Regional Committee for the Eastern Mediterranean

Tenth Session

Agenda item 12

Technical Discussions

Tuberculosis Control with Particular Reference to Domiciliary Treatment
# TABLE OF CONTENTS

## I REVIEW OF TUBERCULOSIS PROGRAMMES
1. Tuberculosis as a problem in the Eastern Mediterranean Region ........................................... 1
2. Tuberculosis Control Efforts ........................................................................................................ 1
3. Programmes with International Assistance ............................................................................... 2
4. Basic Weapons for Tuberculosis Control .................................................................................... 2

## II THE ANTIBACTERIAL DRUGS
1. Historical Review .................................................................................................................... 3
2. Efficacy of Antibacterial Drugs .............................................................................................. 4

## III MANAGEMENT OF THE TUBERCULOUS CASE
1. Definitions .................................................................................................................................. 4
2. Objectives and Methods of Management .................................................................................. 5
3. Methods of Management ........................................................................................................... 5

## IV PRACTICAL CONSIDERATIONS OF MANAGEMENT
1. Bed Rest ......................................................................................................................................... 6
2. Antibacterial Therapy .................................................................................................................. 9
3. Collapse and Resectional Therapy ............................................................................................. 11
4. Measures for Prevention of Tuberculosis .................................................................................. 11
   (a) Primary Chemoprophylaxis .................................................................................................. 12
   (b) Secondary Chemoprophylaxis .............................................................................................. 12
   (c) BCG Vaccination .................................................................................................................. 12

## V FORMULATION OF A TUBERCULOSIS CONTROL PROGRAMME
EMPHASIZING DOMICILIARY CHEMOTHERAPY
1. The Case of Domiciliary Chemotherapy ..................................................................................... 14
2. Problems of Organization of Domiciliary Chemotherapy ....................................................... 15
   (a) Technical Problems .............................................................................................................. 16
      (i) The choice of drug regimen ............................................................................................ 16
      (ii) Drug resistance of tubercle bacilli ................................................................................. 17
      (iii) Tests for checking the self administration of drugs ....................................................... 18
      (iv) Inclusion of chemoprophylaxis in the programme ....................................................... 18
      (v) Categories and training of staff, especially home visiting staff .................................. 18
      (vi) Diagnostic examinations for assessment of chemotherapy ........................................ 20
      (vii) Management of therapy failures ................................................................................... 20
   (b) Administrative Problems ....................................................................................................... 21
      (i) Adequacy of drugs ............................................................................................................ 21
      (ii) Sufficiency of staff and frequency of visits ................................................................. 21
      (iii) Availability of transport .................................................................................................. 21
      (iv) Record System .................................................................................................................. 21
      (v) Acceptability of drugs ..................................................................................................... 22
      (vi) Funds for social assistance and rehabilitation ............................................................... 22

## REVIEW

## REFERENCES
I REVIEW OF TUBERCULOSIS PROGRAMMES

1. Tuberculosis as a Problem in the Eastern Mediterranean Region

The importance of tuberculosis as one of the major causes of disability and death has been consistently expressed in the medical literature of the countries in the Eastern Mediterranean Region.

Unfortunately, reporting of morbidity and mortality in most of these countries (as in many other areas of the world) has been deficient, hence no accurate statistics are available except for one or two countries.\(^1\)

Some idea of the tuberculosis problem through the prevalence of infection as determined by tuberculin tests during the WHO/UNICEF-assisted BCG Vaccination Campaigns and by the WHO BCG Assessment Team reveals widely divergent figures. In children under age ten there were, for example, less than 2% reactors in Cyprus, against 55% in Somalia.

However, even in those countries with reportedly low tuberculosis morbidity and mortality, tuberculosis is an important disease among segments of the population. In one country of the Region, for instance, whose overall mortality rate in 1957 was only 5.1 per 100,000 an ethnic group of its population showed a rate of 19.1 per 100,000.

2. Tuberculosis Control Efforts

Since the early years of the century, sporadic efforts to control a disease originally thought to be incurable consisted primarily of sanatorium treatment and, later, treatment from tuberculosis dispensaries. The first sanatorium in the Region was founded as early as 1906 in Lebanon and the first dispensary in Syria in 1924.\(^2\)

Voluntary tuberculosis associations were, to a considerable extent, responsible for initiating the care and treatment of the tuberculous.

However, the real impetus to control tuberculosis came after World War II, when international cooperation brought nations closer together and the development of diagnostic procedures especially X-rays, improvement of vaccine products, and discovery of antibiotics and other antibacterial agents, revolutionized the field of preventive and therapeutic medicine.
3. Programmes with International Assistance

The first anti-tuberculosis programmes established on a significant scale with international assistance were the BCG mass vaccination campaigns begun in 1948, collectively known as the International Tuberculosis Campaign, under the auspices of UNICEF and the Scandinavian Red Cross Societies. These campaigns were then taken over by UNICEF and WHO in 1951.

The BCG vaccination campaigns marked the first global programmes of such unprecedented magnitude, and were responsible for raising the awareness of many nations to the fact that tuberculosis is a public health problem and has to be solved along public health lines. Of the 234 million persons tuberculin tested, and 88 million vaccinated at the end of 1958, 1,422,213 and 15,870,883 respectively pertained to the Eastern Mediterranean Region. A Tuberculosis Research Office was established to study various problems associated with these tuberculosis campaigns. BCG assessment teams were also created to demonstrate methods for retesting and for assessment of the BCG vaccine, and to study the question of specific and non-specific reactions to tuberculin.

