

WORLD HEALTH  
ORGANIZATION

SCIENTIFIC GROUP ON TUBERCULOSIS RESEARCH<sup>1</sup>

Geneva, 26 January - 2 February 1959

INDEXED

ORGANISATION MONDIALE  
DE LA SANTÉ

WHO/Tuberculosis Research/1 ✓  
9 March 1959

ORIGINAL: ENGLISH

REPORT

CONTENTS

	<u>Page</u>
1. Research in Tuberculosis . . . . .	3
2. Recommendations . . . . .	7
Appendix: Fields of Research . . . . .	12



<sup>1</sup> This meeting was convened in pursuance of resolution WHA11.35.

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## 1. RESEARCH IN TUBERCULOSIS

Tuberculosis research must expand considerably and in certain new directions today, if we are to realize for our peoples the full potential of recent developments in this field. Chief among these potentials is that it may soon be feasible to place in the hands of a non-literate villager more real power to affect the outcome of a tuberculous infection than could have been exerted by the most highly-trained physician of a little more than a decade ago. This same power, applied in the economically developed countries, holds forth the prospect of approaching tuberculosis eradication. This is a technological development that is truly revolutionary in character and one that has immense challenge in terms of research. If this great new power is to be harnessed for the relief of the millions of people now dying from or crippled by tuberculosis and for the protection of their intimates, it must be used wisely. It can only be used wisely to the extent that the results of research, particularly experimental epidemiological research of a somewhat new and different type, can be rapidly accumulated.

The very fact that WHO is established and recognized as a leading force in the field of health presents an unprecedented opportunity for conducting epidemiological research on a very broad basis. In particular, a unique opportunity exists for conducting international research under central leadership and with uniformly trained personnel using uniform techniques, thereby ensuring that information collected at different points in time and place become comparable. This is the ideal situation for development of effective control measures in public health under a variety of geographical, economic, social and cultural situations.

Another factor of prime concern here is the possibility of using WHO as an instrument for pooling of resources in health research. Certain problems in public health are of interest to many countries but require studies that are too expensive for any one government to cope with. Many of these problems are of the greatest concern precisely to those governments that have limited resources and personnel at their disposal.

It is fortunate indeed that WHO was quick to perceive the emergence of this new situation and had the foresight and courage in 1949 to set up the Tuberculosis Research Office. This pioneer venture, in the opinion of the Scientific Group on Tuberculosis, has clearly justified itself. It has done this not only in terms of its many achievements in new directions in tuberculosis research but above all in its contribution to the concept of internationally conducted and internationally assisted research.

What are the implications of this situation and how can WHO's imaginative beginnings in international tuberculosis research be expanded and supplemented to come closer to approaching today's needs?

At the outset it should be recognized that for tuberculosis - unlike such great killing diseases as cancer or atherosclerosis - the initial "break through" of the mysteries of etiology, early diagnosis, and effective therapy have already been made. Most of this information we have and we have it from the accumulated scientific research of the last hundred years.

What is urgently needed for tuberculosis today is information on how this knowledge can be effectively applied in public health programmes. In essence we need detailed and precise information in several broad fields. Among these are perfection of ways whereby the new drugs can be used safely and wisely in both the treatment and prevention of tuberculosis on a large scale in widely different environments; the many environmental factors - including the relevant cultural factors - that relate to how an individual person can be encouraged to assume a large share of the responsibility for maintaining his treatment or preventive practices with respect to tuberculosis; more precise epidemiological studies on tuberculous infection and disease and also on their possible relation to the newly recognized "atypical mycobacteria"; a better understanding of both naturally acquired and artificially induced immunity against tuberculosis.

But how is this knowledge to be obtained? Careful consideration and reflection on this question make certain points seem abundantly clear. First, it is important to recognize the parallel between international health services and international

health research. As international health services require a central headquarters manned by broadly experienced full-time staff and guided by committees of experts, so international health research requires a central office of broadly experienced full-time research workers and special committees of research experts. Some international services must be directed by an international health organization and some need only assistance from such an organization; similarly, some international research must be directed as an international research activity while some needs only international assistance. With regard to field projects there is a very important difference between service projects and research projects, which has a strong bearing on the financing aspects. WHO-assisted service projects are by their very nature geared to strengthening of national health services in a particular country. Although WHO research projects may also to some extent strengthen the health services in a host country, they will usually be of equal benefit to a number of countries. For this reason, WHO research projects should ordinarily be financed from WHO research funds without any substantial contribution from the host government.

