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THE CONTROL OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

AN OUTLINE OF WHO ACTIVITIES

by

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THE EXTENT OF THE PROBLEM TODAY

In a number of affluent countries the incidence of rheumatic fever has considerably decreased during the last decades. In some countries, for instance, cases of florid rheumatic fever are hardly seen any more. As a result, a tendency to minimize the public health importance of rheumatic fever has appeared, on the assumption that the disease may subside or even vanish spontaneously as the standard of living of mankind increases.

However, even in societies with a high average income there may remain islands of poverty where, among other endemic diseases, a relatively high rate of occurrence of rheumatic fever may persist, rendering the "eradication of rheumatic fever an unfulfilled hope".<sup>1/</sup>  
(It may be interesting to mention that a small streptococcal epidemic with cases of rheumatic fever occurred in Geneva in 1971.)<sup>2/</sup> Moreover, rheumatic heart disease may not be preceded by a clinically apparent

attack of rheumatic fever. In many countries a great number of commissurotomies are performed each year, indicating that rheumatic heart disease remains an important problem even where the incidence of acute rheumatic fever is insignificant. But above all, the major part of mankind is still far from that level of welfare at which a decline of rheumatic fever could be expected solely by improving living conditions. In rheumatic fever, as in any disease, the circle poverty-disease-poverty should be attacked from both sides. The question is only what should be the level of priority of rheumatic fever control among the many health problems in view of the limitations of resources in any society.

There is no generally valid answer to this difficult question, because it depends on an undefined number of factors related to the texture of health and social conditions in a given area. Nevertheless, a number of considerations should be taken into account concerning rheumatic fever itself. Mortality data, with some reservations due to inherent uncertainties, show the interesting fact that in 1968, in the age group 15 - 24, rheumatic fever with rheumatic heart disease - a disease of youth - was the leading cause of death (accidents excluded) in six countries, and was at the second or third place in a further four countries (Table 1). Most of these ten countries are neither at a low nor at a high level of affluence. It could be assumed that a similar pattern of mortality will emerge in developing countries, when their present leading health problems are overcome. Endeavours in developing countries to control rheumatic fever and rheumatic heart disease thus might be an investment into the future.

Rheumatic fever and rheumatic heart disease are preventable by treating the streptococcal infections adequately, as stated in several WHO documents. <sup>3-6/</sup> Prevention of relapses is relatively easy and cheap,

it costs probably several hundred times less than e.g. the surgical treatment of a patient with mitral stenosis or aortic incompetence. Patients with rheumatic heart disease may live as invalids for several decades, and society cannot disregard the humane nor the economic aspect of invalidity.

Data on the magnitude of the problem are becoming available in an increasing number of countries. At a recent WHO consultation <sup>I/</sup> the situation in some countries of the Mediterranean was reviewed. According to the reports given at this consultation, Algeria has a significant rheumatic fever problem, and it seems to be on the increase. In a pilot study of an area with a general population of 45 000 inhabitants (all ages), three per thousand of the total inhabitants sought medical care for rheumatic fever and rheumatic heart disease from June 1970 to June 1971. Eighty percent of these were children under 16 years of age. More than 470 000 school children underwent systematic health examinations: nearly 7 000 children (1.5 per thousand) were found to have rheumatic heart disease. In Cyprus, the importance of rheumatic fever can be judged from hospital admissions. These seem to be relatively common over the past 10 years: 40 to 65 new cases per year are admitted to Nicosia General Hospital, serving a general population of 150 000 inhabitants. Most of these patients are children. In Egypt, in a field study on school children 6-12 years old, a prevalence rate of 10 per thousand of definite rheumatic heart disease cases was found. Group A streptococcus infections were found to have a high incidence - approximately 30 percent of school children per year. In Iran, on the 70 000 general population of Abadan, an incidence rate of 1 per thousand was reported in 1971. A group of school children in a socio-economically underprivileged area of Teheran was found to have a rheumatic heart disease prevalence rate of 22 per thousand, and a