WHO and UNICEF went a step further and gave assistance in the establishment of centres for demonstration of tuberculosis control methods and for training of national public health workers. These centres were to serve as the nuclei of anti-tuberculosis work in the country, working closely with already existing hospitals and institutions and the public health services.

In recent years WHO, with UNICEF assistance, has also initiated prevalence surveys and research and pilot area programmes as an aid to countries for rational planning of national tuberculosis control programmes. By these surveys more accurate information on the tuberculosis situation in each country will be obtained, which will serve as a baseline for future evaluation of the tuberculosis control programmes.

In the pilot area and research programmes more feasible and practical tuberculosis control methods will be taught.

4. Basic Weapons for Tuberculosis Control

All these programmes, however, are premised on the possibility that tuberculosis can be controlled effectively, economically, and on a wide community basis. This possibility has shown promise of reality with the availability of two basic weapons which have been sufficiently tested to merit confidence: vaccines for prevention, and antibacterial drugs for treatment.
In this paper, the use of antibacterial drugs for the purpose of reducing tuberculosis to the point where it ceases to be a public health problem is discussed in some detail in accordance with the decision of the Regional Committee for the Eastern Mediterranean at its meeting in 1959.

II THE ANTIMICROBIAL DRUGS

1. Historical Review

Ancient and modern medicine have one thing in common: the perennial quest for a specific cure for tuberculosis. However, modern chemotherapy has come a long way from the time of the "Prince of Physicians", Avicenna, who recommended a mixture of honey and extract of red roses for treating tuberculous laryngitis.

The discovery of the sulphonamides by Domagk in 1932(5) actually paved the way for the experimental researches in modern chemotherapy. Ten years later, Prontosil, synthesized from the sulphonamide family, was shown to have some antituberculous activity.

One might say, however, that 1944 was the turning point in the fight against the tubercle bacillus. In this year, the antibiotic streptomycin was discovered.(6) In 1946 PAS (para aminosalicylic acid) as an effective drug against human tuberculosis was announced.(7) Also in 1946, a thiosemicarbazone, better known as TB-1, was shown to have some antituberculous activity.(8)

The enhanced activity of combined administration of PAS and streptomycin was demonstrated by various observers(9, 10) between 1949 and 1951. Also in 1951 oxy-tetracycline was found to have a bacteriostatic effect on human tubercle bacilli.

It was in 1951 that the most important discovery took place when, in three separate countries, independent observers found that the hydrazide form of nicotinic acid (isoniazid) had a strong antibacterial effect on the tubercle bacilli of man and animals. Domagk in Germany, (11) Fox in England, (12) and Bernstein, Lott, Steinberg and Yale in the USA(13) made the independent researches.

In rapid succession, other drugs were discovered and demonstrated to have antituberculous activity in clinical as well as experimental conditions. They are in the order of chronological discovery: viomycin, pyrazinamide, cycloserine, kanamycin, and the latest, ethionamide or thiamid or Th.
2. **Efficacy of Antibacterial Drugs**

While many points remain controversial in the chemotherapy of tuberculosis, one may say that there can be no serious debate on the following:

(a) Isoniazid (INH) is the most effective and least toxic antituberculosis drug known today.

(b) Bacterial resistance is delayed and chemotherapeutic effect is enhanced by giving INH with a companion drug, preferably PAS and/or streptomycin.\(^{14}\)

(c) Chemotherapy should be administered daily for at least one year to be effective.

(d) Combination of INH with other antituberculosis drugs (streptomycin, pyrazinamide, etc.) has practically no therapeutic superiority over INH-PAS in most forms of tuberculosis.\(^{15}\)

(e) INH is effective in preventing tuberculosis in persons who are recent tuberculin converters but without evidence of disease.\(^{16}\)

(f) While most forms of tuberculosis can be successfully treated with chemotherapy, there will always remain a small percentage of failures, some of which could be assisted by collapse therapy or surgery.

### III MANAGEMENT OF THE TUBERCULOUS CASE

1. **Definitions**

It is appropriate, for purposes of discussion, to clarify certain terms which apparently do not carry the same meaning for all persons. The following definitions are proposed:

(a) **Domiciliary or Ambulatory Chemotherapy**

Only the term "domiciliary chemotherapy" should be used, to avoid confusion, and should refer to persons receiving treatment outside a hospital, clinic, or institution.

(b) **Case of Tuberculosis**

WHO has at one time defined a "case" as a person excreting tubercle bacilli. As experiences were gained in the use of new chemotherapeutic agents, with their early effects on the reversal of sputum and potentialities for preventing disease, a change in the definition appeared to be in order.
Some tuberculosis workers have proposed that a "case" should be defined as an individual infected with tubercle bacilli "requiring action". The majority of infected individuals, however, do not require action. Action, in the therapeutic field, would then mean treating 1) a definite case of tuberculosis excreting tubercle bacilli, 2) a suspected case of tuberculosis with radiological evidence suggesting tuberculosis but without bacilli in the sputum, and 3) a potential case of tuberculosis with no signs or symptoms of tuberculosis outside a strong tuberculin reaction, and at a special risk of contracting the disease.