The above points could only be met by there being a tuberculosis research organization with its own funds and staff with full responsibility for the selection, initiation, organization and actual conduct of tuberculosis research and its evaluation. The major portion of the international tuberculosis research conducted by WHO can only be accomplished as a responsibility of such a central unit. It is anticipated, however, that certain suitably selected projects would be conducted on a delegated basis through an existing national research organization. One example of this is the Tuberculosis Chemotherapy Project, Madras, India, the research being carried out by the British Medical Research Council. The Danish Tuberculosis Index is an example of an internationally sponsored and partially supported research activity conducted nationally which would not be conducted were it not for its international importance.

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It is anticipated that the WHO-conducted research in tuberculosis will be continued by a central research unit and its field-operating arms. The planning and selection of research projects would be done in the central research unit by appropriate mechanisms with respect to adequate scientific consultations and within the administrative framework of the proposed new WHO research activity. The field work requires skilled technical teams which will follow centrally-prepared protocols for the collection of uniform data for analysis and interpretation by the central unit. It is anticipated that many of the same personnel will be engaged at one time in the central research unit, at another time in the conduct of field operations. Moreover, every effort should be made to ensure the free and easy travel between the internationally-conducted research projects.

The above WHO research effort will represent only a small portion of the total tuberculosis research that is going on and should continue to go on in the various institutions throughout the world. These many independent investigations have provided and will continue to provide certain basic biological information and biological products that are absolutely essential to the conduct of the field-oriented WHO research. The Scientific Group believes strongly that studies of this sort are best conducted on a within-a-nation basis and the Group has no intention of suggesting that WHO should get into such research within its own organization on any substantial scale.

By the same token, there is a problem which stems from the fact that in the technologically highly-developed countries, more compelling national health problems make it difficult for the still relatively small pool of laboratory scientists to devote their efforts and facilities to research in tuberculosis. As a consequence there are already a few highly-specialized instances and more may be anticipated, in which the field research of WHO in tuberculosis cannot continue unless a particular laboratory effort can be assured.

Accordingly, the Scientific Group recommends that the central research unit have a mechanism whereby special technical problems emerging from the Organization's field research programme could be studied in a laboratory outside WHO but with WHO financial support, either direct or through a Member government. The financial

support could take the form either of a grant or a contract negotiated by WHO and the chosen laboratory. It is emphasized that what the Scientific Group is recommending is not that WHO should set up a "grants programme" in the usually accepted sense of the term involving unrestricted applications by individual investigators for the support of their research.

The Scientific Group also believes that the central research unit should have sufficient funds to arrange for the training of young scientific recruits in the special subjects necessary for the conduct of international research. It is important that the training period be of sufficient length to permit a reasonably satisfactory grasp of the particular areas of knowledge involved. In order to build up also a national cadre of research personnel in the under-developed countries, the persons to be trained should include promising nationals from the country in which the research is to be conducted. This training might take place both on the project, at the central unit or elsewhere in suitably selected institutes.

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The considerations set forth above have been based on a careful scrutiny by the Scientific Group of the outstanding unanswered questions in tuberculosis today and what is needed in tuberculosis research. This scrutiny has been made against the Group's collective background of a reasonably complete knowledge of the total research effort now being made in the various countries of the world by independent investigators, by governments, and by WHO. Moreover, the possible availability of the necessary skilled investigators has been taken into account. A detailed presentation of the results of this scrutiny are presented in the Appendix.

## 2. RECOMMENDATIONS

The Scientific Group particularly wishes to emphasize that the present tuberculosis research programmes being conducted by WHO all represent important beginnings in the very fields of research activity considered to be of the most immediate importance by the Scientific Group on Tuberculosis. Accordingly, the Group hereby presents the following recommendations to the Director-General of the World Health Organization and strongly urges their adoption:

1. There should be a substantial increase in tuberculosis research by WHO, both in the form of WHO internationally-conducted research and WHO-assisted research. This should consist of expansion and strengthening of currently operating projects as well as the start of new ones.
2. There should be a central research unit charged with full responsibility for the selection, initiation, organization and actual conduct of international tuberculosis research and its evaluation. The Group has not formed an opinion whether this unit should be part of a general research unit for several diseases or whether there should be an independent unit for this disease.
3. In formulating the terms on which the central research unit should be based the following points, among others, should receive consideration:
  - (a) there should be a permanent cadre of research staff that may be rotated, as the needs arise, between field and central operations;
  - (b) the director of the unit should have considerable freedom to transfer funds from one heading to the other within the total allocation;
  - (c) there should be the closest links between field and central operations with a liberal budget for travel between them;
  - (d) the need for special research projects should be recognized; such projects should be financed by WHO without any substantial contribution from host governments;
  - (e) a part of the budget must be explicitly designated for training posts for senior and junior research personnel;
  - (f) facilities for adequate scientific consultation should be available.

Proposed programme and budget

The particular activities strongly recommended for immediate support are:

I. EXISTING RESEARCH TO BE STRENGTHENED AND EXPANDED

A. WHO-conducted

1. Laboratory and field studies on BCG vaccines and vaccination.
2. Studies on isolation and classification of mycobacteria.

3. Epidemiological studies including methodology.
4. Mass chemotherapy in under-developed countries.
5. Chemoprophylaxis.

B. WHO-assisted

1. Danish Tuberculosis Index.
2. Tuberculosis Immunization Research Centre.
3. Tuberculosis Chemotherapy Centre, Madras.

II. PROPOSED NEW RESEARCH

A. WHO-conducted

1. Specific studies on the factors involved in acceptability of long-term self-administration of anti-tuberculosis drugs.
2. Studies on atypical mycobacterial infection and disease (including bacteriology, pathology, clinic, prevalence and spread).
3. Development of internationally acceptable standards for measuring drug resistance in mycobacteria.
4. Studies on risks to contacts of chronic excretors of INH-resistant strains.
5. Ascertainment, on a wide geographic scale, of prevalence of drug-resistant strains in apparently new cases with special reference to primary INH-resistance.
6. Controlled trial of BCG vaccination in areas with much low-grade tuberculin sensitivity.

B. WHO-assisted

1. Nutritional factors in tuberculosis (with special reference to relationships of INH to vitamin B metabolism, etc.).
2. Pharmacodynamics of INH, etc., including dosage forms.
3. Specialized studies on the mechanisms of host resistance.

4. Studies on management of far-advanced cases.
5. Studies on problems involved in revaccination and in the "boosting" effects of tuberculin.

The Scientific Group found it desirable to make it reasonably clear what was meant by a "substantial increase in research" by giving at least an indication of what order of expenditure the expanded programme could be expected to entail. Having been informed about the approximate cost of WHO personnel and supplies and equipment, the Group believes that roughly \$ 200 000 can be effectively and wisely used in 1959; \$ 650 000 in 1960 and \$ 1 000 000 in 1961.

These figures, which of necessity are rough estimates, are in addition to the cost of present field research projects, but include the cost of continued operation of the central research unit which, it is envisaged, would absorb the present allocations for the Tuberculosis Research Office. During 1959 a considerable strengthening of the central research unit would take place, the present TRO not being able to cope properly with ongoing research projects. In 1960 and 1961 new projects, as indicated in the table below, would gradually be initiated. For example, three projects on acceptability of chemotherapy (A.1) would have started in 1961, and the large BCG control study in a country with high prevalence of low-grade sensitivity would be in full operation after January 1961.

	1959	1960	1961
	\$	\$	\$
Central research unit (absorbing TRO)	140 000	190 000	250 000
Danish Tuberculosis Index	15 000	25 000	25 000
	155 000	215 000	275 000
<u>Proposed new research</u>			
<u>A. WHO-conducted</u>			
A.1 Acceptability projects	25 000	100 000	300 000 (3 studies)
A.2 Atypical infection projects	-	25 000	50 000
A.3 Drug resistance standards	9 000	-	-
A.4 Contact risk with INH-resistant strains	-	100 000	100 000
A.5 Prevalence of drug-resistant strains	-	25 000	25 000
A.6 BCG vaccination trial	5 000	100 000	150 000
	39 000	350 000	625 000
<u>B. WHO-assisted</u>			
B.1-5 inclusive	-	100 000	100 000
<b>GRAND TOTAL</b>	194 000	665 000	1 000 000

## FIELDS OF RESEARCH

### A. Fundamental Research in Tuberculosis

The importance of the problems of immunity in tuberculosis is illustrated by the fundamental fact that of the very large number of subjects infected with the tubercle bacillus only a small minority will develop tuberculous disease.