rheumatic fever annual incidence rate of 4 per thousand. In a population of 40 000 socially insured Teheran workmen and their families, a prevalence rate of 2.5 per thousand was observed. Hospital statistics in Iran show that 30-60 percent of all cardiological admissions are due to rheumatic fever. In Morocco, the findings of A. Tazi and colleagues indicate a rheumatic heart disease prevalence rate of 9.85 per thousand in school children. Up to 4.5 percent of all hospitalized patients are admitted for rheumatic fever. An organized control programme seems highly desirable. In the Sudan, 14 885 cases of rheumatic fever and rheumatic heart disease were admitted to hospital in 1970. As the total population amounts to about 14 million, one per thousand inhabitants was admitted to hospital for rheumatic heart disease. A large number of these were children; 45 percent were below 20 years of age. The number of those not hospitalized is unknown.

Data from other places such as Barbados, Columbia, Ethiopia, Polynesia, India, Jamaica, Mongolia, Nigeria, Peru, Senegal, show that rheumatic fever and rheumatic heart disease present a problem anywhere on the globe.

#### PREVENTION

Fortunately, all germs from group A streptococci are sensitive to penicillin. Unfortunately, the group consists of a great number of immunologically different types, and there is no satisfactory cross-immunity to other types after infection with one type. Therefore, no immunization to rheumatic fever is practicable at present, and prevention has to rely on the bactericidal effect of penicillin (or on other antibiotics, if the subject is allergic to penicillin).

Streptococci are ubiquitous and, practically, cannot be eradicated. The ideal way of prevention is early penicillin treatment of any group A

streptococcal infection. The practical difficulty lies i.a. in identifying all streptococcal infections. Though the bacteriological diagnosis is simple and relatively inexpensive, the incidence of throat and skin infections which might be due to streptococcal infection is so great that a bacteriological diagnosis could hardly be established in all cases, especially if laboratories are under the strain of other important work. Besides, many patients with minor streptococcal infections do not reach the physician. An acute throat infection may be due to another cause, e.g. a virus, and streptococcus may still be present, if the subject is a carrier. Rheumatic fever may often occur without being preceded by a clinically manifest streptococcal infection. Furthermore, rheumatic fever may produce in some patients only mild or atypical symptoms. About a third of patients with rheumatic heart disease have never had an attack of rheumatic fever. If all this is taken into account, together with the fortunate fact that rheumatic fever develops only in a small percentage of (untreated) streptococcal infections, it may be realized that several thousands of cases of group A streptococcal infections should be treated early and efficiently in order to prevent a single case of rheumatic heart disease.<sup>8/</sup> This clearly shows the magnitude of the task, if primary prophylaxis in entire populations is aimed at. Nevertheless, much can be done for primary prophylaxis, e.g. in collectivities or families, particularly if outbreaks of streptococcal infections are announcing an impending epidemic, or at the time of any increasing exposure to streptococci.

If a person has contracted rheumatic fever, it is essential to prevent development or deterioration of rheumatic heart disease by administering penicillin at regular intervals for a long time. Details are given in the recommendations of WHO.<sup>4/</sup> There is no doubt that regular penicillin

prophylaxis of recurrences considerably improves the prognosis of rheumatic fever, yet in many cases prophylactic treatment is given irregularly or is not given at all, and organized community action has remained limited. The crucial problem in this field is how to extend prophylaxis to all those who need it. WHO has therefore developed a programme of rheumatic fever and rheumatic heart disease prevention in communities.

#### WHO CONTROL PROGRAMMES

WHO's activities started with the Expert Committee's recommendations for the prevention of rheumatic fever and rheumatic heart disease. <sup>3-4/</sup> They were taken up by the Fifth World Congress of Cardiology (N. Delhi, 1966) <sup>10/</sup> where the necessity of establishing model centres of prevention was outlined at a symposium on rheumatic fever. This was followed by a WHO Seminar in the Western Pacific Region in 1968, <sup>11/</sup> where the epidemiology and control of rheumatic fever in the region was discussed. In 1970, WHO issued a proposal for the epidemiological study and control of streptococcal infections and their sequelae, rheumatic fever and glomerulonephritis. <sup>6/</sup> The protocol was tested and reviewed in February 1972, at a meeting in Cairo <sup>1/</sup> and the agenda of the Regional Seminar on Cardiovascular Diseases to be held in Teheran in December 1972 includes also the control of rheumatic fever and rheumatic heart diseases.

