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**WHO EXPERT COMMITTEE
ON TUBERCULOSIS**

Eighth Report

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WHO EXPERT COMMITTEE ON TUBERCULOSIS

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WHO EXPERT COMMITTEE ON TUBERCULOSIS

Eighth Report

The WHO Expert Committee on Tuberculosis met in Geneva from 18 to 24 August 1964. The previous committee to consider all aspects of tuberculosis had met from 28 September to 3 October 1959.¹

The meeting was opened by Dr M. G. Candau, Director-General of the World Health Organization. In welcoming the members of the Committee, Dr Candau referred to the development that has taken place since 1959, pointing out that not a single country has succeeded in reaching a point of control where there is less than 1% "prevalence of natural reactors to tuberculin among children in the 14-year age-group", a criterion set by the previous Committee as an indication that tuberculosis is no longer a public health problem. He said: "Tuberculosis remains a public health problem of major importance in almost all countries. Looking at this situation from a global epidemiological viewpoint, there is also the disturbing fact of a rapidly increasing gap... between the economic 'have' and the 'have-not' countries." Dr Candau went on to say that he believed that this unsatisfactory position in tuberculosis was to a large extent due to the inadequate application of existing knowledge.

The Committee was asked to review present knowledge in tuberculosis and to consider how this can be best applied under different socio-economic conditions and how WHO can assist national tuberculosis programmes.

1. INTRODUCTION

The Committee noted the comment in the last report of the Expert Committee that tuberculosis is "generally conceded to be the most important specific communicable disease in the world as a whole, and its control should receive priority and emphasis both by WHO and by governments".²

The Committee noted that the specific tools now available for preventing and curing tuberculosis make it possible to plan and execute effective

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1960, 195.

² *Wld Hlth Org. techn. Rep. Ser.*, 1960, 195, 4.

antituberculosis programmes under practically any epidemiological or socio-economic conditions. It stressed that the relatively slow decline in the tuberculosis problem observed in many countries seems to be in contrast to the resources expended on tuberculosis programmes, and that localized increases in incidence have even occurred recently in several developed countries. The Committee thought that this unsatisfactory situation is due mainly to insufficient realism in selecting priorities for application; lack of national planning, co-ordination, and evaluation; and failure to re-orient traditional approaches to present knowledge. Particularly, there seems to be inadequate recognition that an efficient tuberculosis control programme depends upon reliable epidemiological and operational data, permitting its continuous adaptation to changing circumstances. The Committee therefore emphasized that, in order to bridge the gap between knowledge and application, an objective and systematic approach to formulating policies in tuberculosis control is urgently needed. It wished to put on record also that the very perfection of currently available control measures, on the one hand, and the gap in their application between developed and developing countries, on the other hand, make international co-operation, co-ordination and assistance mandatory if tuberculosis is ever to be eliminated as a global public health problem.

As it had to cover such a broad subject, the Committee decided to focus its attention mainly on the control of pulmonary tuberculosis, and in particular its control in countries where tuberculosis is a serious public health problem and where the best possible use has to be made of limited resources in order to achieve an impact on the problem.

2. THE TUBERCULOSIS PROBLEM

2.1 Social significance

The formulation of an efficient tuberculosis control programme under widely varying and rapidly changing conditions rests on the ability to measure the tuberculosis problem. This problem must be seen in its broadest sense as one of human suffering resulting in a demand for alleviation and leading to the subsequent development of services.

Sociological enquiries into the *awareness* of chest symptoms in the general public have provided strongly suggestive evidence that such awareness is commonly underestimated as a motivating force in control programmes, in that symptoms are usually sufficient to induce patients to seek relief by consulting existing health services. That this felt need is not linked to any particular social setting is demonstrated by the fact that, in both developed and developing countries, the large majority of

new cases of tuberculosis are diagnosed by means of services that rely essentially on the initiative of the individual patients.

It was agreed that the problem of tuberculosis can be conceived of as the sum total of the individual suffering caused by the disease and the related social costs. In this connexion, the Committee stressed the importance of obtaining information on the actual economic losses resulting from tuberculosis in different countries, and expressed the hope that efforts would be made to collect such information.

Although tuberculosis is due to a specific micro-organism, *Mycobacterium tuberculosis*, in the absence of which it cannot occur, its development is so notoriously related to social and economic conditions that it is often given as an example of a disease of multiple causation. Before specific measures were available for its control, these social and economic conditions were the predominant factors in affecting the waxing and waning of tuberculosis in a given community.

Such factors are still very important, but the Committee agreed that, although antituberculosis agencies, both governmental and voluntary, should be actively concerned with programmes aimed at improving the social and economic status of the population, they would make their most effective contribution by concentrating their particular skills and limited resources on the specific aspects of tuberculosis control.

2.2 Epidemiological indices

Three main epidemiological indices are relevant to problem measurement and programme strategy : prevalence of persons with specific tuberculin reactions, prevalence of persons who are excretors of tubercle bacilli, and prevalence of persons with chest X-ray shadows.

The availability of a standard tuberculin product and of standard techniques for performing the tuberculin test and analysing its results has made it much easier to estimate the prevalence of infection with *Mycobacterium tuberculosis*, despite the difficulties that exist in areas where low-grade sensitivity is widespread. It was re-emphasized that the tuberculin test must be seen as an instrument particularly suited for the examination of groups. Thus the prevalence of specific tuberculin reactors in children is the best indicator of the current transmission of infection in the community concerned, and, if repeated, of its trend in the community. By means of this index, the annual infection rate may be estimated ; also, one area may be compared with another.