Hence highly effective immune processes occur in tuberculous infection, but the actual mechanism of these processes is still largely unknown. The difficulty of the problem is due to several factors: the complex antigenic structure of the tubercle bacillus; the important part played by specific hypersensitivity in the course of the tuberculous infection; the constant interplay in tuberculosis between hypersensitivity and immunity, both operating through distinct mechanisms but influencing one another; finally, the very marked influence of certain non-specific nutritional and hormonal factors on the result and the effectiveness of the immune processes. There is no other infection in which the analysis of the mechanisms of immunity presents such difficulties because there is no other infection in which as many different factors have to be considered.

The concrete problems which it would be particularly desirable to study are:

1. A more precise analysis of the antigenic structure of different types of tubercle bacilli, and the isolation in a more highly purified state of the antigenic fractions.
2. Induction of tuberculin-type allergy with bacillary components.
3. Production of specific immunity with bacillary components as distinct from whole bacilli.
4. The so-called cellular antibodies which are responsible for the tuberculin type allergy. Relationships between these antibodies and the circulating antibodies which under certain conditions appear during the course of the immunization.

Appendix

5. The cellular mechanisms that are at the basis of immunity.
6. The non-specific effects produced by anti-tuberculosis immunization, such as increased resistance to other infections and heightened capacity to develop sensitivity to other antigens.
7. The influence of nutritional factors and, in particular, of certain deficiencies (proteins, lipids, vitamins) on the response of the organism to tuberculous infection.
8. The hormonal factors playing a role in immunity.

More detailed knowledge in these different fields would be not only of theoretical interest, but also of considerable practical importance. Several epidemiological and prophylactic problems of far-reaching importance probably cannot be solved before considerable progress has been made in the fields listed above. Thus the study of the spread of infections due to atypical mycobacteria is closely dependent on the preparation of more specific tuberculins that will permit a distinction to be made between those infected with atypical bacilli and those infected with human-type or bovine-type tubercle bacilli. Similarly, the preparation of vaccines not inducing hypersensitivity, a very desirable objective, is closely linked to the isolation and purification of the bacillary components responsible for the immunity. Finally, a better knowledge of the role of the nutritional factors would be of particular importance for tuberculosis control in the under-privileged countries where deficient diets are of such common occurrence.

The research projects listed above are not strictly speaking of an international character absolutely requiring the collaboration of several countries. They may be carried out in specialized national institutions. However, a detailed review of the existing situation reveals that the number of centres in which such research is going on is extremely limited, and that there is every prospect that their number will further decrease. Thus, many of the scientists who are particularly active in this field are advancing in age and young research workers willing to enter the field are difficult to find. It is therefore recommended that WHO

Appendix

attempt to stimulate and even co-ordinate such research by giving selected research workers such support as they need to enter the field. Of considerable interest in this connexion is the work carried out by the Tuberculosis Immunization Research Centre in Copenhagen, an institution established jointly by WHO and the Danish Government, and subsequently subsidized by WHO. This work is remarkable and shows the quality of the results that may be obtained by a team working over a long period in the same direction. Continuation of the work of the TIRC appears highly desirable.

B. Research on BCG Vaccination

BCG vaccination has long been used on a large scale and legitimately so. However, numerous problems remain to be solved in this field. Among the most important are those relating to methods for the biological assay of the immunizing potency of BCG vaccine, revaccination, oral administration of BCG and evaluation of the effect of BCG vaccination in countries with a high prevalence of low-grade sensitivity to tuberculin.

1. Methods for biological assay of the immunizing potency of BCG vaccines

It seems indicated to continue and to accelerate the elaboration of criteria that will permit comparisons to be made of the immunizing potency of vaccines produced by different centres and of successive vaccine batches from a given centre. This problem concerns both fresh and freeze-dried vaccines. By their very nature, such studies require both the collaboration of the various institutes producing the vaccines and the co-ordination of the work by a central unit - this co-ordination includes the protocol for the studies, the supervision of their conduct and the interpretation of the results. The role which WHO will have to play in this field is extremely important since WHO obviously will have to act as co-ordinator. A study of the immunizing potency of the Japanese freeze-dried glutamate vaccine is at present being conducted by TRO in collaboration with several other specialized institutions. It appears, however, that the present lack of personnel at TRO

Appendix

makes the execution of its task very difficult and thus carries the risk of reducing the efficacy of the work undertaken.

