of dental hygiene at all times.

2.2 Such patients should also have specific antibacterial prophylaxis prior to dental, surgical or obstetrical procedures, as follows:

(a) For dental procedures, the above patients, irrespective of whether or not they are already receiving chemoprophylaxis against Group A streptococcal infection, should receive:

600 000 u. of aqueous procaine penicillin intramuscularly, one to two hours beforehand and daily thereafter for at least two days.

(b) Patients undergoing surgical, obstetrical or urological procedures should be given:

600 000 u. of aqueous procaine penicillin and  
600 000 u. of aqueous crystalline penicillin G in  
a single injection intramuscularly and streptomycin  
1 gm\* intramuscularly one to two hours before the  
procedure. Subsequently, aqueous procaine penicillin  
600 000 u. and streptomycin 1 gm should be given  
intramuscularly daily for two days.

2.3 Where it is not practical for trained medical personnel actually to give the injections prior to dental or obstetric procedures, 250 mgm of penicillin V or 500 000 u. of buffered penicillin G should be taken four times daily by mouth, commencing two to four hours before the procedure and continuing for two days afterwards.

#### 2.4 Contra-indications to penicillin

All patients should be carefully questioned for a previous history suggesting penicillin sensitivity. If such a history is obtained, even if equivocal, penicillin should not be given. Under such circumstances, erythromycin should be used in a dose of 250 mgm by mouth four times daily for adults and older children or 40 mgm per kg per day in divided doses for small children.

#### 2.5 Education measures

The satisfactory use of these preventive measures will depend on the co-operation of patients, their parents, dentists, surgeons, anaesthetists, midwives and nurses and it is essential that a programme of education be specifically directed to them.

#### 2.6 Early diagnosis and treatment

Early diagnosis and institution of effective therapy is important and requires both clinical skill and adequate bacteriological services.

Every effort should be made to identify the organism prior to the institution of therapy. In order to achieve this, at least three samples of blood should be taken on the first day. Aseptic technique in taking blood samples is essential. Close co-operation between clinician and bacteriologist, particularly in relation to previous antibiotic therapy is important.

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\* Children's doses should be adjusted for weight.

### 3. Miscellaneous Preventable Diseases of the Heart (Agenda Item IV)

#### 3.1 Diphtheria

Diphtheria remains a serious and common form of heart disease in some parts of the Region. A professional education programme should be organized to alert physicians to the threat of its occurrence, to its appearance without obvious diphtheritic croup or prominent sore throat and to its confusion with other forms of myocarditis and heart block. There is also a need to increase the effectiveness of immunization programmes in some countries.

#### 3.2 Rubella

Congenital cardiovascular defects in children whose mothers had been affected by rubella in pregnancy were common in some countries in the Region. A live virus vaccine will soon be available which will provide effective protection. Because it is not advisable to vaccinate females of child-bearing age, it is important to vaccinate pre-pubescent girls promptly. In addition, exposure of the pregnant female to the disease will be reduced further by prompt vaccination of all children and of adult males.

#### 3.3 Syphilis

Cardiovascular syphilis remains a clinical problem only in certain areas of the Region. Prevention depends on control of primary and secondary syphilis. This is a well-recognized public health problem in all countries and should be dealt with effectively.

#### 3.4 Scrub typhus

Scrub typhus is endemic in a number of countries. While there is a need for more information as to its cardiovascular complications, it does not appear to be a significant public health problem.

#### 3.5 Tuberculosis

Despite active tuberculosis control programmes in all countries, tuberculosis pericarditis is not uncommon in several areas of the Region. Prompt chemotherapy is important for prevention of constructive pericarditis. Difficulties in establishing the etiologic diagnosis in apparent cases of primary tuberculous pericarditis should not delay treatment.

#### 3.6 Chronic cor pulmonale

This is a common form of heart disease and heart failure in some areas. Pulmonary tuberculosis, recurrent non-specific lower respiratory infections, bronchiectasis, and chronic bronchitis, appear to be major causes of chronic obstructive lung disease leading to cor pulmonale in the Region. There is a great need for further information on the nature and causes of the underlying lung diseases and further study of the condition in the Region should be undertaken urgently.

#### 4. Preventable Arterial Hypertension (Agenda Item V)

4.1 Arterial hypertension appears common in most areas of the Region with the exception of some Polynesian countries. In populations where ischaemic heart disease is not a major cause of death, cerebrovascular accidents and heart failure are the presenting complications of arterial hypertension.

4.2 Among the renal parenchymatous diseases which may lead to hypertension, chronic glomerulonephritis and chronic pyelonephritis were recognized to be common by most participants. The incidence of these conditions, however, could not be accurately assessed. Streptococcal diseases, particularly in the skin, should be diagnosed and treated to prevent acute glomerulonephritis and exacerbations of chronic glomerulonephritis. Control of chronic and recurrent urinary tract infection, particularly in females, should help to prevent chronic pyelonephritis. For these reasons, screening for renal involvement by examination of the urine should be done in such susceptible populations as pregnant females and children with pyoderma.

4.3 Attention was called to the presence of arterial hypertension and ischaemic heart disease in the obese Maori with gout and other Polynesian groups in which obesity is common. A possible etiologic role of diet should be explored further.

4.4 Hypertension frequently appears or is aggravated during the course of pregnancy. The incidence of hypertension in pregnancy is, therefore, a useful index of the prevalence of hypertension in the female community. The high incidence of hypertension and the apparent absence of toxæmia of pregnancy reported from some countries is noteworthy and should be studied further.

4.5 The treatment of established hypertension and prevention of its complications was considered beyond the scope of this seminar. Control of hypertension in its early stages represents an important means of preventing cardiovascular disease in the Region and should receive further consideration in a seminar devoted to this subject alone.

#### 5. Ischaemic Heart Disease (Agenda Item VI)

5.1 It is apparent that a problem of ischaemic heart disease exists to a high degree in Australia and New Zealand Europeans, the Maori, the Indians in Fiji, Singapore and Malaysia, and in Malays. In contrast, in Cambodia, Republic of Viet-Nam, Tonga, Western Samoa, Republic of Korea, natives of French Polynesia and Taiwan aborigines, ischaemic heart disease does not appear to be a problem. There are early indications that ischaemic heart disease is increasing. This is certainly the case in Japan, Hong Kong, the Philippines and among Chinese in Singapore and China (Taiwan).

5.2 There exists a remarkable contrast in the vulnerability of the same ethnic group in different locations, e.g., Malays in Singapore as opposed to those in Brunei, and Maoris in New Zealand as opposed to Polynesians in French Polynesia, Tonga and Western Samoa.

5.3 A unique opportunity exists for examination in depth of the reasons for these striking differences, with potential for further enlightenment as to ethnic and environmental factors in aetiology. Such studies should be attempted soon before the present opportunities are lost by further homogenization of the distinct ethnic groups and their cultures.

5.4 The subject of ischaemic heart disease could not be discussed completely, and as it appears to be an increasing problem, a seminar dealing with this subject should be held in the Region in the near future.

#### VIII. FINAL SUMMARY AND RECOMMENDATIONS

1. Participants from sixteen countries of the Region and WHO consultants and advisers held a seminar in Manila, 5-12 November 1968, at which they defined the size and nature of the problem of preventable heart disease for the Region, reviewed the resources, and formulated recommendations for preventive programmes.

2. Rheumatic fever and rheumatic heart disease was identified as a major problem particularly in areas where crowding, low socio-economic conditions, increasing urbanization, rapid industrialization and changing ways of life were most striking. Other forms of preventable heart disease due to infections were considered and opportunities for possible study and control of preventable arterial hypertension, ischaemic heart disease and chronic cor pulmonale were noted.

3. Specific programmes for heart disease control, particularly for rheumatic fever, were formulated which are immediately applicable in each country of the Region.

4. These programmes include: (a) use of existing health resources for the specific purposes of rheumatic fever prevention, (b) professional and lay education, (c) the collection of more accurate data, (d) the provision of necessary prophylactic agents and (e) the development of an organization motivated to create the interest in, and accept the responsibility for, implementing and maintaining the measures necessary.