(c) **Chemoprophylaxis**

It is proposed that the terminology used by the WHO Expert Committee on Tuberculosis\(^{(17)}\) be adopted, namely:

**Primary Chemoprophylaxis** - refers to the use of anti-tuberculosis drugs in those not infected, i.e. non-reactors to tuberculin.

**Secondary Chemoprophylaxis** - refers to the use of anti-tuberculosis drugs in those who are infected, demonstrated by a significant reaction to the tuberculin test but who have no pathognomonic signs or symptoms of tuberculous disease.

2. **Objectives and Methods of Management**

(a) The principal aim in managing a case of tuberculosis is to arrest the person's disease and, if possible, to cure him completely. This objective embodies the obligation of a health worker or a health organization to the individual.

(b) Equally important is one's obligation to protect the individual's environment and community, and this is expressed in the second objective, namely, to prevent further disease from taking place as a result of the presence of tuberculous cases in the community.

3. **Methods of Management**

(a) The traditional and well known methods of treating tuberculosis are:

(i) Bed rest (hospitalization)

(ii) Antibacterial therapy

(iii) Collapse and resectional therapy

(b) Prevention of disease can be ensucred by either of two methods, namely:
Effective separation of the infectious tuberculous case from non-tuberculous contacts

Rendering the tuberculous case non-infectious by treatment. Where these two methods are impossible or imperfect, other methods of specific prevention have been found to be useful and effective to a considerable degree, namely:

BCG vaccination for persons still non-infected, i.e. non-reactors to tuberculin

Secondary chemoprophylaxis with anti-tuberculosis drugs. It is recognized that certain non-specific measures, such as improved nutrition and raising of hygienic standards also play a role in increasing a person's resistance to tuberculous infection, but will not be dealt with in this paper.

IV PRACTICAL CONSIDERATIONS OF MANAGEMENT

From a questionnaire on domiciliary chemotherapy sent to sixteen countries within the Region where tuberculosis control programmes are known to exist, answers were received from twelve from which some indication has been obtained on the usual practices of management of tuberculous cases. It must be pointed out that seven of these reflect the practices in individual chest centres or projects, and only five give the overall programme for the country as a whole.

It is useful at this juncture to review the capacity of the countries to undertake the methods of treatment and prevention outlined above and to discuss the relative merits of each method as applied to the circumstances obtaining within the Region as a whole.

(1) Bed Rest

Bed rest may be obtained either at home or the hospital. It is assumed that patients with disease presenting active symptoms would voluntarily obtain some bed rest at home. The symptomless cases will rarely take to bed. Tuberculosis workers generally feel that unsupervised bed rest at home is far from desirable, and therefore their concept of bed rest usually refers to that which can be obtained in a hospital or sanatorium.

Although all the countries possess at least one tuberculosis hospital or sanatorium, only three of these countries admit to a sufficiency of tuberculosis beds. The inadequacy of beds is not simply a numerical problem but one of unsatisfactory utilization, for turnover of patients is generally
slow, the type of cases admitted being those on whom hospitalization could hardly have an appreciable effect.

It is not know what proportion of the patients who have returned to their homes with bacteriologically negative sputum have relapsed. A significant number leave the hospital with positive sputum.

As a whole it would appear that tuberculosis hospitals are playing a very minor role in the control of tuberculosis in the community, nevertheless, the consensus of opinion is, that initial hospitalization should be aimed at, to be later combined with domiciliary treatment.

The main arguments given in favour of hospitalization are:

(a) Necessity of limiting the mobility of lung tissue during the process of healing. Healing presumably cannot progress satisfactorily when a person is allowed normal activity and physical exercise.

(b) It separates the infectious case from his healthy contacts, thus fulfilling one of the fundamental methods of prevention.

(c) Where surgery is indicated, it can obviously be done in an adequately equipped and manned tuberculosis hospital.

(d) There will always be a group of persistently positive cases unfit for surgery who are homeless and who will need to be confined in hospitals.

(e) The period of hospitalization serves to educate the patient and his contacts to accept the disease and how to adapt to it.

(f) It ensures regular administration of drugs under supervision.

The arguments that have been given against keeping specialized tuberculosis hospitals or sanatoria are as follows:

(a) One tuberculosis hospital bed, even in primitive circumstances, costs at least ten times more to maintain than centres for domiciliary treatment. Where funds for tuberculosis control are inadequate, these should be used to treat the greatest number. The present manner of utilization of most tuberculosis beds makes one doubt whether hospitals are treating cases more effectively than the centres undertaking domiciliary treatment.

(b) Provided that effective chemotherapy is administered, evidence is available to show that treatment at home is as effective as treatment in a hospital. The recent report coming from the Tuberculosis Chemotherapy Centre in Madras shows that, with combined INH-PAS treatment for twelve
months, a group treated at home "approach sufficiently close the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home." (18)

The first report that physical activity had no influence on the healing process of a tuberculosis lesion when adequate chemotherapy was given was demonstrated at the Rockefeller Research Institute in New York. (19)

Further evidence was reported earlier this year by a group of Colorado researchers to the US Veterans Administration - Armed Forces Conference on Chemotherapy of Tuberculosis where they indicated that for patients with active pulmonary tuberculosis who are receiving adequate doses of combined chemotherapeutic agents, strenuous physical exercise, even competitive athletics, from the earliest phase of treatment, caused no harm. (20)

(c) That the hospital affords separation of the infected case from his healthy contacts is recognized as desirable, and certainly where hospital beds are available they should be utilized for this purpose.