2. Revaccination and resensitizing effect (booster effect) of tuberculin

The problem of the biological basis for revaccination has been very much neglected so far. Systematic revaccination at regular intervals is carried out in a number of countries but this is done on purely empirical grounds: neither the duration of the vaccine-induced immunity nor the criteria for determining its waning or its disappearance have been studied in detail. The problem is complicated by a particular phenomenon, the reinforcing (boosting) effect of tuberculin injections on the post-vaccination allergy. The importance of this phenomenon has recently been demonstrated. Repeated post-vaccination tuberculin testing, it has been found, tends to counteract waning of the allergy, which is the only available indicator of a decrease in the vaccine-induced immunity. A detailed study of this phenomenon is indispensable if the problem of revaccinations is to be solved. The problems relating to revaccination and the boosting effect of tuberculin should be studied both experimentally and in man. It is considered most important that use be made of the Danish Tuberculosis Index for the latter part of the studies.

3. Oral administration of BCG vaccine

In many Latin American countries BCG is given orally in large, repeated doses (technique of de Assis). Under certain conditions, this vaccination is given not only to tuberculin-negative subjects but to all subjects, without any preliminary tuberculin testing. It appears that these procedures, viz. oral vaccination by large, repeated doses of BCG and the use of this vaccination without any previous screening of the subjects to be vaccinated, have never been the subject of very detailed experimental studies. Furthermore, no large-scale comparative field study has ever been made between this form of vaccination and the other, more generally used, methods of vaccination. Such a study would be highly desirable. The Institute of Tuberculosis of Bahia, Brazil, has declared itself ready to

Appendix

co-operate closely with WHO. The assistance of a team trained and supervised by WHO would be of great value. Such collaboration between the Institute of Tuberculosis, Bahia, and WHO could, it is believed, lead to studies of many other problems of particular importance for tuberculosis control in the countries of Latin America, where tuberculosis is still highly prevalent.

4. Studies of the effects of vaccination in countries with a high prevalence of low-grade tuberculin sensitivity

With the present criteria for vaccination, a considerable proportion of the subjects with low-grade - so-called non-specific - sensitivity to tuberculin will be vaccinated. Certain observations, experimental as well as epidemiological, indicate that those who have this type of sensitivity also have a certain degree of specific immunity. This makes it very difficult to assess accurately the benefits of vaccination in the many regions where low-grade sensitivity is prevalent: the groups vaccinated will comprise both persons who had no specific immunity at the time of vaccination and persons who had some specific immunity, and the proportion of these two categories may vary considerably from one community to another. In the opinion of the Group, the above represents an important problem and a specifically designed study seems clearly indicated. In such a study, which would have to be conducted in a country with a high prevalence of low-grade tuberculin sensitivity as well as a high prevalence of tuberculosis, both the persons to be vaccinated and the controls would be carefully further divided into two groups - those without any detectable sensitivity and those with low-grade sensitivity.

C. Research on Tuberculin

The recent studies by ERO on the adsorption of tuberculin to glass and the means to prevent this adsorption (by addition of Tween to the diluent) and on the stabilization of tuberculin dilutions are very important and should be continued.

The following investigations are held to be of extreme epidemiological importance:

Appendix

1. Tests with tuberculins from different strains of atypical mycobacteria in tuberculosis prevalence surveys in different geographic regions.

In view of the present lack of knowledge concerning the geographic distribution of infections due to atypical mycobacteria it would seem indicated, in certain surveys of the prevalence of tuberculous infection, to use several tuberculins in order to bring out any stronger sensitivity to tuberculins from atypical mycobacteria. The chances that such studies will succeed are, however, rather limited because of the low specificity shown by these tuberculins in experimental infections with atypical organisms.

2. Preparation of more specific tuberculins

There is thus every reason to intensify the research on the fractionation and purification of tuberculo-proteins from the various types of typical and atypical mycobacteria, in order to obtain more specific tuberculins. It is not likely that studies on the distribution of infections due to atypical organisms will make any decisive progress before this goal has been attained. This circumstance, already referred to in the foregoing, illustrates the great importance that research of seemingly purely theoretical interest may have for the advancement of our knowledge of the epidemiology of tuberculosis.