The prevalence of pulmonary tuberculosis proved bacteriologically by microscopy of a single sputum specimen is the best available index of the size of the infectious pool in a community. Such microscopy makes it possible to identify the majority of persons who are excreting tubercle bacilli, and who are particularly dangerous to the community. This index

lends itself to international comparison. Similarly the *incidence* of new cases proved bacteriologically by microscopy is another helpful index of trend. In a community where antituberculosis chemotherapy has been in use, the prevalence of drug-resistant bacilli (more particularly those resistant to isoniazid) provides additional useful information.

The development of photofluorographic equipment permitting the systematic examination of communities has resulted in the collection of a vast amount of information from which, it was hoped, a new epidemiological index of tuberculosis would be evolved. Accumulating evidence indicates that X-rays cannot determine with any certainty whether the shadows detected are tuberculous in origin; bacteriological confirmation is necessary for such determination. Furthermore, clinical "activity" cannot be determined by a single chest X-ray film. No definite epidemiological significance can be attached to so-called "radiological prevalence and incidence rates". However, it is recognized that, even in the absence of positive bacteriological findings, radiological abnormalities in persons with positive reactions to tuberculin indicate a risk of future tuberculous disease.

2.3 Epidemiological methods

2.3.1 *Tuberculosis registers*

The adoption of precise terminology, combined with standardized collection, recording and analysis of field data, makes it possible through these registers to establish sound priorities and schedules for the follow-up of individuals and groups.

2.3.2 *Surveys*

Prevalence surveys have been valuable in indicating the relative significance of epidemiological indices, in providing the data necessary for estimating the extent of the problem in many countries, and particularly in revealing world-wide patterns in the behaviour of tuberculosis. In this way, the surveys have made it possible to formulate a consistent epidemiological strategy in tuberculosis control. It is recommended that, in future random surveys, the number of individuals who are aware of having symptoms suggestive of tuberculosis should be ascertained.

Longitudinal surveys—that is, the long-term follow-up of a group of individuals—although expensive and difficult, provide additional information, especially on the flow of individuals from one given status to another (non-infected to infected, infected to active disease, etc.). They also give information on such important aspects as healing, relapse rates and case-fatality rates. More generally, they make it possible to introduce probabilities

in the epidemiological study of tuberculosis. To that extent, they are relevant to predictive epidemiology and deserve continued attention.

2.3.3 *Epidemetric models*

A more recent development in epidemiological methodology is the development of epidemetric models, which systematize the available knowledge—supplemented, when needed, by estimates—and apply it to demographic tables corresponding to given national situations. In so far as these models permit prediction of epidemiological trends, they can indicate in quantitative terms the tuberculosis problem at a given time in the future, and the degree to which various changes in type or intensity of programme might be expected to reduce the tuberculosis problem. It was suggested that the validity of such epidemetric models could be tested retrospectively by using the data collected in a few of the good national registers.

All these methods for collecting and treating epidemiological information need further improvement if they are to contribute to a more rational formulation of programmes.

2.4 **Epidemiological trends**

The Committee noted that there is very little valid information on the world-wide trend of the tuberculosis problem. Circumstantial evidence would indicate some decline. Therefore, it would be most useful to collect internationally comparable data on the true trend of prevalence of infection in the youngest age-groups. In this connexion, it would seem logical to start with the tuberculin data already collected with standard techniques in many countries. Some long-term studies have demonstrated the slowness that characterizes epidemiological changes in tuberculosis. These studies have shown also how much endogenous reactivation and treatment relapse have contributed to the present tuberculosis problem in developing countries.

In view of the possible influence of primary drug resistance on future epidemiological trends in tuberculosis, and in view of the conflicting evidence on the amount of primary drug resistance existing at present in different countries, the Committee felt that there is a strong need for collecting on a permanent basis internationally comparable data on primary drug resistance. In countries where adequate testing facilities are available, long-term investigations of the frequency of primary drug resistance should be organized with adequate sampling techniques on a nation-wide scale. Standardization of testing techniques and of resistance criteria are prerequisite for such investigations.

3. DIAGNOSIS AND CASE-FINDING

The available diagnostic tools were reviewed with regard to their potential contribution to case-finding, and with a view to defining priorities in the selection of methods and examination groups.

The Committee re-emphasized that persons with pulmonary tuberculosis discharging tubercle bacilli are the infectious sources through which transmission is maintained in the community, and that the object of tuberculosis control is to break the chain of transmission. One way in which this can be achieved is to detect the infectious sources as early as possible and to render them non-infectious.

The Committee believed that it was essential first to agree on a definition of a "case" of tuberculosis. It was decided that, from the epidemiological point of view, a "case" of pulmonary tuberculosis means a person suffering from bacteriologically confirmed disease. Acceptance of this definition would lead to the provision of statistical information that would be internationally and intranationally comparable, and would establish the basis for notification to the public health authorities. All other possible sufferers from tuberculosis, i.e., those in whom the disease has not been confirmed bacteriologically, would be classified as "suspect cases" and would remain so classified unless or until the presence of tubercle bacilli or some other etiology was established. Both groups should be entered in the local register to facilitate follow-up procedures.