5. Implementation of the recommendations evolving from the seminar require that:

- (a) participants in their respective countries promote interest in the problem among their colleagues, professional societies, health agencies and students as well as explore their own resources for initiating preventive programmes;

- (b) health agencies support these efforts by bringing their own resources to bear on the problem;
- (c) WHO provides full assistance to the health agencies of the Region particularly with regard to educational activities and technical advice;
- (d) the report of the seminar be distributed, in addition to the usual recipients, to interested organizations and individuals, both within and outside the Region who have responsibility for the control of the cardiovascular diseases.

6. The regular collection and dissemination throughout the Region of reports of the experience of the various countries should be arranged by WHO to provide information on progress and to encourage and ensure continued interest and activity in the prevention of heart disease. Subsequent regional seminars should be held to further these objectives.

7. The seminar drew attention to the remarkable variation in cultures, ethnic groups and geographical features of the Region and the influence these factors may have on cardiovascular diseases. This provides opportunities for studies of the influence of environmental and genetic factors that are related to the etiology and pathogenesis of arterial hypertension, ischaemic heart disease and chronic cor pulmonale. Further studies of these conditions in the Region should be arranged by WHO.



ANNEX 1

LIST OF CONSULTANTS, TEMPORARY ADVISERS, PARTICIPANTS,  
OBSERVERS AND SECRETARIAT  
LISTE DES CONSULTANTS, CONSEILLERS TEMPORAIRES, PARTICIPANTS,  
OBSERVATEURS ET DU SECRETARIAT

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### SUMMARY OF OBJECTIVES

1. To evaluate the size and nature of the problem of preventable heart diseases in the Region:
  - 1.1 rheumatic heart disease;
  - 1.2 sub-acute bacterial endocarditis;
  - 1.3 miscellaneous infectious diseases of the heart, e.g., syphilis, tuberculosis, cor pulmonale secondary to chronic pulmonary diseases, viral myocarditis, rubella, diphtheria, scrub typhus, acute endocarditis, and suppurative pericarditis;
  - 1.4 non-infectious diseases of the heart, e.g., hypertensive cardiovascular disease, ischaemic heart disease.
2. To review present resources within the Region for prevention of the above conditions.
3. To consider and propose preventive measures appropriate for the various circumstances in the Region.

### A G E N D A

#### I. INTRODUCTORY SESSION

1. Introductory remarks - Dr Francisco J. Dy
2. Objectives of the conference - Dr G.H. Stollerman

#### II. RHEUMATIC FEVER

1. Consideration of the size and nature of the problem
  - 1.1 Global situation and trends - Report by Dr G.H. Stollerman
  - 1.2 Situation in the Region
    - 1.2.1 Report of consultants - Dr R. Reader
    - 1.2.2 Comments by each participant on local situation
  - 1.3 General discussion
2. Consideration of resources necessary for preventive measures
  - 2.1 General
    - 2.1.1 Organization of medical care - Report by Dr R. Reader
    - 2.1.2 Problems of clinical diagnosis - Report by Sir Kempson Maddox
    - 2.1.3 Diagnosis of streptococcal infections - Report by Dr M. Moody

## 2.2 Resources within the Region

2.2.1 Report of consultants - Dr. Z. Fejfar

2.2.2 Comments by participants

## 2.3 General discussion

# 3. Formulation of preventive programmes

3.1 Data collection - consideration of methods of assessing the problem of rheumatic heart disease

### 3.1.1 Utilization of existing health examinations

- i. School health services
- ii. Maternal and child health services
- iii. Mass X-ray screening for tuberculosis
- iv. Military induction and industrial employment

### 3.1.2 Morbidity statistics

- i. In-patient services
- ii. Out-patient services

### 3.1.3 Mortality data

- i. Death certificates
- ii. Autopsy data

### 3.1.4 Specification of appropriate programmes

3.2 Education - consideration of professional and community programmes

3.2.1 Distribution of WHO and other documents on rheumatic fever control

3.2.2 Organization of conferences, seminars and other methods of post-graduate education at local, national and regional levels.

3.2.3 Education of public health nurses and other health workers

3.2.4 Education of general public, patients and their families through pamphlets, mass media, etc.

3.2.5 Specification of appropriate programmes

3.3 Secondary prevention programmes - consideration of:

3.3.1 Case-finding and registers

3.3.2 Chemoprophylaxis

3.3.3 Follow-up measures

3.3.4 Laboratory support

3.3.5 Specification of appropriate programmes

3.4 Primary prevention programmes - consideration of:

3.4.1 Control of epidemics - mass prophylaxis

3.4.2 Treatment of sporadic sore throat -  
individual prophylaxis

3.4.3 Specification of appropriate programmes

III. SUB-ACUTE BACTERIAL ENDOCARDITIS (SBE)

1. Introduction

1.1 Natural history of SBE - Report by Dr. G. Stollerman

1.2 Diagnosis and treatment - Report by Sir Kempson Maddox

1.3 Preventive measures - Report by Dr. B. Limson

2. Discussion by participants

3. Specification of control programmes

3.1 Necessary diagnostic resources

3.2 Recommended treatment

3.3 Appropriate preventive programmes

IV. MISCELLANEOUS CONDITIONS

1. Infectious diseases of the heart

1.1 Review of present status of: diphtheria, tuberculosis, syphilis, acute endocarditis, suppurative pericarditis, rubella, and viral myocarditis, scrub typhus (R. tsutsugamushi), cor pulmonale secondary to chronic

pulmonary infection

1.2 General discussion

1.3 Conclusion concerning control measures

2. Special cardiovascular diseases of importance to the Region.

V. PREVENTABLE ARTERIAL HYPERTENSION

1. Introduction

1.1 Classification by etiology and severity  
and identification of preventable hypertension -  
Report by Dr. R. Reader

2. Discussion of the nature and magnitude of the problem  
in the Region

3. Specification of control programmes

3.1 Measures for prevention of hypertension

3.2 Measures for prevention of complications

VI. ISCHAEMIC HEART DISEASE

1. Introduction

1.1 Prevention of ischaemic heart disease - present  
situation - Report by Dr. Z. Fejfar

1.2 Magnitude of the problem in the Region

1.2.1 Report by consultants - Dr. M. Alimurung and Dr. R. Reader

1.2.2 General discussion by participants

2. Conclusions concerning control measures

VII. FINAL SESSION

1. Summary and conclusions - Sir Kempson Maddox

2. Presentation and adoption of the report

3. Closing remarks



EPIDEMIOLOGY AND NATURAL HISTORY OF RHEUMATIC FEVER  
AND RHEUMATIC HEART DISEASE\*

by

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An imposing body of indirect evidence which supports the etiological relationship of Group A streptococci to rheumatic fever can be summarized briefly, as follows: (1) Numerous clinical and epidemiological studies have shown the close association of Group A streptococcal infections and rheumatic fever. (2) Antecedent streptococcal infection can always be demonstrated immunologically in the acute stage of rheumatic fever by increased titers of antibodies to streptococcal antigens. Moreover, in long-term prospective follow-up studies, rheumatic fever does not recur in the absence of intercurrent streptococcal infections. (3) Both primary and secondary attacks of the disease can be prevented by prompt treatment or prevention of streptococcal infections with antimicrobial therapy.

### Incidence and Epidemiology

The geographical distribution, incidence, and severity of rheumatic fever are, in general, a reflection of the frequency and severity of streptococcal disease. The attack rate of rheumatic fever following exudative streptococcal pharyngitis in epidemics averages approximately 3 percent. When streptococcal pharyngitis is sporadic and mild, the incidence of rheumatic fever may be very much lower. Two important variables of streptococcal infection which influence the attack rate of rheumatic fever have been emphasized: (a) the duration of throat carriage of Group A streptococci during convalescence from the pharyngeal infection and (b) the magnitude of the immune response to the antecedent streptococcal infection. Controlled studies have shown, for example, that rheumatic fever followed streptococcal pharyngitis in 3 percent of patients who carried the infecting strain for at least three to five weeks during convalescence, whereas the incidence in those who did not was only 0.3 percent. Similarly, more than 5 percent of patients may develop rheumatic fever following a streptococcal infection which is associated with an antistreptolysin O response of more than 250 units per ml, whereas less than 1 percent of patients with a weak antistreptolysin O response (less than 100 units per ml) will develop this complication. Although pharyngeal carriage of Group A streptococci is frequent in all populations, particularly in schoolchildren, the frequency with which rheumatic fever appears will depend upon the virulence and epidemicity of the strains encountered and upon the frequency with which infections are produced which are associated with prolonged survival of the organism in the host and with strong antigenic stimulation.