D. Research on Mycobacteria

1. The problem

In connexion with the WHO-assisted tuberculosis projects, a co-operative study on mycobacteria has been started by WHO and a number of national research institutions. Its aim is to obtain more information on the prevalence of the various types of mycobacteria occurring in different parts of the world, to study their virulence and drug sensitivity and their epidemiological and immunological importance to man.

The first - preliminary - results have clearly shown that the problem under study is more complex than was anticipated. Besides the problems posed by the

Appendix

typing of the different mycobacteria, a new problem has appeared which concerns the isolation of mycobacteria and, in particular, their atypical variants; the latter seem to be more frequent in some parts of the world, being particularly common in countries with a high prevalence of low-grade tuberculin sensitivity. No suitable techniques exist for the detection of these atypical strains, which may well be of great importance from the immunological and epidemiological standpoints.

2. The research required

The elucidation of the important problems outlined above will involve:

- (a) The development of a simple culture technique suitable for use in small laboratories with limited facilities.
- (b) Elaboration of methods for preserving typical and atypical mycobacteria contained in sputum specimens, etc.
- (c) Studies on the classification of atypical mycobacteria.
- (d) Experimental studies of the relative pathogenicity of the different atypical strains for various animal species. These studies would also serve to determine the degree of immunity to tuberculosis induced by these strains.
- (e) A large internationally-conducted research effort to define the geographic pattern of the various mycobacterial diseases in man.
- (f) A broad ecological study of atypical mycobacteria not causing disease in man, to ascertain their prevalence in domestic animals, their distribution in nature and their significance for man (viz. their ability to produce infection in man and to induce sensitivity to tuberculin).

These studies might be followed by the setting up of a WHO-supported reference laboratory for tuberculosis in one or more national institutions. Such a reference laboratory would serve as a centre for collection and classification of mycobacteria. Other functions would be to elaborate bacteriological methods and techniques for consideration as international standards and to train national personnel in such standard techniques.

Appendix

E. Research on Epidemiology

There is an urgent need for further studies on the epidemiology of tuberculosis. Thus, before effective control of tuberculosis can be attempted in the less developed countries more must be known about the nature and extent of their tuberculosis problem. In a number of these countries surveys of the prevalence of tuberculosis have been or are being conducted by WHO and this work should be continued and considerably expanded. The large amount of data accumulated during these surveys constitutes an important source of epidemiological information which should be utilized more fully than has been possible so far. Furthermore, the prevalence surveys should be supplemented by longitudinal surveys to provide data also on the incidence and trend of tuberculosis.

1. The problems

(a) Studies on the extent of the tuberculosis problem must be based on relevant indices of the presence of tuberculosis. The group agreed that prevalence of "infection" and incidence and prevalence of "bacillary tuberculosis" would be the most valuable comparative indices.

(1) In many parts of the world determination of the prevalence of infection is seriously hampered by the presence of low-grade sensitivity to tuberculin. Specific tuberculin tests would be desirable. This involves, among other things, field studies of the value of certain fractions of tuberculin found to be promising in experimental work.

(2) Co-ordinated laboratory research is required for the identification and classification of mycobacteria isolated in the course of the epidemiological studies.

(b) Results from BCG vaccination trials in different parts of the world indicate that the low-grade sensitivity to tuberculin may be associated with a certain increase of the host resistance and may interfere with the immunizing effect of BCG vaccination. This possibility is of great importance in many countries and large-scale studies of the prevalence and the epidemiological significance of low-grade sensitivity are therefore strongly indicated.

Appendix

(c) Epidemiological studies on the spread of isoniazid-resistant tubercle bacilli in the general population are going on in some countries (United States of America, United Kingdom, Denmark - including Greenland). The value of such studies would be further increased if, with the assistance of WHO, uniform internationally-accepted criteria for isoniazid-resistance could be established.

(d) In some technically developed countries with a low and declining prevalence of tuberculosis it should soon become possible to reorientate the tuberculosis programme towards eradication. Before such a reorientation can be envisaged, however, a number of special epidemiological problems must be solved.

A research project - the Danish Tuberculosis Index - designed to study these problems has been operating in Denmark for some years. This country is some years ahead of most other countries in the progress towards the eradication phase and it offers particularly favourable conditions for the epidemiological studies required to guide future eradication programmes.