Diagnostic techniques and case-finding methods should not be judged solely on their technical merits, but also on all their public health implications. For instance, it is implied that all "cases" diagnosed would have to be treated—and treated fully—and all "suspects" investigated and followed up carefully. In this light, the superiority of one case-finding programme over another is to be assessed by the numbers of "cases" treated and of "suspects" followed up, and not by the number of cases with bacilli or shadows detected. This principle takes into account both the technical aspects (the intrinsic diagnostic accuracy and sensitivity of the tests) and the operational aspects (centralization, mobility, acceptability, etc.). A scale based on the criterion of cost per case (which would vary with the local situation) provides the elements for designing a *progressive* case-finding programme, namely, one that gradually increases its efficiency by the adoption of more refined—usually also more expensive—tools as and when required and feasible.

The Committee emphasized that persons with chest *symptoms* and with positive direct smears are genuine "cases". Repeated cultures—when there are facilities to cope with the workload involved—would reveal most of the remaining infectious cases not found by direct microscopy. If no culture facilities exist, tuberculin-positive "suspects" should be referred for X-ray

examination, if possible, so that those without significant radiological findings may be eliminated from further follow-up. Those having X-ray evidence of cavity should be submitted to intensive follow-up by direct microscopy. By concentration on such a symptom group with direct microscopy as the basic test, the proportion of the total infectious pool diagnosed would increase as the reputation of the diagnostic and treatment services established itself in the community. This case-finding procedure would also reduce over-treatment.

Mass X-ray examination of selected, apparently healthy, groups is expensive but may be indicated if there is an adequate basic diagnostic and treatment programme and if financial resources permit. However, mass X-ray examination should never precede the development of such basic services as will adequately meet the needs of persons seeking help because of symptoms. The main objectives of mass X-ray examination are to find unknown infectious cases or suspect cases, and to determine groups whose further investigation will be ensured through the established routine follow-up procedure. Great care should be taken not to label as "cases" persons simply at risk.

A local register must be maintained for the follow-up of cases, suspects, and special high-risk groups such as contacts and patients whose disease has become inactive. There must be a national statistical service to which local subdivisions submit basic epidemiological data. These data, after analysis, are included in a national report. With the present development of electronic automatic data processing, it may soon be practicable to have a detailed national register in even the largest countries, with the advantages of considerably greater efficiency and economy.

Like any other component of a tuberculosis programme, case-finding must be assessed operationally and technically so as to achieve the highest possible performance.

4. BCG VACCINATION

In recent years, much has been added to the already existing knowledge on the extent and the nature of protection induced by BCG. Substantial protection has now been demonstrated in an area with a high prevalence of low-degree tuberculin sensitivity. Controlled trials have shown that the protection afforded by BCG is of longer duration than had been supposed previously. A post-mortem study has revealed that in BCG-vaccinated persons the frequency and the size and spread of latent primary tuberculous foci are considerably less than in unvaccinated persons. With the increased chance of early sterilization of the foci that is, in all likelihood, the consequence of this situation, it seems permissible to infer that in the vaccinated there exists, in addition to the experimentally proven protection against

exogenous infections, a long-lasting reduction in the risk of endogenous exacerbation. In view of the growing evidence on the value of BCG vaccination, and in view of its comparatively low cost and ease of application, the Committee recommended the continued and expanded use of this control measure on a mass scale in countries where tuberculosis is a serious public health problem. However, the impact of mass BCG vaccination necessarily varies with the frequency of exogenous infection and the proportion of the population already infected in the community. The strategy of its application should be adjusted accordingly.

In countries with a high level of transmission, the widest possible coverage with BCG vaccination should be ensured as early in life as feasible. In strictly controlled trials under varying epidemiological conditions, the difference in the incidence of tuberculosis between the vaccinated and the controls has been found to remain practically unchanged for many years after BCG vaccination. There is no indication so far that revaccination would be necessary within five to ten years after successful vaccination—i.e., vaccination followed by a satisfactory level of allergy on sample retesting a few months after vaccination. Thus, the second vaccination coverage should take place before school-leaving age (12-15 years).

In countries with low transmission—that is, of the order of 2% of specific tuberculin reactors at school-entering age—primary BCG vaccination could be postponed until the children leave school, and this one vaccination may be sufficient.

Vaccination programmes should continue at least until tuberculosis has been eliminated as a serious public health problem.

In developing countries, a high proportion of the population can be covered by special BCG teams in a first round, subsequent generations being reached as part of the vaccination programme through the general health staff (e.g., maternal and child health, school health). The rationale of this approach is that an initial mass campaign is the most suitable operational pattern to achieve the high population coverages required if BCG vaccination is to result in an epidemiologically significant reduction of tuberculosis, and that, once a high coverage is demonstrated in any area, the pace of operation can be reduced, the aim now being to maintain the advantages achieved. In order to “compete with the birth-rate”, which would otherwise reduce to a critical level the protected proportion of the community, a high proportion of the new generations should be covered regularly, say, within the first two or three years of life, and again when leaving school. It is considered that this maintenance phase is often compatible with an integrated programme operating at the same level of efficiency as with all other vaccinations. Naturally, such a process must take place under strict statistical control in order to make sure that the new generations are covered adequately; if analysis reveals inadequate coverage, new phases of a local mass campaign may have to be resorted

to. From experience, it would appear that, in areas where BCG vaccination is indicated, there are no economic or operational justifications for not keeping at least 75% of the eligible population protected by BCG vaccination.

The Committee recommended continuous assessment of the BCG programme by sampling so as to check its operational and technical performance (coverage, potency of vaccine at the time of injection, post-vaccination allergy, vaccination lesions), to ensure that it is maintained at the highest possible level, and to identify the reasons for any failures.