WHO's current approach to the community control of rheumatic fever is to establish pilot programmes in various countries and environments which, if successful, should serve as a model in the respective area. The main objectives of the programme are : (a) surveillance of known cases of rheumatic heart disease and rheumatic fever in a community, and regular

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\* A limited number of copies of the operating protocol are available on request from CVD Unit, WHO, Geneva.

penicillin prophylaxis in order to prevent relapses and deterioration of the heart disease, and (b) studying the incidence and prevalence of the disease, and its natural history, as compared to other areas. Other important subjects to be studied are the cost of prophylaxis programmes; patients' response including the causes of ~~missed~~ missed appointments, drop-outs, and effects of migration into and out of the study area; promotion of primary prevention of rheumatic fever; bacteriological and sero-immunological research in group A streptococcus epidemiology; promotion of training of physicians and other health workers.

Patients known to have had rheumatic fever and patients with rheumatic heart disease are registered and followed up. An information system is built up in order to include all known cases in a community. This involves gathering data from the hospitals, the school health service (if any) and the physicians in the area. Besides, systematic screening of high risk groups, mostly school-age children, is carried out in order to include hitherto undetected cases. Good working relationships are established between all factors involved in the programme. A scheme of these relationships is given in Annex II. Health visitors are an essential part of the programme, as they are sent to all those registered patients who do not appear for the prophylactic treatment in due time. It should be stressed that wherever this suits the health care system, the intention is to bring the patients, at regular intervals, to their treating physicians, and not to take them away from their doctors.

Circumstances may require that the protocol be adapted to specific situations. The organizational design of the programme may differ, in details, from place to place. The principles, however, should be conserved

in any situation. Defined communities or population groups should be covered as completely as possible and, for the sake of comparability, the data should be recorded in various places in a uniform way.

Studies and control programmes of rheumatic fever were started according to the WHO design in several areas of the world. A pilot project, initiated in Barbados in 1970, has demonstrated that good coverage of the population and satisfactory patient response to an organized preventive programme of rheumatic fever relapses may be obtained in a relatively unsophisticated population. <sup>2/</sup>

A similar programme in Egypt includes all school-age children of the Qualyub area, near Cairo. Qualyub Hospital, the rural health services and the school health service in the study area are co-operating with the Rheumatic Fever Project Centre in Cairo. Bacteriological and clinical examinations are made on a population of 10 000 school children annually.

Another programme in Nigeria covers several thousands of school-age children in the Lagos metropolitan area. In Iran the programme is conducted in Teheran, by the School of Public Health in co-operation with the social insurance medical service; the study area has a population of 100 000 made up of 26 000 socially insured workers and their families. A programme on the same lines has been prepared to include a population of similar size in the city of Abadan. In Senegal, the Cardiology Department and two other departments of the Medical School in Dakar and the school health services are co-operating in preparing a pilot programme of the same kind for school children. Another such programme is being organized in Ulan Bator, Mongolia.

At the 1972 consultation on Rheumatic Fever Control in Cairo, there were participants from Algeria, Cyprus, Egypt, Iran, Morocco and the Sudan.



Lively interest was shown in all these countries and preparations were started for extending the WHO rheumatic fever control programme to new areas. It was also agreed to launch a co-operative study on the validation of the diagnostic criteria for rheumatic fever, co-ordinated by WHO and based on the Rheumatic Fever Project Laboratory in Cairo and the WHO International Reference Centre for Streptococcus Typing in Prague.