The work of the Danish Tuberculosis Index, an enterprise sponsored and partially supported by WHO, was reviewed. It was agreed that it was of great international importance representing probably the most important research activity in the field of eradication problems. Among the problems it has taken up for study are the benefit, if any, of BCG vaccination in the eradication phase and the possibility of subdividing the general population - mainly on the basis of simple examinations such as tuberculin testing and chest radiography - into groups with markedly different risks of developing tuberculosis disease. The definition of low-risk groups would permit a reduction of the enormous number of routine X-ray examinations and the pinpointing of high-risk groups would allow a concentration of the preventive efforts.

In view of the above, it was recommended that every effort be made to strengthen and considerably expand the Danish Tuberculosis Index.

Appendix 1

F. Research on Chemotherapy

How anti-tuberculosis chemotherapy should be applied to be most effective is a problem that is far from solved anywhere and least of all in the under-developed countries where the prevalence of tuberculosis is highest. The restricted health services and present economic difficulties in the under-developed countries demand an original approach needing considerable research.

1. Domiciliary versus sanatorium treatment

The first stage of the Chemotherapy Research Project in Madras (of which WHO is a major sponsor) is designed to show whether domiciliary chemotherapy under present-day conditions in India can compete with institutional treatment. Should it prove justifiable to dispense with hospitalization (except in special cases), there will be an immediate need for determining the most efficient and economic methods for mass application of chemotherapy on a domiciliary basis.

2. Methodology of mass chemotherapy

(a) The methodology of mass chemotherapy is being, or will be, studied in several projects started by WHO. These include the Chemotherapy Research Project, Madras, and the Chemotherapy Pilot Projects in Tunisia and Kenya. A further WHO-assisted project dealing with this problem is in the planning stage. The plans for this project - the National Tuberculosis Centre, India - envisage research on a realistic socio-medical approach to the control of tuberculosis in urban and rural communities in India. As the results may have application to many other areas this investigation should have the strongest support.

(b) Studies of the acceptability of long-term self-administration of drugs in the chemotherapy and chemoprophylaxis of tuberculosis form part of the above-mentioned projects. Nevertheless, there is a need for trials specifically designed to investigate this problem. These should involve consideration of psychological and cultural factors, methods of supervision and distribution of drugs, and the forms of the drug used. Assessment of the attitude of the population to tuberculosis would also be of value.

Appendix

3. More effective drugs and drug regimens

(a) In spite of the advances in the chemotherapy of tuberculosis, there is still a great need for further research on the drugs to be used, particularly in domiciliary treatment. Work is in progress (e.g. in East Africa by the British Medical Research Council) to improve the effect of chemotherapy by finding cheaper and more effective companion drugs for INH than PAS. New ways of administering isoniazid, and indeed new drugs altogether, are needed.

(b) The metabolism of INH varies between individuals and is possibly altered after long periods of treatment; measurement of INH blood levels may assist in indicating these differences. High dosage regimens (which some workers consider desirable) may produce toxic effects which can be obviated by the use of pyridoxine. Because of its relatively high cost the latter cannot be used in the under-developed countries but cheaper vitamin alternatives may possibly do as well.

These problems are of considerable importance. Some lend themselves to international co-operative studies and this applies in particular to the question of variations in INH metabolism.

4. Nutrition and chemotherapy

INH appears to have an effect on the vitamin B metabolism of the body and indeed may have a relationship to other nutritional factors. This becomes of great importance when the drug is used in under-nourished populations. Also INH and its analogues may prove a useful tool in basic studies on nutrition.

It is considered desirable that intensive research be undertaken in this field with the co-operation of nutritionists. Some of this research might be done in the Chemotherapy Centre, Madras, and this possibility should be actively explored. Furthermore, it is suggested that WHO promote such research in a well equipped university centre.

Appendix

5. Drug resistance

(a) In some parts of the world there is already evidence of a build-up of drug resistance, due largely to inadequate courses of treatment and possibly to some extent to the transmission of drug resistant organisms from patient to contact. More observations are needed on the prevalence and significance of this phenomenon and its potential in reducing the effects of mass chemotherapy. WHO is in an excellent position to organize and to partake in collaborative surveys in various areas of the world. As a corollary it is most important to establish agreed bacteriological criteria for drug resistance.