Environmental, bacterial, and host factors which appear to play a role in the development of rheumatic fever are important, therefore, primarily as they are related to the incidence and severity of preceding streptococcal infection. Thus, such factors as latitude, altitude, crowding, dampness, economic factors, and age all affect the incidence of rheumatic fever because they are related to the incidence of streptococcal infection in general.

The attack rate of rheumatic fever following streptococcal infections in patients who have had previous attacks of rheumatic fever is increased to as high as 5 to 50 percent and is also related to the intensity of the immune response to the reactivating infection. Furthermore, the frequency of rheumatic recurrences following streptococcal infection is consistently greater in those with rheumatic heart disease than in those who escape cardiac injury during their previous attacks. The tendency to suffer recurrences of rheumatic fever following streptococcal infections declines with the passage of years since the preceding attack. It appears, therefore, that certain host variables, as well as differences in the severity of the antecedent infection, also influence the development of rheumatic fever. To what extent such variables are genetic or acquired has not been settled. It is common to obtain a family history of rheumatic fever as well as to encounter multiple cases among siblings of a single family. However, the concordance of rheumatic fever in identical twins (approximately 20 percent) does not exceed that of poliomyelitis or tuberculosis, suggesting only a limited penetrance of genetic predisposition to rheumatic fever.

The mortality of acute rheumatic fever has been declining steadily for the past thirty years in North America and Western Europe. However, it is still a major cause of death and disability in children and adolescents. Rheumatic fever is the most common cause of heart disease in patients below the age of forty, and is second only to hypertension and arteriosclerosis as a cause of heart disease in the older age groups. Accurate determination of the true incidence of rheumatic fever and rheumatic heart disease is impossible, since the disease has not been made reportable generally and its diagnosis is frequently indefinite. The best estimates of the current prevalence of rheumatic heart disease in elementary and high school children of large cities in the temperate zone of the United States is approximately 2 to 3 per 1000. The incidence of rheumatic fever is at least two to three times this rate, because approximately 60 to 70 percent of patients with rheumatic fever recover without permanent stigmas of rheumatic heart disease. It is generally believed that the incidence of rheumatic fever, like that of streptococcal sore throat and scarlet fever, has been decreasing for several years in countries where housing and economic conditions have been improving steadily. The rate of decrease may have been accelerated by the wide use of antimicrobial therapy. Rheumatic fever remains, however, a worldwide disease having its greatest prevalence wherever poor economic conditions, overcrowding, and substandard housing are most common.

#### Course and Prognosis

The course of rheumatic fever varies greatly and is impossible to predict at the onset of the disease. In general, however, approximately, 75 percent of acute rheumatic attacks subside within six weeks, 90 percent within twelve weeks, and less than 5 percent persist more than six months.

The latter usually consist of severe, intractable forms of rheumatic carditis or stubborn and persistent cases of Sydenham's chorea, both of which may persist for as long as several years. Once acute rheumatic fever has subsided and more than two months have elapsed after withdrawal of treatment with salicylates or corticosteroids, rheumatic fever does not recur in the absence of new streptococcal infections. Recurrences of rheumatic fever are most common within the first five years of the initial attack and tend to decline with increasing duration of freedom from rheumatic activity. The frequency of recurrences is dependent upon the frequency and severity of streptococcal infection, the presence or absence of rheumatic heart disease following an attack, and the duration of freedom from the last attack. Between 50 and 70 percent of patients may survive their initial attack of rheumatic fever without signs of heart disease. The murmurs of rheumatic heart disease usually appear during the first few weeks of the acute rheumatic attack. Approximately 70 percent of patients who develop carditis do so within the first week of the disease, 85 percent within the first twelve weeks of the disease, and almost all within six months from the onset of the acute attack. Thereafter, if significant murmurs have not appeared, the prognosis for a patient in whom recurrences are prevented is excellent. In several large studies it has been shown that about 95 percent of patients who escaped carditis during an acute rheumatic attack have normal hearts when examined five years later if recurrences have been prevented. Moreover, the prognosis differs markedly with the degree of cardiac involvement during acute rheumatic fever as reflected by the intensity and the kind of murmurs heard and by the presence of congestive heart failure. The percentage of patients who, five years after the attack, will have stigmas and presumably permanent heart disease is approximately 20 percent in those whose attack of carditis was relatively mild and characterized only by a soft organic apical systolic murmur, 30 percent in those with louder organic apical systolic murmurs, 52 percent in patients with diastolic murmurs, and 70 percent in those with congestive heart failure or pericarditis. Thus, the healing rate of rheumatic carditis is quite high even in patients with severe attacks. Conversely, however, the patient with a well-established permanent valvular lesion may develop progressive heart disease owing to the mechanical disadvantage imposed on the heart by the valvular deformity or by progressive fibrosis and calcification of the deformed valve, which may occur over a period of many decades. The factors which are responsible for progressive fibrosis and calcification of a deformed valve have not yet been clearly defined.

Recurrences of rheumatic fever tend to be "mimetic". Thus, patients who have Sydenham's chorea as the only manifestation of rheumatic fever frequently have repeated attacks of "pure" chorea. Those who have polyarthritides alone frequently have recurrences of this manifestation and develop acute carditis on subsequent attacks much less frequently than those in whom carditis was present in a previous attack. Recurrences are most damaging, therefore, in patients with rheumatic heart disease

in whom the probability of reactivating carditis in a subsequent attack is greatest.

#### Influence of Treatment and Prophylaxis on the Natural History of Rheumatic Fever

There is no specific cure for rheumatic fever, and no known measures change the course of the attack. Good supportive therapy, however, can reduce the mortality and morbidity of the disease. Attempts to reduce ultimate heart damage by administering penicillin early in the acute attack in large doses have not been successful to date. It is advisable, however, even if bacteriologic examination fails to reveal streptococci in the throat, to administer a course of penicillin adequate to eradicate whatever occult Group A streptococci may be present deep in the laryngeal lymphoid tissues. An effective course is either a single injection of 1.2 million units of benzathine penicillin intramuscularly or 600 000 units of procaine penicillin intramuscularly daily for ten days. After completion of the therapeutic course of penicillin, continuous protection from re-infection with streptococci should be provided by instituting one of the prophylactic regimens recommended by the American Heart Association.

#### Prevention of Recurrences of Rheumatic Fever and its Effect on the Natural History of the Disease

The most efficient regimen for continuous prophylaxis against Group A streptococci is a monthly intramuscular injection of 1.2 million units of benzathine penicillin. The disadvantages and discomfort of this regimen have to be weighed against the individual patient's susceptibility to recurrences. Those with rheumatic heart disease, recent rheumatic fever, and exposure to an environment in which the incidence of streptococcal infection is frequent, deserve the most efficient protection. As a second choice, prophylaxis may be administered orally with either one gram of sulfadiazine daily in a single dose or at least 200 000 units of penicillin given twice daily on an empty stomach. The duration of continuous prophylaxis cannot be fixed arbitrarily for all patients, although the safest generalization is that it be continued indefinitely. Certainly, those under the age of eighteen years should receive a continuous prophylactic regimen. A minimum period of five years is recommended for patients who develop rheumatic fever without carditis over the age of eighteen. The decision to continue prophylaxis beyond this period should take into account a number of variables. Patients with rheumatic heart disease are more susceptible to reactivation of rheumatic fever if they contract a streptococcal infection. Moreover, patients who have had carditis in a previous attack are much more likely to suffer carditis again in a subsequent attack. Climate, age, occupation, household situation, cardiac status, and length of time since the previous attack are all significant variables which influence the risk of recurrence. The decline in recurrence rates with increasing age is due to

(a) decreased rate of streptococcal infection and (b) decrease in the rate of rheumatic reactivation following streptococcal infection in older rheumatic subjects. Despite this decreased rate, however, the risk of rheumatic recurrence in adults remains relatively high when the streptococcal disease encountered is severe or epidemic.