However, it is argued that with present practices and experience it seems probable that by the time tuberculous cases are discovered and sent to hospital they have largely succeeded in infecting their contacts.

This statement is borne out by numerous studies showing higher tuberculin sensitivity among contacts of tuberculous cases than in non-contacts. (21) The Madras Tuberculosis Chemotherapy Centre has been undertaking studies of contacts of patients treated in the sanatorium and the home, and are expected to release their findings this year.

Further proof is given by bacteriological studies made of patients under controlled chemotherapy, where it has been shown that reversal of infectiousness occurs very rapidly in the first four months, and that maximum reversal (75-100%) will take place within six or eight months. (22, 15, 18)

Where a tuberculous case has undergone adequate chemotherapy while waiting for a bed to be vacated in hospital (and this is a most frequent occurrence), it would appear that by the time it became available the bed would no longer be necessary.

(d) The point that hospital beds should be available for cases requiring resection therapy or collapse therapy, is a valid one with which there should be no argument. However, to build specialized tuberculosis hospitals for a small proportion of tuberculous cases that are eligible for surgery would be an unreasonable luxury. Since general hospitals with good equipment and
well-trained staff are available in many countries, it would seem more economical to set aside surgical wards for tuberculous cases within these hospitals.

It is also pointed out that the majority of cases admitted into tuberculosis hospitals are moderately advanced and far advanced cases incapable of tolerating surgical intervention.

(e) With regard to those cases that are persistently positive bacteriologically, without homes to return to, and who are mainly responsible for swelling the roster of tuberculosis beds without any turnover, one might consider establishing simple inexpensive hostels or homes in the charge of trained attendants rather than keeping them in expensive tuberculosis hospitals with professional health staff. They would be supervised periodically by a medical officer from the Tuberculosis Centre, and would have ambulance or other transport facilities to take them to the Centre for clinical examination or to a hospital in case of emergency.

With succeeding generations of tuberculous cases being discovered earlier and treated more adequately, there will gradually be no need for the tuberculosis hostels, and those will eventually disappear, just as similar homes have disappeared in some western countries.

(f) The educational value of hospitalization is not disputed when properly carried out. It is, however, argued that education is more practical and effective when given within the environment of the home and family.

2. Antibacterial therapy

(a) Domiciliary chemotherapy is extensively used in every country in the Region. Besides supervision, drugs are distributed in the homes in only one country, and in a limited area in three others.

Chemotherapy is mostly confined to INH, PAS and Streptomycin in two- or three-drug combinations. Dosages range between 3-8 mg/kg body weight for INH, 1 gm. from two to six times weekly of streptomycin, and PAS at 5-15 grams daily. Dosages for children are reduced (PAS and streptomycin) or increased (INH) accordingly.

INH as a single drug is given as a routine only in one pilot and one research project, and for domiciliary chemotherapy by three centres. Preference to INH combined with PAS and streptomycin is given to cases starting treatment and to acute cases, otherwise INH-PAS is preferred. It often
happens, however, that PAS is gradually stopped because of the patient's dislike of taking too many tablets, and because of rather frequent gastric complications.

Length and continuity of treatment varies widely. While it is generally admitted that chemotherapy should last for a year at least, and preferably longer, this does not occur in practice. Government centres give free drugs when available. After a patient initially receives his tablets (weekly to monthly supply) in the centres, he is expected to return for a renewal of supply, as well as for follow-up examinations. Unless they are visited at home and reminded by the home-visitor to report back to the centre, many patients do not do so, or they may return long after interruption of treatment, when they begin to feel worse. In centres or clinics where drugs are not given free, treatment becomes even more erratic.

Where there are laboratory facilities available, bacteriological diagnoses are performed before, and periodically after treatment. Tests for drug resistance are also sometimes made, but not in sufficient numbers, and except for highly individualized cases, the results of such tests are seldom utilized for changing or modifying treatment regimens.

(b) Home-visiting is at the embryonic stage in most countries, and can be said to be followed systematically and as a routine in only one. Integrated home-visiting, by generalized public health nurses or health visitors is practised to some extent in one other country. The supervision of cases and their contacts is therefore mainly carried out in the centres, with the result that no effective check is possible to ensure continuous administration of drugs, or to check on the extent of the spread of infection in the home.

(c) The difficulties involved in any scheme of therapy, including effective supervision, have been given as follows:

(i) Lack of funds for buying drugs;
(ii) Lack of trained personnel;
(iii) Too much routine work for the professional staff, giving them little time to check more carefully on each case;
(iv) Uncontrollable movement of sick population;
(v) Ignorance, conflicting beliefs, and cultural patterns preventing better cooperation on the part of the patient;
(vi) Feeling of well-being shortly after starting chemotherapy gives the patient a sense of false security so that he discontinues his therapy prematurely.

(vii) Difficulty of home visiting includes inability to trace patients' homes (no numbers, frequent migration, as in the case of desert nomads) and great distances between homes;

(viii) Patients have no money for transportation to the Centre or hospital;

(ix) Opposition of some physicians to domiciliary chemotherapy and lack of interest in contact investigation;

(x) All other debilitating diseases and conditions common among the people, especially the poor, which contribute to their apathy and low resistance.

3. **Collapse and Resectional Therapy**

Pneumothorax and pneumo-peritoneum have rapidly been abandoned in favour of chemotherapy in most countries. In some centres they have been eliminated altogether.