#### THE RHEUMATIC FEVER CRITERIA STUDY

The diagnosis of rheumatic fever is a straightforward one in typical cases of the disease. However, very often the symptomatology of rheumatic fever is far from being typical. The sensitivity and specificity of the criteria at present used for the diagnosis of rheumatic fever is not known. The pattern of the disease may have undergone some changes during the last decades, and it might show some differences according to various geographical regions. Recent advances in laboratory assessment of the organism's reaction to streptococcal infection may facilitate an attempt to validate the diagnostic criteria for rheumatic fever. In suspect cases, when a decision must be taken as to whether or not prophylactic treatment should be instituted, the validity of diagnostic criteria becomes highly relevant. The WHO study therefore aims at validation of the currently used criteria for the diagnosis of rheumatic fever.

A significant number of cases with both clinically clear and suspect rheumatic fever will be analyzed. Clinical symptoms and signs are confronted with laboratory findings, and patients are followed up. Eventually, it will be assessed with what probability various combinations of clinical and immunological findings can be attributed to rheumatic fever.

Both cases of first and of subsequent attacks of acute rheumatic fever and cases of active rheumatic heart disease are studied, whether the diagnosis is established definitely, or whether it is equivocal. "Definite" cases

are those complying with Jones' modified criteria. Guidelines for considering a patient to have "equivocal" acute rheumatic fever or active rheumatic heart disease are the presence of any one of the major criteria; or combination of any minor criterion with arthralgia; or established rheumatic heart disease being the opinion of the physician highly suspicious of a recurrent episode of rheumatic activity.

The diagnostic procedures include a detailed clinical work-up and a series of laboratory investigations, including grouping and typing of the streptococcus, if present. Serological tests, such as ADPNase, ADNase B, cross-reactive heart antigen and ACHO antibody assays are included. The patients are followed up and carefully observed as to whether Rheumatic Heart Disease will develop or deteriorate after a spell of "equivocal" rheumatic fever.

#### THE WHO INTERNATIONAL REFERENCE CENTRE FOR STREPTOCOCCUS TYPING

Bacteriological and serological procedures are of basic importance for the diagnosis of streptococcal infections and their sequelae and for setting up a prophylaxis programme of streptococcal infections in rheumatic individuals or in larger population groups. In order to ensure reliability of laboratory results and comparability of findings obtained in various parts of the world, standard laboratory procedures and reference biological materials are to be used. The recognition of such a need led WHO to the decision to establish the WHO International Reference Centre for Streptococcus Typing. The Centre was created at the Institute of Hygiene and Epidemiology in Prague in 1966.

In the past five years, the Centre has maintained a collection of reference strains for the preparation of grouping and typing sera, and for the production of extracellular streptococcal products. A total of 8 176 ampoules were made and 1 047 lyophilized strains meeting 114 requests were

sent abroad. Sera for group A to U of hemolytic streptococci, precipitation sera for the majority of types 1 to 61 for group A strains (anti M sera), agglutination typing sera for group A strains (anti T sera), and group B typing sera are currently used by the Centre in research, and may be supplied to other laboratories, on request, as reference sera. In past years, the Centre has met a considerable number of requests for grouping and typing sera, and identified by both agglutination and precipitation techniques several hundreds of streptococcus strains sent from other laboratories.

A large part of the Centre's work is concerned with the determination of antistreptolysin O titers in human sera originating from various parts of the world. The serological surveys provided valuable information on the occurrence of streptococcal infection among the population of the tropical and subtropical zones. The sera were collected by study teams within WHO activities relating to various health problems in several developing countries. In general, the population sampled can be considered "average" with respect to streptococcal infections, since no effort was made to include or exclude individuals who might have been suffering from streptococcal infection at the time of sampling. The collections of sera were sent to Prague and were stored at the WHO Regional Reference Serum Bank. Antistreptolysin O was determined by a modification of the photometric method of Liao.

A total of 4 000 sera were examined, collected in various surveys, from Algeria, Burma, Kenya, Mongolia, Nigeria, Pakistan, Thailand and Togo. Annex III shows the percentage of sera with antistreptolysin titres above 199 units in these countries. While the tested sera from some countries covered a wide age range, only school-age children's sera were titrated from other countries, after it became apparent that, similarly to the temperate zone, the age group of 6-14 years is at the greatest risk from streptococcal infection in the tropics and subtropics.