#### Prevention of Initial Rheumatic Attacks

Early and adequate treatment of respiratory tract infection due to Group A streptococci will prevent initial attacks of rheumatic fever. If clinical streptococcal disease were properly detected by the use of throat cultures and adequately treated, the spread of infection in a given population would be prevented, the epidemiology of streptococcal disease would be modified markedly, and the incidence of rheumatic fever in the community would be diminished. In communities where Group A streptococcal disease has been diagnosed early and treated well and where socio-economic standards are high, the Group A organisms cultured from schoolchildren's throats are frequently of relatively low virulence and cause rheumatic fever less often than in epidemics wherein virulent strains are prevalent.

Streptococcal pharyngitis is adequately treated by a single intramuscular injection of 600 000 units of benzathine penicillin in children less than ten years of age or 1.2 million units in older children and adults. Any alternate plan of parenteral therapy or combined parenteral and oral therapy should provide for treatment over a period of ten days. If oral penicillin is employed, at least 800 000 units per day in four divided doses must be given for no less than ten days to achieve results comparable to a single injection of benzathine penicillin. Erythromycin in daily doses of one gram for ten days may be substituted in penicillin-sensitive individuals. Tetracycline is not recommended because some strains of Group A streptococci have acquired resistance to it. All Group A streptococci have so far remained extremely sensitive to penicillin.

Although the pathogenesis of rheumatic fever and rheumatic heart disease remains obscure, there is little question that the epidemiology and natural history of the disease can be enormously modified by interrupting epidemics of streptococcal pharyngitis and by early detection and continuous prophylaxis in the rheumatic subject.

DIAGNOSTIC CRITERIA OF RHEUMATIC HEART DISEASE\*

by

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## 1. Acute Rheumatic Carditis

It probably requires three or four weeks for valvulitis to reveal itself on auscultation. Functional murmurs due to dilatation of the valve ring, as part of the general stretching of heart walls in the acute stage of pericardiac inflammation can appear early, particularly in the mitral and tricuspid areas. The vegetations on the valves are too small to produce any turbulence, but oedematous thickening of the cusps and chordae tendineae may contribute to malfunction of the valve in the acute stage before any fibrosis ensues. The papillary muscles also must share in the general myocarditis and their brisk shortening modified. Frequently, murmurs may be present which represent the sequels of previous unrecognized episodes of acute rheumatism.

Involvement of the heart occurs more commonly and more severely in countries with low standards of living, in malnourished children living in an overcrowded environment. It is probable that few such individuals escape an acute attack of rheumatic fever without some permanent heart damage. Relapses are more frequent, and progression to advanced stages of valve disorganization are found in children as young as 12 - 15 years of age.

Recognition of acute carditis in the phase of high fever is not at all easy. Tachycardia, with raised cardiac output, loud heart sounds and soft murmurs are of little aid to diagnosis. Careful day to day observation by the same observers is more likely to detect the first appearance of a diastolic murmur, a pericardial rub or cardiac enlargement; all dependable criteria. Rapid and considerable cardiac enlargement suggests an effusion, and will lead to examination for jugular venous distension, pulsus paradoxus and radiographic confirmation. Examination of the child while it kneels on its elbows and knees, may reveal pericardial sounds not heard otherwise. Muffling of the heart sounds by an effusion is not a dependable criterion in small children.

Dr Lawrence Hughes of Sydney was struck by what he called the "tumultuous" character of the heart sounds in acute juvenile carditis. As the heart rate lessens, the observer must listen for the third heart sound to lengthen into the mid-diastolic murmur described by Carey Coumbs, and for the persistence and augmentation of the systolic murmurs at the mitral area.

Obviously, congestive heart failure, occurring in the course of an acute attack of rheumatic fever, is diagnostic of heart involvement. It is to be remembered however that liver enlargement and congested cervical veins are commoner than peripheral oedema or serous effusions.

In summary therefore, neither pallor, fever, tachycardia arthralgia, systolic murmurs are singly or together dependable diagnostic criteria of acute rheumatic carditis. Even congestive heart failure may be due to subacute bacterial endocarditis. Still's disease, familial Mediterranean fever, brucellosis, leukaemia, sickle-celled anaemia, lupus erythematosus, are some of the disorders with similar characteristics, and are accompanied by disturbances of the non-specific laboratory findings



in common use for the diagnosis and control of rheumatic fever. Dependable criteria are progressive cardiac enlargement, pericarditis and diastolic murmurs.

2. The Diagnosis of Chronic Rheumatic Heart Disease, in so far as the signs remain fairly constant from day to day, murmurs are louder, heart rate is slower, specific chambers are involved, techniques can be employed for modifying the murmurs, is more certain than in the acutely ill, crying child. Nevertheless, some problems exist.

The past history is not necessarily helpful as some 40% of the patients with proven rheumatic heart disease give no history of rheumatic fever or chores. The nature of the illness was unrecognized or misdiagnosed, or occurred in a subclinical or unusual fashion. A definite history of rheumatic fever, on the other hand, calls for a meticulous search for organic heart murmurs, using posture, exercise, or even drugs to enhance the volume of the murmurs, but again does not necessarily identify a murmur as rheumatic in origin. A history of minor criteria such as sore throat, epistaxis, growing pains, arthritis is still less certain to be positively rheumatic. Electrocardiographic evidence of early heart block can occur during and after other infectious diseases. Even a patient with a known history of clinical rheumatic fever, with dependable documentation of organic murmurs afterwards may, many years later, show a normal heart.

Cardiac enlargement is not universal in established rheumatic heart disease. Some of the sufferers from advanced degrees of mitral stenosis, as revealed at surgery, have normal cardiac volumes on clinical or X-ray examination. Estimation of cardiac enlargement and of obesity, thoracic deformity, or emphysema, interfere with clinical assessment, two metre X-ray films in three planes are essential. In field work and rural areas where good X-ray assistance is unavailable, the practitioner must try to perfect himself in percussion, and in recognition of right versus left ventricular hypertrophy. Employing the augmentation of thrills and murmurs by the use of posture, exercise and phenylephrine, he should attempt to establish whether true valve disease is present.

Classical mitral stenosis, manifested by right ventricular hypertrophy, presystolic thrill and murmur, an abrupt first sound, and often an opening snap is the easiest rheumatic lesion to diagnose. Similarly, aortic stenosis with a well marked apical heave, a basal thrill, and a rough systolic bruit in the aortic area, is rarely missed. However, the murmurs but not the thrill, may be as loud or louder at the apex, and systolic bruits unassociated with significant aortic stenosis may be heard in the base of the neck. The pulse is only sometimes anacrotic and the pulse pressure low. Pure aortic stenosis of rheumatic origin in my experience is uncommon, a considerable degree of aortic incompetence is the usual accompaniment, with an increase in pulse pressure. Again, listening with the patient leaning forward and the breath held on expiration, permits the observer to recognize minor degrees of incompetence.

The major diagnostic errors in aortic disease are the murmur of degenerative calcific aortic stenosis, occurring particularly in males over the age of 50, and the murmur of obstructive subacute myopathy. This murmur is frequently less located at the classical aortic area, is accompanied by a double systolic pulse wave, and no incompetence. Many older patients have an aortic systolic murmur due to minor degrees of stiffening and narrowing of the aortic orifice, but this is never due to preceding rheumatism. The main clinical problem in aortic valve disease is the decision as to whether the mitral valve is simultaneously diseased, in view of the frequent presence of a systolic murmur at the mitral area, and the ability to hear a diastolic murmur along a straight line joining the aortic and mitral areas. Helpful guides in this situation are the knowledge that the presence of auricular fibrillation, of a mitral thrill, or left atrial and right ventricular enlargement on X-ray, or bifid P waves in Lead II of the E.C.G., are in favour of additional mitral disease.