The Committee reviewed recent studies carried out on direct BCG vaccination, that is, vaccination without a prior tuberculin test. These studies have not demonstrated local, regional, focal, or general complications detrimental to the health of the tuberculin reactors among the vaccinated individuals; nor is there any indication that this procedure has reduced the acceptability of BCG vaccination by the public. In countries where BCG vaccination is essential to the effective control of tuberculosis, where cost is of major importance, and where prior tuberculin testing would considerably reduce coverage, direct BCG vaccination is recommended by the Committee as a public health procedure. However, before this procedure is applied throughout a country, a pilot study should be conducted in order to determine its acceptability and the age-groups in which it will be carried out during the subsequent country-wide programme. The Committee thought that it was urgent to have studies made on the acceptability of revaccination without prior tuberculin testing.

The Committee reviewed studies on simultaneous BCG vaccination and smallpox vaccination. In these studies, no contra-indications were noted and there seemed to be no evidence of suppression of the effect of one vaccination by the other or of synergism. Therefore, the Committee did not see any objection to the simultaneous application of these two vaccines in countries where this would lead to appreciable economic and operational gains.

The Committee confirmed the superiority of the intradermal route of BCG vaccination, because it alone allows a uniform, strong dose of vaccine to be given.

The Committee recognized in general the operational advantages of using freeze-dried BCG vaccines and, in particular, of heat-stable, freeze-dried vaccines in hot climates.

In view of the technical complexity and cost involved in producing uniformly potent freeze-dried BCG vaccines, the Committee wished to reiterate the recommendation made by the WHO Expert Committee on Tuberculosis in its sixth report: "that the multiplication of BCG vaccine production centres should be discouraged".¹ In this connexion, it

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1954, **88**, 4.

strongly supported the efforts being made to introduce requirements for BCG vaccines and to provide international reference facilities for the testing of BCG vaccines used in national tuberculosis programmes.

5. CHEMOPROPHYLAXIS

5.1 Primary chemoprophylaxis

The Committee considered that chemoprophylaxis of the uninfected as a public health measure to eliminate the risk of tuberculous infection represents a poor return on the resources invested and therefore does not merit serious consideration at present in either developing or developed countries. The Committee felt that, for tuberculin-negative persons likely to be exposed to infection, the prophylactic measure of choice remains BCG vaccination.

5.2 Secondary chemoprophylaxis

The Committee reviewed the results of a number of studies published since the last report of the WHO Expert Committee on Tuberculosis.¹ In some trials, a considerable reduction in incidence resulted when a high degree of co-operation in drug-taking for one full year had been achieved. In one trial carried out in a developing country, on the other hand, the drug intake was so low as to eliminate almost entirely the prophylactic effect. These different results point to the fact that the acceptability of this measure may weigh as much as its intrinsic efficacy. In this connexion, it was noted that, in the high-risk groups so far studied, about 100 healthy persons had to receive isoniazid for one year for every case prevented.

Apart from the possible diversion of funds that could be used more fruitfully for treating known cases of tuberculosis, the practical difficulties in mass application of chemoprophylaxis are: the identification of the infected individual (particularly the recently infected) by repeated tuberculin testing, and the necessity of ensuring adequate drug-taking over the period.

In view of the great number of healthy persons who would have to consume drugs for a long period, the utmost care should be taken to assess all, even trivial, toxic implications of secondary chemoprophylaxis when this is applied on a public health scale.

Summing up, the Committee felt that, at the present stage of knowledge, it could not recommend secondary chemoprophylaxis for mass application but only for individuals and groups at special risk. Even this application was justifiable only in a programme that had achieved a high degree of perfection in its case-finding and treatment activities.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1960, 195.

The Committee thought also that the immediate step forward is to investigate how far short courses of isoniazid in a high dosage (perhaps given intermittently) approach the effectiveness of one year's continuous administration of isoniazid. Success in this direction would improve considerably the applicability of secondary chemoprophylaxis on a mass scale.

6. TREATMENT

6.1 Organization

The Committee emphasized the fundamental epidemiological importance of giving adequate chemotherapy to every "case" of infectious pulmonary tuberculosis, and considered that, in view of the public health implications of the tuberculosis problem, treatment should be available, free of cost, to every known sufferer from the disease. Such universal availability of treatment services can be provided only if careful attention is paid to the funds and health personnel available in the country. It is neither possible nor necessary for developing countries to model their treatment services on those currently existing in the technically advanced countries.

Having reviewed results from developing countries of controlled comparisons of bed rest and ambulation and of domiciliary and institutional treatment of pulmonary tuberculosis, the Committee concluded that, in terms of the immediate response to treatment, of subsequent relapse, and of the risk to contacts, there was no evidence in those studies of special benefits resulting from hospitalization. It recommended, therefore, that all financial resources and manpower available for tuberculosis control in the developing countries be confined to organizing efficient ambulatory services and not to constructing new beds. Tuberculosis beds, where they already exist, should be integrated into the ambulatory and domiciliary services so as to ensure their most rational use (e.g., for emergencies).

The Committee noted that similar controlled comparisons of bed rest and ambulation and of domiciliary and institutional treatment carried out in technically advanced countries also did not indicate any superiority of institutional over ambulatory treatment. It emphasized that the application of these results could lead to impressive economic savings in national tuberculosis programmes. In this situation, the Committee felt that it was incumbent on those advocating the superiority of institutional treatment to conduct studies to determine whether their contention is substantiated by objective evidence.