In the temperate zone of the Northern Hemisphere elevated titers are usually found in 5 - 20 percent of healthy individuals. The higher percentage in most of the tropical and subtropical countries investigated calls for further comparative bacteriological and epidemiological investigations in order to assess the real significance of these serological findings.

The Centre's research programme is focussed on microbiological, bio-chemical and immunological aspects of streptococcal infections and their sequelae, with special reference to the role of streptococcal cellular and extracellular products in the pathogenesis (cell wall mucopeptide, M protein, erythrogenic toxin, streptolysin O), to the virulence of streptococci and immunity in streptococcal infections. Furthermore, the research programme includes the study of the submicroscopic structure of haemolytic streptococci and their L forms and of various problems of the epidemiology of streptococcal infections, rheumatic fever and acute glomerulonephritis. The Centre endeavours to co-ordinate the work of national streptococcus reference laboratories and to assist WHO in the co-ordination of national and international studies of the control of streptococcal infections and their sequelae. It is ready to supply, on request, reference streptococcus strains. These strains are representative cultures of the individual groups and types, suitable for the production of grouping and typing sera. Moreover, preferential strains for the preparation of different extracellular streptococcal products are available. The Centre can supply to interested laboratories grouping and typing sera in small quantities as reference material. The Centre is also ready to test grouping and typing sera prepared in national streptococcus reference laboratories or pilot centres, if requested. Facilities are available for grouping and typing of limited numbers of streptococci, and aid may be provided for the assay of antistreptolysin O titration or, if necessary, of an alternate antibody, if sera compiled for research are to be analyzed.

## INTERNATIONAL CO-OPERATION AND ITS ADVANTAGES

The control programmes are carried out according to the same basic design, and uniform data are collected. This will allow a parallel to be drawn between the programmes in various parts of the world. It is also expected to obtain comparable data on the prevalence and incidence of rheumatic fever and rheumatic heart disease in the various study areas. As there is a great diversity between the areas where the studies will be conducted, comparable data should be valuable, particularly because no population-based data on the occurrence of rheumatic fever and rheumatic heart disease are available from tropical and subtropical countries.

The rheumatic fever criteria validation study is conceived largely on the basis of international co-operation for two reasons. A considerable number of cases with active rheumatic fever are needed, and if they are collected from several centres, the study may be completed sooner. Furthermore, a great number of sophisticated laboratory assays will be done. By division of labour, some of the centres will make certain analyses centrally. Thus, the laboratory workload will diminish and comparability of the results will be increased.

Central computer data-processing by WHO is foreseen, both for the community control and criteria validation study, based on the use of uniform record forms in the various co-operating centres. Its advantage is an identical treatment of the data coming from various centres, hence easier comparison of the results. Another advantage is that central data processing is economical. It also provides the opportunity for timely spotting of methodological deficiencies, e.g. incomplete or erroneous recordings. Such information is fed back to the centre immediately, and the methodological fault can be corrected.

The International Reference Centre promotes the "common language" between streptococcal laboratories in various parts of the world. For instance, the Centre carried out a co-operative evaluation of streptococcus T-typing with the participation of 15 national streptococcus reference laboratories. The participants unanimously stated that this type of co-operating was useful, but the study made it obvious that T-typing requires further attention to technical details before world-wide results can be compared with certainty.

In another evaluation study, 11 national reference laboratories participated in assessing the bacitracin test as a screening method for identifying group A streptococci. This study revealed that the bacitracin test can on no account replace the serological identification of Group A streptococci which alone gives reliable results.

International co-operation is not always an easy task. It may require sometimes considerable effort from the participants e.g. to drop a laboratory method and to adopt another, or to comply with some standards. Communications may be slower than desired. Intercultural differences may cause some difficulties in the interpretation of questionnaires. However, these inconveniences are amply compensated by the advantages of a co-operative project.

Streptococci are complicated, fascinating micro-organisms. Rheumatic fever is a complicated, in many respects still mysterious, response of the human body to streptococcal infection. It is to be hoped that international co-operation will contribute to a better understanding of the germ and the disease, and that eventually the desired level of control will be achieved.