The perennial problem in diagnosis in rheumatic heart disease is the significance of the mitral systolic murmur. At what point does such a murmur become indubitably organic? If cardiac enlargement, especially of the left ventricle, is present, with a holosystolic murmur transmitted preferentially to the axilla or back, there can be no argument about the presence of considerable mitral incompetence. This may not be rheumatic, if for example papillary muscle damage has followed a myocardial infarct, or if a chordum has ruptured, but in the vast majority of cases, the origin is rheumatic scarring, with shrunken leaflets and shortened chordae. The problem devolves upon the minor degrees of incompetence. If the heart is very enlarged, accompanying valve ring dilatation can be responsible for the so-called "functional murmur". Late systolic apical mitral murmurs are frequently ascribed to extra-cardiac causes or to origin at the pulmonary or aortic valves. In spite of advice that benign apical murmurs disappear on inspiration or exercise, vary with the pressure of the stethoscope, with posture, and change on serial examination, difficulties still remain. Inhalations of amyl nitrite enhances the functional systolic murmur and lessens the organic murmur of mitral incompetence. The physician should study the actual configuration of the murmur, preferably with the aid of the phonocardiograph. The true regurgitant systolic murmur is holosystolic. Any holosystolic murmur denotes a pathological situation. In general, murmurs of mitral regurgitation are of greater intensity than functional murmurs, but the intensity has no fixed relation to the degree of backflow. Gross incompetence with giant left atrium may cause sternal lifting and audibility of the murmur to the right of the sternum. A third heart sound due to rapid left ventricular filling is an important additional finding. Splitting of the second sound is common due to shortening of left ventricular systole. A muffled first sound is said to be due to incompetence of both mitral leaflets.

Other causes of mitral regurgitation besides rheumatic damage, are associated with considerable left ventricular dilatation such as aortic incompetence, myocardial infarction, cardiomyopathy as well as congenital cushion defects. Other causes of error are the systolic murmurs of ventricular septal defect and tricuspid incompetence, anaemia and other high output syndromes.

Rheumatic damage to the tricuspid valves may result in stenosis or incompetence or both. Mitral or mitral plus aortic disease generally coincides. Sometimes it is virtually impossible to distinguish the murmur of tricuspid incompetence from that of mitral incompetence or to decide whether it is an organic or functional regurgitation. Reliance can be placed on an increase of intensity following inspiration, and systolic pressure waves in the neck and liver. Functional tricuspid incompetence of course is part of the picture of right sided failure and disappears with recovery.

Rheumatic valve disease and its recognition have been discussed from the clinical standpoint. Great assistance from the qualitative and surgical points of view is to be obtained from left sided cardiac catheterization, and in particular from cine-angiocardiography. Experience with the fluoroscope is rewarding in office or outpatient practice.

In summary, the diagnostic criteria of greatest everyday value are as follows:

- (1) The distinction of the organic from the functional murmur.
- (2) Consistent diastolic murmurs.
- (3) Correct discrimination of the cardiac chambers under strain.
- (4) Appreciation of the diagnostic importance of the quality of the first heart sound, and the relative spacing and intensity of the components of the second sound.
- (5) Recognition of late systolic murmurs as opposed to "holosystolic" or pansystolic murmurs, i.e. the timing, shape and pattern of the murmur, as well as its intensity, location, quality and transmission.
- (6) Finally, it cannot be assumed that all organic murmurs on the left side of the heart are due to rheumatic heart disease. Atrial tumours or clot, endocarditis due to collagen disease, endomyocardial fibrosis, or Coxsackie myocarditis can also, in rare instances, produce identical findings. The age, origin, sex of the patient as well as country of origin and history of past health must also come under review.

ORGANIZATION OF MEDICAL CARE AND REHABILITATION  
FOR PUBLIC HEALTH CONTROL PROGRAMMES AT VARIOUS LEVELS\*

by

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## 1. GENERAL CONSIDERATIONS

Preventive measures are particularly effective in controlling rheumatic fever. Morbidity and mortality rates have fallen markedly since the availability of sulphonamide and antibiotic therapy and there appears to have been a downward trend in countries where records are available even before that.<sup>1</sup>

While the mechanism whereby streptococcal infection leads to joint, heart and cerebral disease is still not clearly understood, the primary aetiological role of this organism is well established. Two factors which have played a major role in reducing the morbidity and mortality from rheumatic fever have been the effective treatment of streptococcal infections by anti-bacterial agents<sup>2</sup> and the prophylactic use of such agents<sup>3,4</sup> in patients who have already suffered an attack of rheumatic fever.

Reduction in the incidence of rheumatic fever, however, cannot be explained entirely in this way. The reduction appeared to precede the advent of antibiotics and this suggests that other factors have also contributed to the declining morbidity. It is possible that improved hygiene and nutrition could have played some part. It is also probable that alteration in the virulence and other characteristics of the haemolytic streptococcus may have occurred during the past half century. The virtual disappearance of the clinical entity, scarlet fever, in many countries before the antibiotic era began, is consistent with such a hypothesis.

In summary, the control of rheumatic fever in a community depends on one or more of the following:

- (a) spontaneous changes in the characteristics of beta haemolytic streptococci;
- (b) improvements in living standards in relation to overcrowding and nutrition;
- (c) early diagnosis of streptococcal infection, mainly sore throats, with isolation and other simple nursing measures and treatment with antibacterial agents;
- (d) secondary prevention of rheumatic fever by long term prophylaxis.

## 2. PUBLIC HEALTH MEASURES

### 2.1 Defining the problem

Decision as to the type and extent of public health programme for the control of rheumatic heart diseases must depend in the first instance on the epidemiological characteristics of the disease in the country concerned. Whether to attempt such a programme at all will depend on incidence and prevalence. This may not be easy to determine. Examination of a cross section of the community for auscultatory evidence of chronic rheumatic valvular disease could give some indication. Routine examination of schoolchildren possibly using a screening procedure with tape recorded heart sounds may be practical and has been used in the United States of America.<sup>5</sup> Hospital records may also provide some indication but their value will be limited by the adequacy of the records themselves, by hospital admission policy, by ratio hospitals to population and geographic and accessibility factors.

The evidence does suggest that developing countries and even those in tropical climates may experience quite high incidence of rheumatic fever.<sup>1, 6, 7</sup>

It would be wrong to consider instituting a public health programme without some such assessment of the size of the problem.

### 2.2 Secondary prevention measures

If, in the light of the above, a control programme is indicated there can be no doubt that the most practical and important measure is long term prophylaxis in patients who have already suffered an episode of rheumatic fever. This involves:

- (a) a medical service which permits efficient diagnosis;
- (b) a programme of professional education to encourage as wide and as efficient practice of the measures as possible;
- (c) availability of either sulphonamide or penicillin tablets within the economic resources of the patients;
- (d) a community education programme to ensure the effective co-operation of the patient or his parents.

It is likely that some or all the above measures will require partial or complete government subsidy.

Prophylactic antibacterial therapy is indicated in any patient under 25 years who has had an attack of rheumatic fever. Administration of penicillin G 200 000 i.u. or penicillin V 125 mgm by mouth twice daily is safe, simple and relatively inexpensive.

### 2.3 Primary prevention

Reduction of streptococcal infection in the community generally will undoubtedly have a significant effect on the incidence of rheumatic fever. The rather indirect but nevertheless important role of improved hygiene, prevention of overcrowding and improved nutrition must already be an established part of a public health programme in any country contemplating control of rheumatic fever.

A vigorous professional education programme for the early diagnosis and treatment of streptococcal infection particularly of the upper respiratory tract and the skin would be the next stage of a public health programme. Ideally, this should be based on a bacteriological as well as clinical diagnosis. Public health measures to facilitate this might provide a bacteriological diagnosis service. "Mail in" services using Dacron<sup>8</sup> and even filter paper swabs have been shown to be fairly effective. The necessary bacteriological services, however, may not be practical and in that case it may be warranted to recommend initiation of treatment on clinical grounds. In this case certain clear-cut diagnostic criteria, e.g., as described in WHO Expert Committee Report<sup>1</sup> should be laid down to avoid unnecessary or excessive use of antibiotics. Penicillin is the most effective form of therapy and a single intramuscular injection of dibenzyl penicillin 1 200 000 units is a convenient and efficacious method.

More extensive prophylactic measures have been proposed involving routine throat swabbing of entire communities and treatment of carriers of the beta-haemolytic streptococcus by antibiotics. Experience with such programmes in the United States of America suggests that they are not practical or warranted, except in very particular circumstances.<sup>9</sup>

### 2.4 Treatment

Management of the acute attack of rheumatic fever has no implication for a public health control programme in the ordinary sense. Diagnosis is a matter of individual patient care and depends on clinical judgment aided to a limited extent by measurement of anti-streptolysin titres and ESR. Treatment is directed to the infection by penicillin, and to joint, heart and other symptoms by bed rest, salicylates or in certain cases by cortico-steroids.<sup>10</sup> Institution of secondary prophylaxis as indicated above is essential. Diagnosis and treatment of chronic endocarditis and cardiac failure will also be along the usual lines of individual medical care.