The Committee underlined that, in countries in which the treatment of tuberculosis is based on ambulatory services, the authorities must ensure that the patients actually take the drugs regularly throughout the prescribed period. The efficiency and quality of these surveillance operations are decisive in keeping down the default rate. The patterns of motivation that

will ensure maximum co-operation of patients and community in the ambulatory treatment programme must be determined according to the local cultural and social settings, and for this social scientists may prove helpful.

6.2 Priorities in chemotherapy in developing countries

The Committee stressed that the first priority goes to giving one year of chemotherapy to every newly diagnosed "case" of infectious pulmonary tuberculosis. The "first-line" drugs that come into consideration at present in national tuberculosis programmes are isoniazid, streptomycin, para-aminosalicylic acid (PAS) and thioacetazone. Deployment of these drugs will depend upon local resources, as indicated below.

In reviewing experience gained during recent years in the treatment of initially drug-sensitive cases, the Committee underlined three important trends in the application of chemotherapy in developing countries.

6.2.1 *The importance of especially intensive chemotherapy at the beginning of treatment*

The early stages of chemotherapy are crucial for the final outcome of treatment. During this initial period of intensive chemotherapy, a very high regularity of drug intake is of the utmost importance. In areas where supplies of first-line drugs are as plentiful as in the technically advanced countries, standard practice should be to start with an initial course of triple chemotherapy (including isoniazid) followed by a two-drug regimen (including isoniazid) for the rest of the year. In areas where drug supplies are so severely limited that two drugs cannot be given throughout the year, an acceptable practice is to start by a two- or if possible three-drug regimen (including isoniazid) followed by isoniazid alone for the rest of the year. The guiding line for choosing the moment at which the number of drugs given may be reduced should be the time when the sputum becomes negative.

6.2.2 *The efficacy of thioacetazone as a cheap oral companion drug to isoniazid*

This combination costs about one-tenth as much as the combination of isoniazid and PAS. The dosage is critical. In a recent study, the regimen of isoniazid 300 mg and thioacetazone 150 mg in one daily dose combined in a single tablet for an average adult was found to be effective and to have no undue toxicity. The Committee recommended that this combination should certainly be considered in any community where, because it is inexpensive, isoniazid alone is the only drug being used. Nevertheless, whenever it is decided to use isoniazid plus thioacetazone on a wide scale in a community for the first time, it is essential first to undertake a careful

investigation of the efficacy and toxicity of the regimen in an adequate sample of cases.

6.2.3 *The efficacy of directly supervised intermittent chemotherapy*

An important recent advance in the chemotherapy of tuberculosis has been the finding that an intermittent regimen of streptomycin plus isoniazid was effective when applied twice weekly. The regimen is : streptomycin 1 g plus isoniazid in a single dose of approximately 14 mg per kg of body-weight, given together on two days each week (with a 6-mg pyridoxine supplement twice weekly to prevent peripheral neuritis). This differs from previous regimens of intermittent streptomycin plus daily isoniazid in that the isoniazid is given (a) intermittently, (b) in a very high dosage, and (c) in a single dose on a given day. Intermittent combined chemotherapy has the advantage that it can be entirely supervised, thus overcoming the major difficulty of irregularity inherent in the long-term self-administration of drugs. The results of a study of once-weekly regimens which is currently in progress are awaited with great interest. A short initial period of intensive daily chemotherapy followed by adequate intermittent chemotherapy would seem particularly promising. The efficacy of intermittent chemotherapy by isoniazid in high dosage and streptomycin, especially when preceded by a short period of daily chemotherapy by the same drugs, is strongly substantiated by animal experiments.

The Committee recognized that there still may be circumstances in which the resources do not permit the treatment of all newly diagnosed infectious cases of pulmonary tuberculosis except with isoniazid alone. Where this is so, the dosage of isoniazid should be of the order of 8 mg per kg of body-weight, administered once a day as a single tablet which also contains 6 mg of pyridoxine.

The Committee emphasized that the long-term solution to the problem of drug resistance in developing countries is to concentrate efforts and resources on giving effective chemotherapy with the first-line drugs to all newly diagnosed (presumably drug-sensitive) cases.

Use of second-line drugs (ethionamide, pyrazinamide, cycloserine, kanamycin, viomycin—all of which are expensive and relatively toxic), which requires hospitalization of the patient and must be preceded by sensitivity tests, should not be allowed to compete for the funds available for tuberculosis control before all newly diagnosed cases of tuberculosis have been ensured the best possible treatment with the first-line drugs.

The Committee noted that there is no evidence that dietary, vitamin or mineral supplements improved the results of an effective regimen of chemotherapy in terms of either the attainment of bacteriological quiescence of the disease or the avoidance of subsequent relapse.

6.3 Follow-up

The Committee noted that it is more informative to follow the progress of therapy by bacteriology than by radiography and that, for this purpose, smear examination of the sputum is remarkably efficient. The additional information obtained from culture examinations and X-ray in initially smear-positive cases is marginal; culture facilities, if scarce, should be concentrated on diagnosing infectious tuberculosis rather than on following the progress of patients under treatment.