Resectional therapy is quite limited for tuberculosis, being more frequently undertaken for other chest conditions.

The fact remains that a certain proportion of all tuberculosis cases would have persistent cavities despite adequate chemotherapy, and be eligible for collapse therapy and/or surgery. As diagnostic and surgical facilities improve in each country, and earlier case-finding becomes the rule rather than the exception, one might expect a greater number to be included in this group.

4. **Measures for Prevention of Tuberculosis**

Earlier in this paper the argument has been stated that hospitalization, under conditions obtaining at present in the Region, is not generally available, is ineffective, and is even unnecessary in the attainment of the two absolute methods of preventing the spread of tuberculosis, namely, separation of the infectious case, and rendering the infectious case non-infectious. The validity of this argument is conditional however on the institution of adequate chemotherapy by other means.

This brings us to the rather new concept of chemotherapy as a form of specific prophylaxis:
(a) Primary Chemoprophylaxis

This form of chemoprophylaxis is not recommended at this time as not enough work has been done to prove that INH actually prevents tuberculosis from developing in a tuberculin-negative individual. Under experimental conditions INH has been shown to suppress hypersensitivity and the development of immunity occurring from a primary infection. It has prolonged the incubation period, yet upon withdrawal of the drug the bacilli originally present in the primary infection have multiplied rapidly, with hypersensitivity and eventual death. Whether the same picture would apply to tuberculin-negative humans who might be in the pre-allergic stage of primary infection is currently being studied by Ferebee and associates in trials carried out by the US Public Health Service. Other big trials in primary prophylaxis are being undertaken by Prof. Zorini and his associates in Italy and Groth-Petersen and his associates in Greenland.

It is also doubtful if INH would be useful in latent infections, as it has been shown to act effectively only on bacteria that are in active multiplication.

(b) Secondary Chemoprophylaxis

The majority of tuberculosis workers are unanimous in accepting the idea that INH given to a recently infected individual (as shown by a strong tuberculin reaction especially following a negative one) can prevent the development of the disease.

It would therefore be indicated primarily for young tuberculin positive children, possibly less than five years of age, or for older persons exhibiting a strong tuberculin reaction following a previous negative reaction.

This type of chemoprophylaxis has been tried on a very limited scale in a few countries in this Region, but is one of the objects of investigation by the WHO-assisted Chemotherapy Research Project in Tunisia.

(c) BCG Vaccination

The use of BCG to prevent tuberculosis in a negative tuberculin reactor is already well-known and substantiated by numerous evidence, and excellently reviewed in the preliminary report presented in 1959 by the WHO Director-General to the WHO Executive Board.

Within the Eastern Mediterranean Region, there is no question concerning the use of BCG for prophylaxis, and this is done as a routine by tuberculosis centres as well as national BCG campaign teams. However, the tuberculosis
centres as a rule see only a relatively small number of infants and children, and therefore BCG vaccination as a tuberculosis control procedure among this young age group is insignificant in those countries that do not carry out a mass BCG campaign. In only one country in the Region is tuberculin testing and vaccination systematically carried to the homes of contacts and to the new-born. There are two countries that do not perform BCG vaccination in the centres.

With the increasingly accepted concept of using INH for chemoprophylaxis, the question of how this would tie up with BCG vaccination prophylaxis has been frequently discussed.

Studies have been made with a strain of BCG which is resistant to the bactericidal effect of INH. This would allow the simultaneous administration of INH and BCG with maximum effect from both, that is, the immunity reaction from BCG would be produced, and in the event of a superimposing tuberculous infection, INH would attack the infecting bacilli. (26)

It has also been demonstrated that the bactericidal activity of INH is enhanced when used on an immune animal (BCG vaccinated), (27) and for practical purposes this could mean that, where a previously BCG-vaccinated individual develops tuberculous superinfection, his chances of recovery are far better, with INH treatment, than an individual not previously vaccinated.

The suggestion was made by Edith Lincoln that young children initially exposed to tuberculosis could be given isoniazid during the incubation period (one to two months), after which time INH is discontinued and ordinary BCG vaccination given to start an immunity process. (28)

V FORMULATION OF A TUBERCULOSIS CONTROL PROGRAMME EMPHASIZING DOMICILIARY CHEMOTHERAPY

WHO has aptly expressed its principles of organization of tuberculosis control, (29) supported by the WHO Expert Committee on Tuberculosis, (17) as follows:

"Tuberculosis is a community problem. Tuberculosis control must, therefore, be considered in relation to other problems in the community and it must be planned in conjunction with, and organized as, a part of the general public health programme for the community".

The Expert Committee, however, added that, although the aim of tuberculosis control should be eradication of the disease, this goal would be difficult to achieve in the near future. They therefore recommended that
"All countries should take the most energetic measures to eliminate tuberculosis as a public health problem and that a high priority should be given by governments to this end."

In the preceding chapters of this paper a picture has emerged of the measures of tuberculosis control being undertaken by the countries of this Region. It would seem that the methods recommended for prevention and treatment of the disease exist in most of the countries, but whether tuberculosis is being adequately controlled as a consequence of their efforts is difficult to evaluate. There are indications, however, that chemotherapy on a domiciliary basis dominates the picture in this area, yet this important measure is not sufficiently widespread, nor has it been properly linked to the overall national public health programmes.