## 2.5 Rehabilitation

Chronic rheumatic heart disease causes varying degrees of disability over long periods in the lives of patients. There is a common tendency on the part of doctor and patient to exaggerate the disability and produce unnecessary invalidism and limitation of the patient's activities. It has been found helpful in heart disease generally to set up special clinics where skilled assessment can be made of the physical and functional state and measures instituted for suitable training or retraining, employment or re-employment and re-establishment in the community. Where chronic rheumatic heart disease is a common problem such units can lead to great benefits in terms of human welfare and also economic savings to the community.

Such rehabilitation units have been set up on the larger population centres by the National Heart Foundation of Australia. Some 1200 patients are seen each year, mainly those suffering from ischaemic heart disease but approximately 10% are patients with chronic rheumatic heart disease.

These units are staffed by a medical director, usually a specialist cardiologist who spends 3 or 4 half-day sessions weekly and other cardiologists and a psychiatrist who are also employed on a sessional basis. One or more social workers, employment advisers and secretarial staff are also employed. The staff numbers vary with the patient load. Patients are only seen at the request of their doctor and the purpose is for assessment of capacity for employment or rehabilitation in society, not for diagnosis or treatment in the ordinary sense.

The success of the units, and they have been very successful, has depended on thorough taking of medical and social history, and careful counselling when the assessment has been made. As a result many patients with chronic rheumatic heart disease have been enabled to undertake suitable employment. There have been cases where patients who have been on invalid pensions for many years and in fact since they reached working age who have been enabled to take up employment and give up their pensions, as a result of the efforts of these rehabilitation units.



LABORATORY DIAGNOSIS OF STREPTOCOCCAL INFECTIONS\*

by

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A reliable diagnosis of streptococcal disease can be obtained by utilizing bacteriological and serological methods along with the clinical examination of the patient. The beta hemolytic streptococcus of Lancefield's Group A (Streptococcus pyogenes) is the principal cause of streptococcal infections in man. None of the three criteria used separately provides satisfactory evidence in all cases to justify a diagnosis of streptococcal disease. Clinicians at one time believed generally that most sore throats were caused by streptococci and that if hemolytic streptococci were present the throat would be sore. They have since learned that "strep infections" are often asymptomatic and that many throats are made sore by causes other than streptococci (1,2).

Streptococcal serology provides evidence that a streptococcus infection has occurred, particularly if a rise in titer can be demonstrated when concomitant comparisons of sequential specimens are made. Serological evidence that a recent streptococcal infection has occurred may not be demonstrable in those cases which were given antibiotics in the early stages of streptococcal infection, as diagnosed on the basis of clinical and/or laboratory evidence.

#### Clinical pattern

The clinical pattern of streptococcal infections in man is determined by the infecting organism, the host and the portal of entry or manner of spread. The Group A streptococci are responsible for infections encompassing many diagnostic categories: tonsillitis or pharyngitis, scarlet fever, osteomyelitis in infancy, cellulitis, erysipelas, puerperal sepsis, pneumonia, meningitis and endocarditis. Generally, streptococcal infections are characterized by suppurative lesions and often manifestations of toxemia, the latter taking the form of the so-called non-suppurative complications of the infection and including fever, carditis, and nephritis. Streptococcal infections vary in the extent to which the body is involved, from local infections such as abscesses of the various tissues, including mucous membranes, joints and serous membranes, infection of the muscle or cellulitis which simulates gaseous gangrene, suppurative processes in all kinds of wounds, to those generalizing to pyemia or septicemia. Other manifestations, such as those of erysipelas, streptococcus sore throat, scarlet fever and the like, are most distinct in clinical character. In general, about one-half of the streptococcal infections which occur may escape detection because they are atypical or the patient is asymptomatic. Other cases can often be suspected on the basis of the clinical impression. In the absence of a scarletinal rash, however, differentiation of streptococcal infections based on clinical grounds alone is fraught with uncertainty. For this reason, bacteriological support of the clinical impression is highly desirable (3).

Markowitz and Kuttner (4) summarized the following symptoms and signs for assisting physicians in making a correct diagnosis of streptococcal infections: symptoms are sore throat with sudden onset and pain on swallowing; headache; fever varying generally from 101 to 104 F.; and abdominal pain, nausea, and vomiting, especially in children. Principal signs are red throat; exudate, usually present but may not appear until after the first day; lymphadenopathy, manifesting swollen, tender lymph glands at the angle of the jaw; rash, if scarletiform; and acute otitis media or acute sinusitis.

Appreciable differences in the character of streptococcal infection in the child and in the adult have been described (5). In infants under two or three years of age, the infection tends to be a prolonged, low-grade variety with frequent suppurative complications, which are seldom followed by rheumatic fever or nephritis. Osteomyelitis caused by streptococci is almost exclusively a disease of infants. In older children and adults, the disease tends to occur as acute tonsillitis or pharyngitis, is self-limiting, and may be followed by non-suppurative complications. Scarlet fever most frequently occurs between the ages of three and ten years, while erysipelas occurs at all ages.

#### Bacteriological and serological methods for isolation and identification of Group A streptococci

Bacteriological methods provide useful information if specimens are properly obtained from the patient. Swabs from the upper respiratory passages are the most common type of specimen. Streptococci may be recovered from throat or nose cultures or both. When only one kind of culture can be taken, it should be a throat culture. Nasopharyngeal cultures often yield almost pure cultures of streptococci, even though throat cultures taken at the same time may give highly mixed flora. Nose cultures of convalescent patients particularly may remain positive. Anterior nasal cultures are of particular interest in that carriers of streptococci in that site often are important sources of dissemination of streptococci to the environment.

The media used in routine streptococcal bacteriology represent a compromise among the many media available, each of which may be superior from a particular point of view. It is advisable to select a set of media, to become thoroughly familiar with their use and how streptococci appear on them, and then to stay with them. Liquid media used generally for routine purposes are compounded from peptone and meat extract or infusions. The addition to such media supplements of serum, blood, or fluid of ascites improves streptococcal growth. The optimal pH for initiating growth of streptococci is about 7.8. When maximal bacterial yield is important, as in preparing extracts for grouping and typing, a buffered glucose-containing medium, such as Todd-Hewitt Broth, Modified (Difco) is used. In the presence of certain peptones, some Group A streptococci produce an active proteolytic enzyme that digests M substance. For successful M-typing, it is necessary to use a peptone, such as neopeptone, to prevent formation of the active enzyme. Otherwise, if grouping only is to be performed, any medium that will give adequate growth is satisfactory.

For primary isolation, blood from sheep is preferred for blood agar plates, because it contains a factor that inhibits the growth of Hemophilus hemolyticus, an organism which may cause confusion in nose and throat cultures (9). Human blood, either freshly defibrinated or discarded from blood bank reserves, should be used only when sheep blood cannot be obtained, as its hemophilus-inhibiting factor is irregular; furthermore, levels of antibiotic content may be sufficiently high that growth of streptococci will be inhibited. Rabbit or horse blood lack the hemophilus-inhibiting factor but are useful for subculture in the study of colonial form and hemophilus.

Blood agar recommended for primary isolation should contain no glucose, because hemolysis is favored by this omission. A tryptose extract agar serves this purpose satisfactorily. When M-typing is to be performed, the use of neopeptone agar makes it possible to read hemolysis as well as to provide the proteinase-inhibiting factor.

If the swab can be delivered to the laboratory within 2 to 4 hours, it may be placed in a sterile tube or inserted into a tube containing 1 ml of broth and delivered to the laboratory. On the other hand, if the swab is to be mailed to the laboratory, one of at least three satisfactory methods may be used: a. The swab may be placed in a sterile screw-cap test tube or aluminum foil packet containing a drying agent, indicator silica gel, for mailing (6, 7); b. The swab may be streaked on the surface of a blood agar slant in a screwcap tube, stoppered, and mailed; or c. The swab may be rolled and scrubbed onto a piece of sterile filter paper (8). The filter paper is allowed to air-dry 3 to 4 minutes, refolded in its paper-carrier, returned to its envelope, labeled, and mailed to the laboratory.