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TABLE I

THE RANK OF MORTALITY DUE TO RHEUMATIC HEART DISEASE AND  
RHEUMATIC FEVER IN VARIOUS COUNTRIES, IN YOUNGER AGE GROUPS

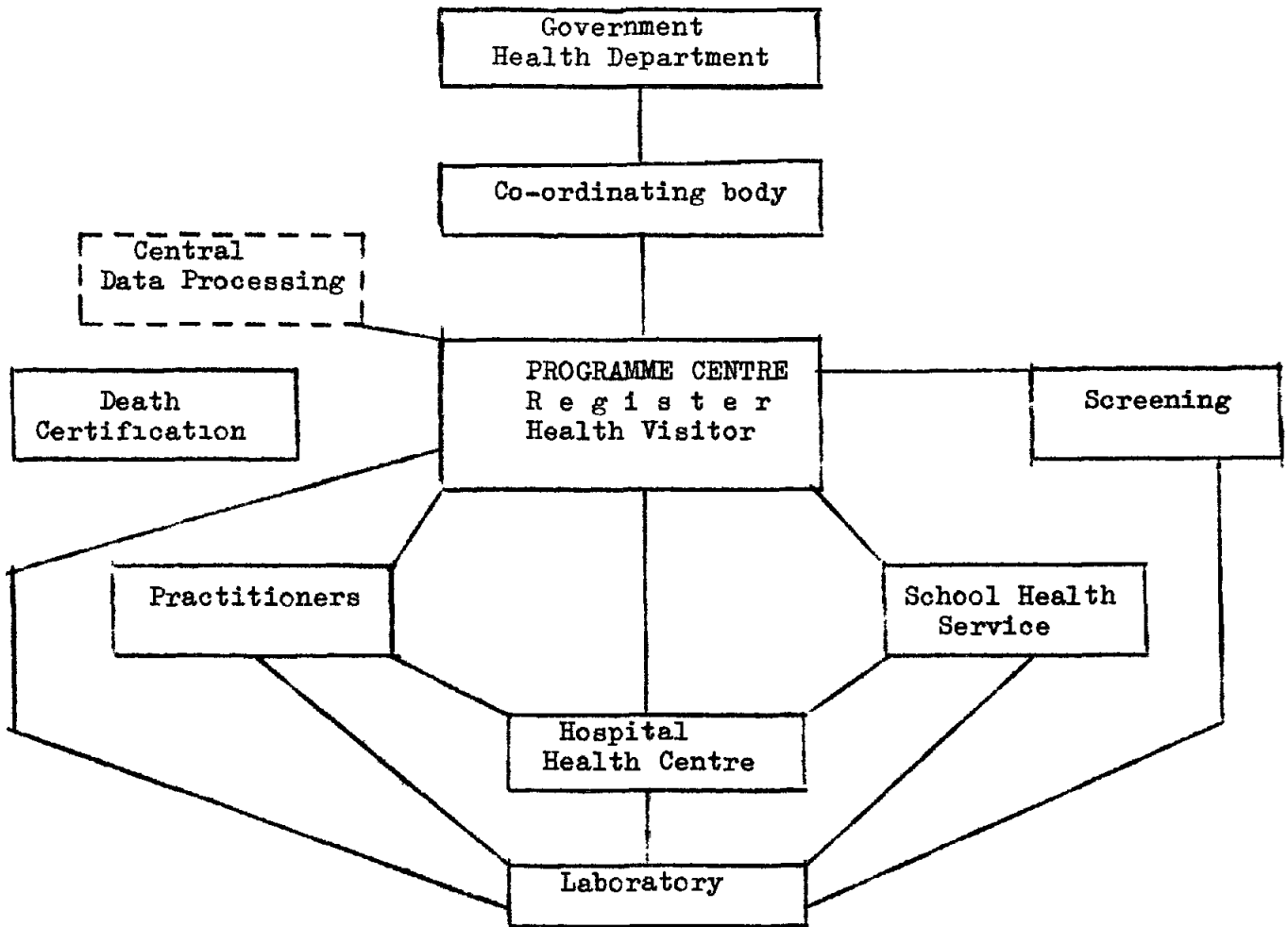
Data for 1968 (Source : World Health Statistics Annual, Geneva, 1971)