(b) An important question in the epidemiology of drug resistance concerns the risks run by the contacts of patients who are excreting tubercle bacilli with various levels of resistance to isoniazid, and varying virulence to guinea-pigs. An answer to this question is urgently needed in view of possible national programmes involving the widespread use of isoniazid with, and especially without, a companion drug.

Information on the spread of isoniazid-resistant organisms in areas with adverse social conditions will be obtained from the Chemotherapy Research Project, Madras, and the Chemotherapy Pilot Project, Kenya (spread from patients to their household contacts) and from the Chemotherapy Pilot Project, Tunis (spread from patients to other members of the community). More exact experimental studies on the transmissibility of these resistant organisms are being undertaken in monkeys in the United States of America. Information of a complementary type has been obtained by national surveys of primary drug-resistance both in the United States of America and Great Britain, and these might well be repeated periodically there and elsewhere. In addition, valuable information could be obtained if the WHO surveys into the prevalence of tuberculosis were to include measurement of the drug resistance of any strains of bacilli isolated from persons newly diagnosed as tuberculous. Finally, attention is drawn to a special opportunity for research that presents

Appendix

itself in certain localities where for many years wide use has been made of ambulatory treatment with INH. A sample survey of the population in one or more of these localities might well indicate how much risk - in terms of disease - the spread of drug-resistant organisms involves.

G. Research on Chemoprophylaxis

Judging from the established properties of INH it seems reasonable to expect that this drug will be of use in the chemoprophylaxis of tuberculosis. There are two major fields in which chemoprophylaxis could be used: (a) primary prophylaxis and (b) secondary prophylaxis. By primary prophylaxis is meant the administration of the drug to uninfected persons who are at high risk of contracting tuberculous infection; in secondary prophylaxis, on the other hand, the drug is administered to persons who are already infected with tubercle bacilli - as evidenced by a positive skin reaction to tuberculin - but who show no signs of tuberculous disease. (Secondary chemoprophylaxis should be clearly distinguished from so-called preventive chemotherapy - the administration of anti-tuberculosis drugs to persons with certain signs of tuberculosis such as pulmonary X-ray pathology.)

1. Problems

The use of INH in chemoprophylaxis raises three major problems. These concern:

- (a) The possible risks connected with the prophylactic administration of INH.
- (b) The evaluation - by means of field trials - of the benefit of chemoprophylaxis.
- (c) The acceptability of long-term self-administration of INH to entirely asymptomatic persons.

What can be said at present is that while several details of these problems still require research, nothing has yet emerged that would clearly preclude the possibility that INH will be useful, and perhaps highly useful, in chemoprophylaxis programmes.

Appendix

2. Approach and proposed research

(a) The possible risks of chemoprophylaxis with INH are: drug toxicity, interference with the development of immunity and the creation of drug-resistant populations of organisms.

The Group reviewed present knowledge. It was agreed that toxicity and drug resistance were points of minor importance for chemoprophylaxis; this in contrast to their importance for chemotherapy.

As regards the possible effects of anti-microbial drugs on the emergence of specific resistance to tuberculosis, it was agreed that this area of fundamental laboratory research was of considerable importance but that it required no special effort on the part of WHO since it had already attracted a large number of independent laboratory investigators.

(b) The effect of chemoprophylaxis is being assessed in a number of projects. Among these are the chemoprophylaxis studies conducted by the United States Public Health Service - primarily directed at secondary chemoprophylaxis - and the Tunisia and Kenya projects (WHO) which both include primary as well as secondary chemoprophylaxis. Other studies - devoted to secondary chemoprophylaxis - are being conducted by the French Institute of Hygiene, the Forlanini Institute in Rome and the Danish Tuberculosis Index (in Greenland). In the opinion of the Group this research should provide sufficient information on the general value of chemoprophylaxis.

The Group also discussed the advisability of setting-up special studies on secondary chemoprophylaxis in certain high-risk groups such as adolescents, mineworkers and adults with strong skin reactions to tuberculin. Further, the advisability of studies on the association of primary chemoprophylaxis and vaccination in uninfected, highly exposed children was considered. There was general agreement that such studies should be promoted and - if the case arose - co-ordinated by WHO but that there was no need for a WHO-conducted research effort in this field.

(c) The acceptability - to different societies - of long-term self-administration of anti-tuberculosis drugs is a vitally important problem requiring considerable specialized research. (For details of the research proposed see under E. Research on Chemotherapy.)