Swabs received in the laboratory within 2 to 4 hours after taking may be cultured 0 to 2 hours in 1 ml broth at 37 C depending upon the available time remaining in the working day. Swabs that have been in transit 4 to 8 hours should have a minimum of 2 hours' incubation in broth. Those in transit over 8 hours should have 4 to 5 hours' incubation in broth.

Swabs to be cultured on blood agar immediately after collection may be rubbed and twisted onto the edge of a moist sheep blood agar plate, covering only about one-sixth of the plate. This primary inoculum is streaked onto about one-half the plate in 10 to 20 to-and-fro strokes. Without entering the site of the primary inoculation, the loop is streaked through the area of secondary inoculation onto the remainder of the plate. Several stabs are then made into the agar for observations of subsurface hemolysis.

Alternate methods are used for culturing to obtain subsurface growth that will permit accurate determination of the kind of hemolysis and, indeed, to detect those strains which possess oxygen labile streptolysin but not oxygen stable streptolysin S. Sheep blood agar plates inoculated

by a pour-streak method permits observation of color morphology of surface colonies and hemolysis of both the surface and deep colonies on a single plate with material from the primary culture. Pour-streak plates are prepared as follows: Melt 15-20 ml of agar and cool to approximately 45 C before use. Remove the swab from 1 ml of broth, drain against the inside of the tube and place the swab in a sterile tube. Add 0.6 to 0.8 ml of defibrinated blood to the melted agar. Take a loopful of the broth in which the swab had incubated and drain off the excess by touching the side of the tube with the inoculating loop. Transfer the loop to the melted blood agar. Mix the inoculated blood agar well by rotating the tube. Flame the lip of the tube to prevent contamination and pour the mixture into a sterile petri dish. After the agar hardens, rotate the swab over a small section of the surface. Spread the inoculum over half the plate with an inoculating loop, cross-hatching for isolation. Stab the agar after each cross-hatch series. Incubate the plate 18 to 24 hours at 35 C.

Filter paper strips which have been inoculated with throat swabs are placed inoculum side down on the blood agar surface without prior treatment of any kind (8). Before the plate is inverted for incubation, the strip is inspected to see that it has absorbed moisture from the medium. Any part that is dry should be pressed gently against the surface of the agar until it appears wet. After six hours' incubation at 35 C, the filter paper strip is removed from the plate and placed on a second plate, inoculum side down, and the primary plate is streaked with a loop. Both the primary and secondary plates may be examined and subcultured for definitive study after incubation of the plates for 24 to 48 hours at 35 C.

After incubation, the cultures are examined for colony characteristics and kind of hemolysis. Those which resemble beta hemolytic streptococci are examined by Gram stain. The identification of the specific serologic group of a streptococcal strain should be established as an aid in clinical diagnosis. Determination of serological type provides invaluable information in epidemiological studies.

Grouping and typing may be accomplished by testing acid heat extracts of streptococcal cells against absorbed sera of known antibody content. To prepare the extract, 30-40 ml quantities of Todd-Hewitt broth, Modified, without blood are inoculated from pure cultures of the strain and incubated at 35 C at least 18 hours, or until heavy growth results. The culture is centrifuged and the supernatant discarded. To the bacterial suspension is added one drop of 0.04 percent meta cresol purple and 0.3 ml of N/5 HCl in 0.85 percent NaCl, then mixed. If the suspension is not a definite pink color (pH 2.0 to 2.4), another drop or two of the N/5 HCl is added. The mixture is added to a small tube and placed in a boiling water bath, shaken at intervals of 3 minutes for 10 minutes, then removed and cooled. The mixture is centrifuged and the supernatant (the extract) is carefully collected in a clean tube. The extract is neutralized by adding N/5 NaOH (in distilled water) dropwise until it becomes just slightly purple

(pH 7.4 to 7.8). The extract is finally centrifuged. A crystal clear supernatant should result which may be used immediately or stored several days in the refrigerator.

For precipitin grouping, sterile glass capillaries (outside diameter, 1.2-1.5 mm; length,  $140 \pm 2$  mm) are dipped into the grouping serum and a column about 1 cm long is allowed to enter. The capillary is wiped off; then, taking care that air does not enter the end containing the serum, the capillary is dipped into the extract until an amount equal to the serum column is drawn up. The capillary is wiped clean and the end containing the serum extract is plugged with plasticine. The capillary is inverted, then inserted gently into a plasticine-filled groove in a wooden rack. A white cloud or ring forming at the center of the column within 10 minutes indicates a strong reaction. A weaker reaction may occur within 30 minutes. Reactions occurring after 30 minutes may be false positive or negative and should be disregarded.

When typing of Group A streptococci is to be performed, the Lancefield precipitin and the Griffith agglutination tests as described by Moody, et al. (1) may be followed. Both procedures require careful standardization of reagents and interpretation of reactions.

Extracts for grouping (but not for typing) streptococci may be prepared also by the hot formamide method (12), by using an enzyme preparation obtained from Streptomyces albus (13), or by autoclaving suspensions (14).

The fluorescent antibody test is useful for serological detection and identification of Group A streptococci in stained smears made from young broth cultures in which throat swabs or filter paper strips have incubated 2 to 5 hours or from beta hemolytic colonies growing on blood agar plates (16, 17).

The test for bacitracin sensitivity of beta hemolytic streptococci as a means of identifying those strains belonging to serological Group A (15) has gained widespread use. When the test is performed according to the recommendations of the author, a high degree of correlation with the serological grouping tests can be demonstrated.

Serological methods for detection and measurement of streptococcal antibodies. Serological methods for measuring antibodies to Group A streptococci or their products, while of little value in the initial diagnosis, provide evidence of previous streptococcal infections. A documented rise in antibody during convalescence is indicative of the occurrence of a streptococcal infection. When a single serum specimen is tested, a markedly elevated antibody titer is considered indicative of a recent infection. The antibody most commonly measured is that directed against the extracellular hemolysin, streptolysin "O". A significant rise in antistreptolysin "O" (ASO) levels follows Group A streptococcal infection in approximately

80 percent of the patients of school age or adolescents (18). Similar rises in antibody levels can be demonstrated for other streptococcal antibodies, such as antihyaluronidase (AH), antistreptokinase (ASK), anti-deoxyribonuclease B (antiDNase B), or antidiaphosphopyridine nucleotidase (antiDPNase or antiNADase). If two antibodies are measured, a diagnostic rise can be demonstrated in about 90 percent of the patients. If three antibodies are measured, at least one will be elevated in over 95 percent of the patients. Average levels of ASO in various age groups in the United States have been reported generally to be as high as 200 units per ml without reference to experiencing a recent streptococcal episode (19). When ASO titers on single serum specimens are found to be above 200-300 units/ml, a recent streptococcal illness should be suspected. Failure to demonstrate recent streptococcal infection is considered to be an important requisite for ruling out a diagnosis of rheumatic fever as a cause of acute polyarthrititis (18).

The procedure of Rantz and Randal (20) for measuring ASO is in common usage, and reagents are available commercially. A micro ASO test is now available which is highly reproducible, yielding titers within one dilution step 98 percent of the time in validation tests (21). The test permits a savings in costs for reagents amounting to approximately sixty-five dollars per 100 tests, and twice the number of tests can be performed in a given period of time.

Antibodies to type-specific M-substance of Group A streptococci can be measured by means of the bactericidal test (22), provided the somewhat cumbersome requirements of the test can be met. The results provide strong evidence of a previous infection with a specific M type.

Laboratory methods for the diagnosis of streptococcal infections depends upon the use of well standardized reagents and procedures as well as interpretation of the results. The applicability of the methods selected must be considered in reference to the climatic conditions, mail delivery schedules, and workloads of the laboratory. There is a need for simple, rapid, yet reproducible laboratory procedures, and for standardized reference reagents for evaluation of laboratory performance.