	5 - 14	15 - 24
1.	-	Bulgaria, Hong-Kong, Portugal, Romania, Singapore, Yugoslavia
2.	Hong-Kong	Greece
3.	Portugal, Singapore	Israel, Mauritius, Poland
4.	-	-
5-	Bulgaria, Mauritius, Romania	Philippines
6.	Spain	-
7.	-	China (Taiwan), Spain
8.	New Zealand	Ceylon, Mexico, New Zealand
9.	Ceylon, China (Taiwan)	Chile
10.	Dominican Republic, Poland, Yugoslavia	Australia, Austria, USA



FIGURE I

DRAFT CHART OF FUNCTIONAL RELATIONSHIPS



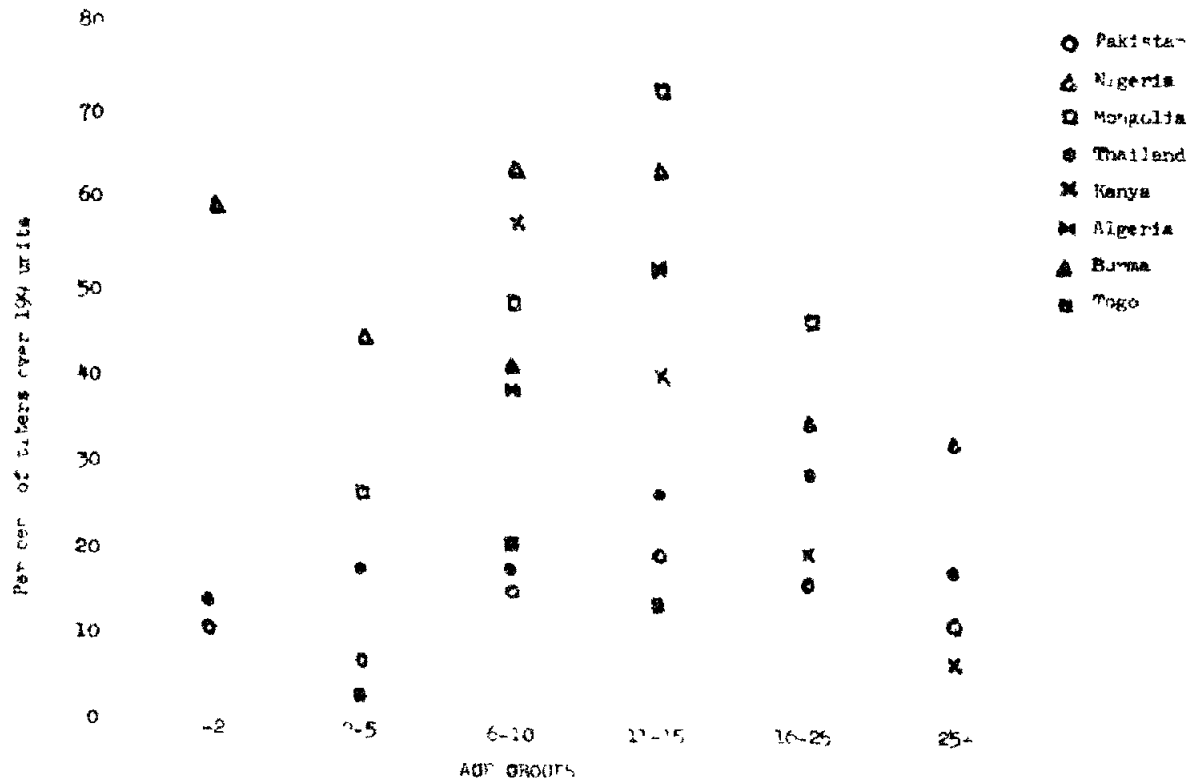


Figure 2 Antistreptolysin O titers over 194 units in sera collected in populations of various Asian and African countries