The difficulties already outlined earlier which have faced each country to a lesser or greater degree are serious enough to discourage any public health administrator. It is therefore to the credit of the governments concerned that despite their difficulties, significant progress has been achieved on which one can further build a more rational, economical, and effective structure of tuberculosis control.

1. The Case for Domiciliary Chemotherapy

On the strength of the evidence already presented, it would seem that the mere existence of tuberculosis centres and tuberculosis hospitals, which have generally been operating in a static and ambulatory manner, cannot guarantee the proper supervision and control of cases and contacts unless control is actively carried into the home and the community. In other words, there is a strong case for the extension of tuberculosis control services into domiciliary health services, using chemotherapy as its principal wedge.

The gains accruing from an intensive domiciliary programme can be summarized as follows:

(a) Practical advice on what the family should know about tuberculosis (diet, sanitation, prevention of spread of infection, care of the patient) can be more effective when imparted on the spot and applied to home conditions than when given in a clinic or hospital. This is particularly important where a home has little or no facilities for isolation and sanitation, and where the family is uneducated.

The WHO Expert Committee on Organization of Medical Care expressed this concept very emphatically in its second report on the "Role of Hospitals in Ambulatory and Domiciliary Medical Care" as follows:
"It is agreed that hospital physicians and nurses are so fully occupied that it is impossible for them to give sufficient time to the health education of patients. In some cases social workers have been trained to establish contacts between hospital services and patients. Utilization of voluntary personnel has not always given good results. ... it is in the family circle that health education becomes really effective, whether it be in urban districts where housing problems are often very acute, or in rural areas where bad housing conditions are further aggravated by environmental sanitation problems.

A domiciliary care service is sometimes considered of very little use at the outset, but after a certain period it begins to make itself felt and gradually becomes indispensable. It is therefore necessary to persist in efforts in this direction for a long time before any judgement can be passed on the system. (30)

(b) There will be closer supervision of the patients' compliance with instructions on the self-administration of drugs, thus ensuring the maximum effectiveness of chemotherapy.

(c) Control of contacts will be intensified, ensuring that they will have proper diagnosis, BCG vaccination for the still non-infected, possibly chemoprophylaxis for the recently infected, and chemotherapy for the newly discovered cases.

(d) Social problems that usually arise in prolonged hospitalization or isolation away from the home will be avoided or minimized. The Madras experiment (18) showed almost three times as many problems disruptive to family life among hospitalized cases as among those receiving domiciliary treatment.

(e) Closer cooperation with other services in the community can be maintained. The tuberculosis staff visiting the home can assist in referring their cases to other agencies for social and health needs other than tuberculosis. Where domiciliary tuberculosis functions are already integrated into generalized or multipurpose health staff, this activity is, of course, routine.

2. Problems of Organization of Domiciliary Chemotherapy

The acceptance of domiciliary chemotherapy as a desirable programme for tuberculosis control carries with it a series of problems that must
first be clarified or resolved. For purposes of simplification these are divided into two categories, technical and administrative, although it is recognized that the two cannot often be clearly separated:

(a) Technical problems

(i) The choice of drug regimen
(ii) Drug resistance of tubercle bacilli
(iii) Tests for checking the self administration of drugs
(iv) Inclusion of chemoprophylaxis in the programme
(v) Categories and training of staff, especially home visiting staff
(vi) Diagnostic examinations for assessment of chemotherapy
(vii) Management of the therapy failures

(b) Administrative problems

(i) Adequacy of drugs
(ii) Sufficiency of staff and frequency of visits
(iii) Availability of transport
(iv) Record system
(v) Acceptability of drugs
(vi) Funds for social assistance and rehabilitation

(a) Technical problems

(i) The choice of drug regimen

Simplicity of administration, little or no toxicity, low cost, and the maximum of effectiveness should influence the choice of drug or drug regimen.

These conditions are fulfilled by isoniazid. In the non-cavitary types, acute miliary and meningeal types, and most primary types, INH alone can favourably compare with combined regimens of INH with PAS or Streptomycin. However, the combination of INH-PAS or INH-Streptomycin (daily) is, in cavitary cases, admittedly somewhat superior.

The question to resolve is, whether the margin of therapeutic superiority of the combined regimens is not offset by a number of factors such as toxicity (PAS can give a high percentage of gastric reactions that may necessitate interruption of therapy), difficulty of administration (routine streptomycin injections defeat the purpose of domiciliary chemotherapy) and expense (PAS and streptomycin are considerably more expensive than isoniazid). Neural toxicity due to INH rarely occurs with doses under 8 kg./kilo body weight, but it should be seriously considered when treating severely under-nourished persons,
The public health administrator who has a limited sum of money to spend will have to weigh the advantage of treating, say, a hundred tuberculous cases with about 60% probability of arrest or cure, against treating 50 or less cases with 90% cure rate.

The desirable programme might be to have the three drugs available, use INH alone where there is clear-cut indication for single regimen and the combined regimens for the smaller number that could best be served by these.

Since maximum reversal of infectiousness takes place from four to eight months from the start of therapy, the economical regimen would be to use combined therapy (where indicated) only for the first few months, and then continue with INH alone. It is worthy of note that the WHO Study Group on Chemotherapy and Chemoprophylaxis in tuberculosis control state that "if a local situation exists in which it is not practicable to use the above drug regimen (INH and PAS) the use of INH alone is justifiable". (32)

(iii) Drug resistance of tubercle bacilli

Continued therapy with any known drug eventually creates resistance in the tubercle bacillus.