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NATURAL HISTORY OF SUB-ACUTE BACTERIAL ENDOCARDITIS (SBE)

by

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The prevalence of sub-acute bacterial endocarditis has always been, of course, a reflection of the prevalence of rheumatic heart disease and of congenital heart disease. As one might expect, a decline in the prevalence of the former has been associated with a decline in the prevalence of sub-acute bacterial endocarditis and a relative increase in the frequency of congenital heart disease as an underlying cause of SBE. Furthermore, the widespread use of antibiotics has reduced the frequency with which both rheumatic heart disease and congenital heart disease are complicated by bacterial endocarditis. In addition, an increase in surgical procedures, the advent of heart surgery, and the increased hospital population with chronic degenerative diseases treated intensively with broad spectrum antibiotics have introduced certain new features into the epidemiology and bacteriology of this disease.

### Pathogenesis

One might, therefore, divide modern SBE into what can be called "wild type" infection as opposed to "hospital acquired" infection. The former represents the conventional kind of disease which still has the following features:

(a) infection with the commonest commensals of the upper respiratory tract, notably the alpha haemolytic or "green" streptococci (*streptococcus viridans*). These are usually penicillin sensitive.

(b) infection of lesions in which there is a small, strong regurgitant jet or shunt rather than a wide open one.

Certain other features of the underlying heart disease influence infection of the valves: congestive heart failure and/or arterial fibrillation are less commonly complicated by SBE. Edentulous patients are also less often involved.

Pathogenesis begins with bacteremia; by far the most common "spontaneous" bacteria, that is, non-surgically induced, due to organisms of low pathogenicity, is from the mouth and often from infected tooth sockets. For this reason, by far the most common "wild type" infection is the *streptococcus viridans* or "green" *streptococcus* (alpha haemolytic) and the great majority, perhaps 90% or more, are sensitive to penicillin.

By the same token, bacteremia from oral flora is more often due to the *enterococcus* (*streptococcus faecalis*), when patients receive antibiotics of broad spectrum type and in large doses. Although enterococci are frequently sensitive to penicillin, their range of sensitivity is very variable and some strains are extremely resistant. Furthermore, infections with even the most sensitive strains in vitro have a great tendency to relapse in vivo. Perhaps, this is because they have a great propensity to survive in L-forms which are alternative morphological forms free of cell walls, resembling PLO organisms, and which are killed by streptomycin, Kanamycin or chloromycetin, but not by penicillin or the other antibiotics whose effectiveness depends upon inhibition of cell wall synthesis.

Bacteremia from the genitro-urinary tract, either spontaneous in patients with urinary tract infections or induced by instrumentation, such as catheterization, is particularly dangerous, again because of the frequency of enterococci in this location.

Bacteremia following heart surgery has led to the most bizarre organisms, those of lowest virulence, such as staphylococcus albus and even candida (monilia) species. Insertion of artificial valves is particularly challenging because infection of these prostheses is rarely curable by chemotherapy alone and valves so infected must be removed and replaced. Wherever foreign bodies such as sutures or "teflon" patches are applied, infection with the commensals of very low pathogenicity is a possibility.

From the above, it can be seen that prophylaxis of SBE depends upon the kind of infection you are trying to prevent and its source and medical setting.

Patients receiving prophylaxis against rheumatic recurrences deserve special comment. Because the dose of penicillin either orally or by injection of benzathine penicillin G is so small and the blood levels so low, they are not adequate prophylaxis against SBE. Although the latter is a rare complication in patients receiving prophylaxis against Group A streptococci, there have been approximately thirty patients reported in articles known to me and I have seen six myself. Interestingly, almost all of these have been due to a strain of streptococcus viridans sensitive to the usual doses of penicillin and almost all have been cured easily by conventional doses of penicillin. Therefore, rheumatic fever prophylaxis against Group A streptococci is neither adequate to prevent SBE nor does it lead to super-infection with either highly resistant strains or unusual organisms.

In the United States of America, the dental associations have been indoctrinated intensely to give prophylactic penicillin. Although most patients we see with SBE have not followed tooth extraction, it is difficult to know how effective the programme among dentists has been.

In conclusion, most of SBE seen is still dominated by strains of streptococcus viridans which are amenable to usual therapeutic courses of penicillin but hospital infections and instrumentation procedures now produce with greater frequency more difficult and resistant infections, especially enterococci. This requires good bacteriologic facilities to make blood cultures and to test organisms for sensitivity in vitro, particularly when such infections are acquired in hospitals. The diagnosis of SBE, however, and especially its differentiation from the diagnosis of recurrent rheumatic fever in the patient with rheumatic heart disease, requires a high index of suspicion by the physician and good laboratory support for blood cultures. This is particularly true in the kind of SBE now seen early before the obvious and advanced stages of the disease make the diagnosis much easier clinically but treatment more difficult. The treatment is less effective in late cases because bacteriologic cure may not prevent irreversible damage to the valves and subsequent death from heart failure, nor prevent cerebral embolism. Early diagnosis by blood culture is, therefore, the key to successful therapy, and prevention by anticipating bacteremia with appropriate chemotherapy is most important of all.

SUB-ACUTE BACTERIAL ENDOCARDITIS (SBE)  
Preventive Measures

by

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Certain established facts regarding sub-acute bacterial endocarditis bear much weight in the formulation of preventive measures against this disease:

1. Individuals with organic cardiac murmurs due to chronic rheumatic valvulitis or congenital heart disease are identifiable as the subjects most susceptible to the development of sub-acute bacterial endocarditis.
2. Bacteria implant on previously diseased heart valves following transitory bacteremia.
3. Bacteremia leading to sub-acute bacterial endocarditis often originates from dental procedures on infected teeth, surgery of the upper respiratory tract, urologic procedures, and occasionally obstetrical procedures.
4. Streptococcus viridans is the most common etiologic agent. In rheumatic patients previously receiving antibiotic prophylaxis against rheumatic fever who develop bacterial endocarditis, antibiotic resistant enterococci (streptococcus faecalis) or staphylococci have become increasingly frequent as etiologic agents.
5. Streptococcus viridans commonly originate from the oral cavity, periodontal or periapical tooth infection, and the upper respiratory tract. The usual source of enterococci is the genito-urinary tract.

The discussion on preventive measures may be divided into specific recommendations and educational programmes. The first includes antibiotic prophylaxis for bacterial endocarditis, optimal dental care and eradication of foci of bacterial infection in other regions such as pyelonephritis, sinusitis, etc.

All individuals with rheumatic or congenital heart disease should receive antibiotic prophylaxis when subjected to dental procedures, surgery of the upper respiratory tract, genito-urinary procedures, and others. The following regimens are suggested:

- (1) For dental procedures (aimed against streptococcus viridans) -  
600 000 units of procaine penicillin I.M.,  
1-2 hours before dental procedures and daily  
for two days thereafter.
- (2) For surgery or genito-urinary procedures (aimed against enterococci) -  
1.2 to 2 million units of penicillin G with  
1 gm of streptomycin I.M., 1-2 hours before  
surgery and daily for three days thereafter.

There are no standard recommendations for drug prophylaxis against staphylococci, particularly resistant strains, and currently the antibiotics that may possibly be used are the penicillinase-resistant penicillins (methicillin, oxacillin, cloxacillin, nafcillin, etc.), the cephalosporin group (cephalothin, cephaloridine), gentamycin, lincomycin, and kanamycin. Some investigators have reported the synergistic action of erythromycin and penicillin against penicillin-resistant staphylococci.

Erythromycin is the second drug of choice recommended as prophylaxis for patients who are allergic to penicillin. Perhaps ampicillin may be recommended also, because of its established efficacy against many coliform organisms, as a prophylactic measure in genito-urinary procedures.

The educational aspect of the prevention of bacterial endocarditis, compared to that for initial attacks of rheumatic fever, is less complex since the campaign is aimed at a small group and not the entire community:

- (1) patients or the parents of minors with rheumatic valvular disease or congenital heart disease;
- (2) dentists;
- (3) surgeons and related specialists.

Bacterial endocarditis should be regarded as at least in part an iatrogenic disease and the responsibility of dentists and surgeons is great. Methods and indications for antibiotic prophylaxis should be re-emphasized repeatedly to dentists and surgeons. The education of the patient himself, and of the parents of a minor, is an effective measure so that they can remind the dentist or surgeon to administer antibiotic prophylaxis. Patients should have regular examination and treatment of their teeth and, under proper antibiotic coverage, all possible foci of infection should be eradicated.

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