6.4 Sensitivity testing

Sensitivity tests for the individual patient are of the greatest importance where the resources permit adjustment of regimens to initially resistant cases and the use of second-line drugs for treatment failures due to drug-resistance. However, in the absence of sensitivity-testing facilities, much information can be obtained on the likelihood of pretreatment drug resistance simply by close interrogation as to prior drug therapy and a check on the continued presence of tubercle bacilli by direct smear examination after some six months of treatment. If limited facilities for sensitivity tests are available, it is best to use them for measuring the prevalence of primary and acquired drug resistance in the community by sampling. The adoption of uniform criteria and adequate standard techniques would lead to great improvement in the regimens applied to many patients, as well as provide more reliable epidemiological information on the problem of drug resistance.

6.5 Assessment

Routine assessment of the administrative organization for treatment and of the treatment results themselves is essential in a tuberculosis programme. The cohort-analysis of drug administration records, covering complete groups of patients who began treatment within a given period, constitutes the basic method of operational assessment. As to the technical assessment, the comparison of the pretreatment and post-treatment culture results and drug sensitivity tests in a random sample of patients, in addition to the routine microscopy in the individual case, provides a sensitive measure of the efficacy of the treatment programme. At the same time, it provides an important epidemiological index of the prevalence of treatment-induced drug resistance.

The Committee stressed the necessity of reviewing the current practice of chemotherapy constantly so that, as both resources and knowledge improve, they will be applied to the best effect.

6.6 Supply of drugs

It was the view of the Committee that checking on the purity and keeping properties of antituberculosis drugs is of great importance, as is ensuring that commercial combinations of antituberculosis drugs contain those drugs in adequate proportion and quantities.

The Committee also recommended that antituberculosis drugs should be made available only to physicians and others authorized by the health authorities.

The Committee felt that, if commercially prepared drugs are available only at exorbitant prices or are of questionable quality, countries in a position to do so might well consider manufacturing their own drugs to permit the greatest benefit from the funds available.

7. NATIONAL TUBERCULOSIS PROGRAMMES

The Committee discussed the organization of national tuberculosis programmes and the following observations were made.

The formulation of a national tuberculosis programme rests on a clear understanding of the epidemiological situation, on the availability of reliable diagnostic tools, and on preventive and curative means that are efficient and cheap. All these conditions can be met today and an effective national tuberculosis programme is possible under any given situation, provided application is guided by sound principles.

To achieve the broad objective of reducing human suffering due to tuberculosis, the national programme must satisfy four basic requirements :

(a) Epidemiological considerations require that a national tuberculosis programme must be on a country-wide and permanent basis—not sporadic or patchy. This principle is essential if the programme is to have a significant and progressive effect on the problem.

(b) Sociological considerations demand that the national tuberculosis programme be adapted to the felt needs of the population ; it must satisfy the existing needs before it promotes the awareness of new ones.

(c) Administrative considerations make it mandatory that the tuberculosis services be integrated into the general health services. The tuberculosis services will be concerned particularly with consultation, training programmes, and co-ordination and assessment of the tuberculosis programme.

(d) Economic considerations require that the programme be such that its application on a national scale is within the resources available. Whatever funds are allocated for tuberculosis control should always be spent as efficiently as possible ; careful attention to the first three requirements will help to achieve this objective.

7.1 Planning

The planning of the national tuberculosis programme must be based on accurate data concerning the local situation : epidemiological and operational data, demographic and social information, and data on existing and planned health services. A limited sample survey, conducted in connexion with training activities, should provide basic data. An inventory of health services must be made with particular reference to the population actually covered by each agency and to the number and type of existing health personnel available for tuberculosis training. Finally, information on the central, provincial and local financing of health services and their planned expansion is essential.

Operational investigations may have to be conducted on, for instance, the influence of distance in intermittent chemotherapy and the coverage of simultaneous BCG and smallpox vaccination. The planning then consists in organizing this information into a schedule for the development of integrated antituberculosis services, both preventive and curative, to cover the total population over a reasonable time—roughly corresponding to the planned phase of development of basic health services.

As the plan would specify for each health agency in the community the area it covers and the personnel to be trained, the operational efficiency of the programme can be forecast quantitatively in terms of the proportion of the community that will be served, the number of patients who would complete treatment annually, and the number of those eligible to receive BCG protection each year. Such figures in the forecast must be accompanied by realistic estimates of costs involved and be adjusted to the funds available.

7.2 National implementation

7.2.1 Training

Adequate training at all levels is a *sine qua non* of any tuberculosis programme. Training of key personnel should preferably be given in specialized institutions (for instance, regional or national training centres). For medical officers, public health nurses, and other key personnel, the efficiency of the training will depend upon the prior instruction in the clinical and public health aspects of tuberculosis given at the undergraduate level. Training of basic staff (for instance, for tuberculin testing and BCG vaccination, preparing and reading slides for microscopy, advising and controlling patients under treatment, and processing and reading miniature films) takes place in the field, that is, in the peripheral health agencies. Regular refresher courses for general practitioners in diagnosis, treatment and prevention should be provided to ensure their active co-operation with the activities of national tuberculosis programmes.

7.2.2 *Evaluation*

This requires basic records, skilled processing, and correct analysis. The first steps in setting up an evaluation unit consist in establishing standard records and reports, training the necessary statistical personnel on the national level in how to collate and analyse the material that will become available, and laying down standard procedures of evaluation. A protocol must describe the method of assessing the quantity and quality of the work against the initial forecast.

7.2.3 *Pilot programme*

As the work of the training and evaluation units proceeds, the programme is implemented in a test area so as to assess whether the plan is suitable for the local conditions. To some extent, the test area may serve also as a demonstration area. The choice of this area is guided more by whether it is representative of socio-economic conditions (especially with regard to density of health services) than by purely epidemiological considerations. The planned programme should be applied to the test area continuously for one to two years, after which time an assessment is undertaken prior to national extension.