Much has been made of the early appearance of bacillary resistance during treatment with INH alone, but the fact of drug resistance has not shown definite evidence of significant loss of effectiveness of INH therapy, at least within the early months. Bacilli susceptible to INH have been shown to persist even in prolonged therapy. (33) On the other hand, resistant bacilli (to INH) have been found at the end of twelve months treatment during combined regimen, indicating that a companion drug may delay, but does not prevent, the emergence of INH-resistant bacilli.

It might be pertinent to consider whether INH-resistant bacilli discharged by INH-treated patients would not eventually infect groups of persons who would no longer be influenced by INH therapy.

Considering that INH has been used (and abused) rather extensively since 1952 throughout the world, it is rather surprising that no significant reports have appeared to demonstrate this theoretical possibility. This is, however, no proof that the continuous emergence of INH-resistant bacilli may not create epidemiological problems in the future.

It is also interesting to note that repeated observations have been made on the non-pathogenicity to animals of strains of INH-resistant bacilli. (34, 35)
(iii) Tests for checking the self-administration of drugs

From present knowledge of the action of INH, in vivo, it is essential to the success of a domiciliary chemotherapy programme that drugs should be taken with regularity.

The experiences reported on this particular problem show that many patients have a tendency to default in taking their drugs. They become more regular after great efforts of persuasion, and constant unannounced visiting (wherein remaining drug cachets are counted and urine specimens are obtained for testing). (18)

The ferric chloride urine test for PAS is fairly easy to perform, and reliable for at least twelve hours, so that a negative test would mean that the patient had defaulted in his last two doses. (36) A ferric-ion paper strip test has recently been developed which is claimed to be good until sixteen hours after ingestion.

Urine tests for isoniazid are more difficult to make under field conditions, and the simplest one to perform (Hoffman-La Roche test with INH capsules) is usually positive in concentrations of 10 μg/ml or more of INH with around 10% accuracy at 12-14 hours. (37) Rapid metabolisers of INH may yield negative results in a certain percentage of cases even within the first four hours after ingestion of the drug.

(iv) Inclusion of chemoprophylaxis in the programme

The decision to include (secondary) chemoprophylaxis in any programme of domiciliary chemotherapy appears to be a justifiable one, but will have to be closely integrated with the BCG vaccination programme.

It might be useful to consider the possibility of integrating both the BCG and INH-prophylaxis programmes also with maternal and child welfare programmes, for it is in the latter where the majority of infants and young children are normally seen.

(v) Categories and training of staff, especially home visiting staff

In a project of this kind, it is imperative that there should be some central technical direction, whether or not it is a specialized programme emanating purely from a tuberculosis centre, or a programme integrated with local health services. This Central Direction would usually come from the medical officer in charge of the Tuberculosis Section in a Ministry
or Directorate of Health. In a country where there is more than one tuberculosis centre operating, the Director will coordinate their work with each other, and with the other health agencies, institutions, and voluntary bodies.

At the operational level would be the staff of a tuberculosis centre with a well-developed section for home-visiting. It is desirable that a social worker be attached to the programme. A health educator need not be employed as staff of the centre but could be loaned temporarily from the office of the Ministry or Directorate, or Provincial Health Department.

The heart of the operations would therefore be the home-visiting section. From the experience in this Region, it has been found possible to utilize home visitors of intermediate grade schooling or even less, with a year's training in home-visiting methods. Training should be given first in generalized home-visiting, and then in specialised tuberculosis work.

It is not known exactly what home-visiting load a home visitor could carry as the circumstances in each country are not the same, with regard to roads, terrain, climate, and cultural patterns. It is roughly calculated that there should be at least one home-visitor to every 150-200 cases to allow each case to be visited about twice a month. The home visitors should themselves be supervised, either by the public health nurse, or a supervising health visitor.

It would be very useful for the medical officer of the centre to make an initial home visit to each case, in order to establish the family's confidence in him and the centre, and to guide him in the management of the case and contacts from first-hand information on home conditions. This, however, may not always be possible where the doctor has a heavy clinic load.

If the home visiting activity is an integrated one, the members of the local health unit (whether urban or rural) should have special training at the tuberculosis centre and other tuberculosis units, and should receive periodic supervision from the tuberculosis centre staff. While voluntary staff from the local community have been found useful where a dearth of official home visitors exists, this is not the general experience in this Region. In some places volunteers are initially enthusiastic, and later become lax in their duties.
(vi) **Diagnostic examinations for assessment of chemotherapy**

The accepted routine methods of diagnosis already practised in tuberculosis centres in the Region, and which carry the recommendation of WHO, are tuberculin testing, radiophotographic screening, and bacteriological examination of sputum (or laryngeal swab) by direct microscopy and subsequent culture (where this is possible).

The same examinations should be performed in the periodic follow-up of cases.

Radiography with large films, when available, may be undertaken to confirm suspicions raised by small films; but small films have generally been satisfactory for comparative X-ray analysis. Dual independent readings are recommended whenever possible, as the personal factor has been shown to influence the interpretation of X-rays.\(^{(38)}\) Whenever the two readers differ they should review the X-rays together to reach some agreement.

Tests for drug resistance to the extent that they are practised today are of little practical value, though where facilities for such tests are available and adequate, they can offer interesting information. WHO has arranged that a certain number of specimens collected in various centres in the Region could be accepted for examination by reference laboratories abroad. There is need for uniformity in techniques for determining bacterial resistance, and WHO has been stimulating research along these lines as well as researches on atypical mycobacteria in various regions of the world.

The erythrocyte sedimentation rate is sometimes valuable for prognostic purposes, but is of minor importance in the assessment, as it could remain high even with bacteriological quiescence.

(vii) **Management of therapy failures**

When the available drugs tried in various combinations for sufficiently long periods demonstrate little or no progress from the standpoint of bacteriological remission or cavity closure, it might be necessary to consider collapse and/or surgical therapy. This would entail referral to a hospital with facilities for chest surgery. The maximum of surveillance and protection should be given to family contacts when it is impossible to remove cases constantly discharging bacilli from the home.
(b) Administrative problems

(i) Adequacy of drugs

If the possibility exists to measure the prevalence of tuberculosis in the area by a sampling survey, some reasonably accurate calculations should be made before the start of the programme as to the load of cases to be managed, and their needs in terms of drugs, diagnostic services, etc. The forms of tuberculosis observed during the survey would also serve as a guide to the probable number of cases that could be placed on single or double drug regimens. The national surveys which have already been started in some countries of the Region with the assistance of the WHO Regional Prevalence Survey Team will be useful in this respect.

The whole programme could easily fail due to inadequate provision of a constant supply of free drugs.

(ii) Sufficiency of staff and frequency of visits

By the same token insufficient staff to supervise with reasonable frequency the self-administration of drugs and the proper clinical control of the cases and contacts would eventually cause the programme to deteriorate into a state of ineffective ambulant chemotherapy.

(iii) Availability of transport

Where public transportation is inadequate, expensive, or irregular, or where distances are great between houses or districts, it may be necessary to give transport for the use of the home visiting staff.

Transport should also be available to carry the tuberculous case to the centre or hospital during an emergency, or to bring specially needy cases and their contacts for clinical examination from their homes.

(iv) Records system

It has been commonly observed that some tuberculosis centres in the Region, even within the same country, have a confusing diversity of forms, records, and referral systems.

It is desirable to standardize the records used in domiciliary chemotherapy programmes to enable statistical evaluation to be made and reasonably valid comparison between programmes in different areas.

It is recognized that, the Region being heterogeneous, the forms can never be identical. However, certain basic information common to all could be incorporated in the principal records.
WHO is in the process of preparing a guiding manual of basic procedures for tuberculosis projects which will include standard basic forms.

(v) Acceptability of drugs

It is foreseen that the greatest obstacle in a domiciliary chemotherapy programme will be the patient's inconstancy in taking his drugs daily for at least a year.

The patience and ingenuity of the home visitors and tuberculosis centre staff will be taxed to a considerable degree. The physician and the social worker in the tuberculosis centre will be valuable in making initial interviews to ensure cooperation from the start. The assistance of an experienced health educator at an early stage will go a long way towards proper understanding of the objectives of the programme.

Non-acceptability of a drug, in the sense of refusal because of gastric irritation, or bad taste, or size, or number, is not necessarily the cause of irregularity in self-administration for, given the same drug, sanatorium patients have been known to cooperate.

This constitutes a medical as well as a social problem that clamours for solution. Research in public health and social methodology might perhaps assist in giving the answer.

(vi) Funds for social assistance and rehabilitation

There is no gainsaying the fact that the populations served by tuberculosis centres in most countries of this Region are in the lower socio-economic strata.

It is outside the scope of the control programme under discussion to consider in detail the question of direct social assistance for the families involved. Any allusion to social assistance or rehabilitation will have to be made in terms of expensive programmes which, though admittedly important, do not have a direct bearing on the control programme per se and which, in some countries, at least, would be premature to establish at this stage.

Indirectly, however, the doling out of material aid either in money or in kind at the same time as the drugs, serves the dual purpose of concretely aiding the patient's well-being and abetting the success of the programme by gaining the patient's grateful cooperation.

It is in the raising of money for social assistance that the voluntary tuberculosis associations and other civic clubs are eminently able to assist.
The Government must realize at an early date, however, that medical programmes for the control of communicable diseases are social programmes as well, and that a person invalidated by tuberculosis must still face the task of earning a living for himself and his family.

The question of rehabilitation for the tuberculous is a tremendous subject by itself and deserves special discussion and consideration.

REVIEW

The tuberculosis control programmes in the Eastern Mediterranean Region over the past years have been reviewed in the light of the new concept of using antibacterial drugs as prophylactic and therapeutic agents. Practical considerations of management of the tuberculous case within a tuberculosis control programme, emphasizing domiciliary chemotherapy has been discussed.

There is much that remains to be learned with regard to the action of chemotherapy on the tubercle bacillus in the human body, but what is known has given great promise for the reduction of tuberculosis to a point when it could cease to be a public health problem and a drain on the national economy.

The administrative and technical problems involved in a national programme embodying domiciliary chemotherapy are many and complicated. Suggestions have been made for solving these problems, which must however be considered within the context of national priorities, resources, experience, and culture.
REFERENCES

(1) Cases, Deaths, and Death Rates from Tuberculosis in Recent Years, in a series of Countries. Compiled or Computed by the Division of Health Statistics WHO. WHO/TBC/INT/10, 31 July 1959.

(2) Endemic Tuberculosis and Fight Against Tuberculosis in the Near and Middle East. International Union Against Tuberculosis, Beirut, 1959.