7.2.4 *National extension*

Extension of the tuberculosis programme begins from the second year of the project and continues until the whole country is served by diagnostic, curative and preventive services in accordance with the planned schedule of extension. The achievement of a national coverage geographically does not mean an end of the extension since additional general health facilities will no doubt be added, for which personnel must be trained etc. By virtue of its dynamic approach, based on the continuous assessment of achievements and optimum allocation of resources, such a national tuberculosis programme is able to grow as the situation requires.

8. DEVELOPED COUNTRIES

While the Committee devoted most of its attention to the control of tuberculosis in countries with limited resources, in almost every item discussed it was obvious that the problem in the developed countries was different only in its extent and in the case with which facilities could be mobilized and put into operation.

It was agreed that, in the economically more fortunate countries, the problem would remain a major one until national tuberculosis control programmes are scientifically planned, integrated into the general health services, energetically implemented, and regularly assessed. In the planning

of programmes, the public health authorities will need the co-operation of economists, statisticians and social service experts.

In the developed as in the developing countries it is necessary to find all the infectious cases in a community and to render them non-infectious by ensuring the acceptance of modern therapeutic measures, by providing adequate follow-up services, and by keeping an up-to-date register of all infectious and suspect cases. In this connexion, it was stressed that high relapse rates could be avoided by ensuring that all infectious cases are given adequate treatment. At the same time, by the use of more and better bacteriology, over-treatment should be drastically reduced.

One of the main advantages enjoyed by the developed countries is that facilities adequate both in quality and in quantity could be made readily available for diagnosis and treatment. Also there is not an acute shortage of technically trained personnel. But stress was laid on the need for the continuous training, in modern tuberculosis control methods, of medical personnel (including general practitioners) and paramedical staff at both the undergraduate and graduate levels. Also it is important for tuberculosis workers to impress on the governments of the developed countries that it is in their own interest to bring their tuberculosis problem under control as soon as practicable and to play their part in the global attack by giving all possible assistance to the economically less fortunate countries.

9. RESEARCH

After reviewing the main trends in tuberculosis research, the Committee felt that, during the next few years, high priority should be given to a number of problems in research on operational aspects of tuberculosis programmes, and in immunization, chemoprophylaxis, chemotherapy, and epidemiology.

In particular, studies should be conducted on the following facets of these problems.

Operation of tuberculosis programmes. To assess thoroughly the social, economic and administrative factors involved in the acceptability of general tuberculosis programmes by communities of widely different socio-economic status. Also to assess the comparative merits of different administrative methods of tuberculosis control.

Immunization. To seek substantiation of the indication from a recent field trial that BCG vaccination is protective in areas with much low-grade tuberculin sensitivity (and not only where there is relatively little such sensitivity). Such an investigation must be designed so that the degree of protection afforded by BCG can be determined both for those having no detectable tuberculin sensitivity and for those with low-grade sensitivity. Also to study the various problems involved in revaccination, e.g., the timing, the persons eligible, and the practicability of revaccination without

prior tuberculin testing. Finally, to develop further heat-resistant, freeze-dried BCG vaccines of adequate and uniform protective potency.

Chemoprophylaxis. To study the protective efficacy of high dosages of isoniazid, given during a short period to tuberculin-positive groups (and possibly intermittently), as a more acceptable alternative to prolonged administration. Also to study the efficacy of the association of a similar prophylactic regimen with BCG vaccination (possibly with isoniazid-resistant BCG) in tuberculin-negative persons who have been strongly exposed to tuberculous infection, i.e., mainly household contacts of recently discovered "cases".

Chemotherapy. To study further how far intensive, daily, multiple-drug chemotherapy at the commencement of a primary course in newly-diagnosed pulmonary tuberculosis permits the use of inexpensive and less exacting regimens during the remainder of the treatment; the minimum duration of such initial chemotherapy should be established. To study further the efficacy of intermittent, supervised, regimens (possibly preceded by a short initial period of intensive daily chemotherapy) and their large-scale applicability. To continue the search for new effective drugs. To study the motivation relevant to regularity of attendance and of taking of drugs during ambulatory treatment, including use of sociological approaches. Finally, to continue the study of the best regimens for patients with bacillary resistance to two or more of the main drugs.

Epidemiology. To study further, using more uniform skin-testing techniques and more specific tuberculins and other antigens, the distribution and causation of low-grade tuberculin sensitivity.

The Committee believed that, in addition to these high priorities, the whole field of predictive epidemiology in tuberculosis, including the use of epidemetric models, deserved more attention in order to improve the understanding of the dynamics of the present tuberculosis problem. Studies of the respective roles of endogenous reactivation and superinfection in producing new cases, particularly in older people, are important. Other aspects of the ecology of tuberculosis that merit investigation are the significance of the geographical variations in the natural virulence of tubercle bacilli; the levels and trends of primary and acquired drug resistance; and the immunogenic characteristics, infectivity and pathogenicity of the atypical mycobacteria. The epidemiology of sarcoidosis requires study.

Research efforts should be devoted also to simplifying culture methods and finding a reliable serological test to recognize activity in tuberculous disease.

Great importance was attached to bringing promising young scientists from developing countries for training in tuberculosis research institutes in the technically advanced countries.

10. FUNCTIONS OF WHO IN THE FIELD OF TUBERCULOSIS

In its comprehensive technical review, the Committee had noted the contribution made by WHO to both research in tuberculosis and application of control methods. It emphasized the obvious need for WHO to strengthen its role as co-ordinator of a global tuberculosis programme in the next decade.

10.1 Assistance to national tuberculosis programmes

The Committee noted with appreciation the technical guides prepared by WHO for use in national tuberculosis programmes but believed that the implementation of a national tuberculosis programme often requires direct WHO assistance, on a short-term basis, through teams assigned to individual countries and, on a long-term basis, through regional epidemiological centres. The importance of programme-oriented training of national key personnel under realistic operational conditions was stressed.

The Committee noted that, in many developing countries, one of the most disquieting factors is the frequent absence of antituberculosis drugs in sufficient quantities. It recommended that WHO bring the seriousness of this problem to the attention of its member governments and stressed that much more material assistance is essential at the international level to improve the application of present knowledge in developing countries. Such assistance should be concentrated first of all on securing adequate supplies of drugs in these countries.

10.2 Technical information

The Committee felt that the diversity of technical policies in countries with similar epidemiological and social conditions was often due to the perpetuation of traditional practices without full and systematic consideration of new knowledge. WHO has therefore the important task, as an unbiased observer, of making a continuous analysis of research and application, and of communicating the results in an effective manner to its member governments and to tuberculosis workers. The Committee expressed its appreciation of the quality of papers published on tuberculosis in the *Bulletin of the World Health Organization* and commended the arrangement made through the International Union against Tuberculosis to give these papers an effective distribution. The tuberculosis Technical Information series of documents issued by WHO constitutes a useful service and deserves wide distribution.

10.3 Development of standards

10.3.1 *Nomenclature and classification*

The Committee was of the opinion that the need expressed by the previous WHO Expert Committee on Tuberculosis¹ for an international standard terminology in tuberculosis remains. The indiscriminate and inconsistent use of epidemiological terms has rendered increasingly urgent a set of intelligible and acceptable definitions of such terms. The Committee welcomed the information that WHO is about to take steps to remedy this situation through the preparation of a glossary of epidemiological terms. The Committee expressed appreciation of the work already undertaken by the International Union against Tuberculosis, and hoped that it would pursue its important studies on establishing a significant classification of radiological terms as well as on establishing a rational clinical terminology for tuberculosis. The Committee considered the International Classification of Diseases as regards tuberculosis, and recommended that bacteriologically proved disease should become the basis for a diagnosis of pulmonary tuberculosis in that classification.

10.3.2 *Products*

The Committee recommended the use of PPD RT 23, an internationally standardized batch of tuberculin, which can satisfy global consumption for several decades.

The Committee noted with satisfaction the progress made in introducing requirements for BCG vaccines and in making available international reference facilities for assaying BCG vaccine used in national tuberculosis programmes. In this connexion, WHO was urged to continue its efforts to establish one or several international reference preparations of BCG vaccine.

10.3.3 *Methods*

The Committee considered that the WHO technical guides on tuberculin testing, surveys and BCG assessment play an important role, and that WHO should continue its efforts to standardize and simplify working methods and techniques (culture, resistance testing, radiology, etc.). In the field of laboratory methodology, WHO reference laboratories can fulfil an important function in establishing standards, in training, and in offering services, especially for the identification of mycobacteria and for the determination of drug resistance.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1960, **195**, 15.

10.4 Research

The Committee reviewed the research activities co-ordinated by WHO and concluded that the yield from this research programme was one of the main contributions to new knowledge in tuberculosis. It felt that WHO should assist a few developing countries to establish their own permanent research facilities in tuberculosis. The technical priorities for WHO's research programme in tuberculosis, as in the past, should be closely related to the applied programme. Research areas that might require WHO's attention over the next few years have been referred to by the Committee under "Research" above.

11. THE ROLE AND FUNCTION OF VOLUNTARY BODIES IN NATIONAL TUBERCULOSIS PROGRAMMES

The Committee's attention was drawn to the statement made by the Executive Director of the International Union against Tuberculosis to the WHO Executive Board in January 1964. This was, in substance, as follows:

The credo of voluntary tuberculosis associations, and of the Union itself, is that, although the chief responsibility for control lies with governments and public health authorities, these same authorities cannot do everything.

The value of voluntary associations was proved decades ago in the few countries where tuberculosis is practically under control, and the usefulness of these associations is again strikingly evident in the developing countries.

The effectiveness of the official programmes can be considerably increased if the action of the public health authorities is supplemented by that of voluntary associations, and such supplementary assistance in the developing countries by voluntary associations might well be in the following areas:

- (a) helping to distribute antituberculosis drugs to patients cared for at home, and to supervise the administration of these drugs;
- (b) ensuring that domiciliary patients regularly attend for check-ups at the treatment centre;
- (c) persuading persons with suspicious symptoms to attend diagnostic and treatment centres for examination (and necessary action);
- (d) encouraging persons who live in contact with patients suffering from open tuberculosis to attend diagnostic and treatment centres for examination;
- (e) helping to assemble children and young adults for tuberculin tests and BCG vaccination during organized campaigns;
- (f) undertaking health education campaigns in close liaison with government measures.

The Committee endorsed this statement, but added the caution that the closest co-ordination should be maintained between the official and voluntary tuberculosis agencies in order to eliminate competition and duplication and to avoid gaps in the total programme.
