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**CHEMOTHERAPY
AND CHEMOPROPHYLAXIS
IN TUBERCULOSIS CONTROL**

Report of a Study Group

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WORLD HEALTH ORGANIZATION

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**STUDY GROUP ON CHEMOTHERAPY AND CHEMOPROPHYLAXIS
IN TUBERCULOSIS CONTROL**

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CHEMOTHERAPY AND CHEMOPROPHYLAXIS IN TUBERCULOSIS CONTROL

Report of a Study Group

The objective of the Study Group was to evaluate the knowledge at present available on chemotherapy and chemoprophylaxis as public health measures in tuberculosis control and to advise WHO as to what should be its next steps in this field.

At the outset, the Group was informed of the technical recommendations made by WHO. A review was made of the existing WHO research projects in antituberculous chemotherapy. The statement of the UNICEF/WHO Joint Committee on Health Policy¹ that it was now appropriate to extend antituberculous chemotherapy programmes, but not unsupervised mass application programmes, was likewise noted. In addition, the Study Group discussed at length the extent to which it believed it was proper to advise the use of antituberculous chemotherapy today. Moreover, the Group formulated certain questions to which answers should be obtained before an unrestricted mass-type country-wide programme could properly be recommended with reasonable assurance.

The Study Group decided that its findings could be most conveniently presented under three headings :

1. A statement on prevalence surveys for tuberculosis.
2. A statement as to what would constitute a reasonably acceptable tuberculosis chemotherapy programme for an area of high tuberculosis prevalence on the basis of the currently available information on the medical, sociological and economic factors conceivably involved. This general statement was prepared with the hope that it might provide current guidance to health administrators pending the acquisition of definitive information on the many important questions which are at present unanswered.
3. Definition of such important but still unanswered questions, and recommendations in broad outline for a series of specific research projects designed for their study.

¹ *Off. Rec. Wld Hlth Org.* 80, 17.

1. TUBERCULOSIS PREVALENCE SURVEYS

The Study Group agreed that the sound planning of a tuberculosis control programme today must be based on prevalence surveys for tuberculosis planned and so conducted that the extent and the nature of the tuberculosis problem in the different population groups will be disclosed with sufficient reliability. The Group further agreed that no one of the techniques available for such prevalence surveys (i.e., tuberculin testing, mass roentgenography, sputum examination) is sufficiently established as completely satisfactory to permit abandonment of any of the others.

Accordingly, the Study Group strongly endorses the policy of WHO with respect to the necessity for tuberculosis prevalence surveys and recommends their continued operation and expansion by present methods while devoting special attention to attempts to obtain simpler techniques.

2. TUBERCULOSIS CHEMOTHERAPY AND CHEMOPROPHYLAXIS PROGRAMMES

While recognizing that certain important questions are not yet answered, the Study Group believes that the following programme would represent a minimal acceptable programme for areas with both a high tuberculosis prevalence and grossly inadequate hospital facilities. However, because of the great complexity of organizing efficient domiciliary or out-patient chemotherapy programmes, the Study Group emphasized that it would be wise in any one country to start with single or multiple projects in specially selected localities rather than on a country-wide basis.

Minimum programme

1. Every known case of pulmonary tuberculosis should receive anti-tuberculous chemotherapy. This can be administered on an ambulatory or a domiciliary basis.

2. Every patient should have a roentgenogram of the chest before therapy is started.

3. Every patient should have an examination of the sputum for tubercle bacilli before chemotherapy is started. Preferably this examination should include a sputum culture; if sputum cultures are manifestly impossible or decidedly impracticable, microscopy of an appropriately stained sputum is acceptable.

4. Antimicrobial therapy should be continued without interruption for 6 months after the sputum has become negative for acid-fast bacilli, but in no case should therapy be given for less than one year.

5. The chest roentgenogram should preferably be repeated at 3, 6 and 12 months. When this is manifestly impossible or decidedly impracticable, every effort should be made to obtain a film one year after the start of therapy and at the completion of chemotherapy.

6. If the patient continues to discharge acid-fast bacilli in the sputum 6 months after the start of chemotherapy, or should his disease at any time show unquestioned deterioration on roentgenography, the case should be reviewed and the question of a change in treatment considered. If possible, drug susceptibility tests and other special investigations should be made at this time. In certain cases, it may be necessary to make a special effort to have the patient transported to a centre where he could receive surgical therapy or various other forms of chemotherapy not now suitable for domiciliary use. If no such changes in management are possible, the question of continuing the previous chemotherapy, especially with INH (isoniazid), for an indefinite period must be considered. The Study Group agreed that a reasonably satisfactory scientific answer is not available concerning the wisdom of such continued INH therapy in the presence of uncorrectable "open" pulmonary tuberculosis. About all that can be said is that from a very limited experience and from certain theoretical considerations it appears that on the whole the practice is more likely to be beneficial than harmful. Every effort should be made to minimize the spread of infection by an education programme in this group.

7. The preferable regimen would consist of daily administration of both INH and a companion drug. In ambulatory and domiciliary patients it is advisable to use PAS as the companion drug.

8. If a local situation exists in which it is not practicable to use the above drug regimen, the use of INH alone is justifiable (see Annex). The Study Group agrees that on present knowledge the use of INH alone cannot be recommended with the same assurance as the use of INH-PAS. Nevertheless, if a local situation exists in which the alternatives faced by the public health administrators are the institution of a programme with INH alone or no programme at all—or one drastically smaller in scope—the Study Group agrees that a programme with INH alone would constitute an acceptable practice today and until definite further evidence to the contrary should be forthcoming. Meanwhile, important relevant questions which remain unanswered should be intensively investigated without delay. Certain of these questions are broadly outlined in section 3.

9. The total daily dosage of INH should be between 5 mg and 10 mg per kilogram of body-weight. Within this range, children tolerate some-

what higher doses than elderly people. Usually a daily dose of 8 mg per kg of body-weight is satisfactory.

10. The total daily dosage of sodium PAS (or its equivalent) should be 10 g.

11. If INH is used alone, the total daily dose may be administered at one time.

12. Every effort should be made to determine the regularity with which the patient takes the drug and to ensure patient, family and community co-operation in such a tuberculosis chemotherapy programme by repeated educational activities with constant emphasis on the importance of continued regular self-administration of the therapy (see section 3).

13. Vaccination with BCG should be performed on all non-reactors to tuberculin who are household associates of patients receiving domiciliary chemotherapy. The management of children who are positive reactors to tuberculin is discussed in the paragraphs on chemoprophylaxis presented below.

Chemotherapy

Although INH is among the least toxic of drugs in general use, it is none the less not completely free of toxicity, notably neurotoxicity (e.g., peripheral neuritis and toxic encephalopathy). In general, the appearance of neurotoxicity bears a relationship to the size of the daily drug dosage, and the toxic manifestations subside with reduction or interruption of the INH therapy. In the programme outlined, much of the day-to-day observation of the patient will be made by household associates and subprofessional trained home visitors. Consequently, it is essential that these people be well educated concerning the early and late manifestations of drug toxicity.

With the knowledge of chemotherapy at present available, the Study Group recommends placing emphasis on developing the most efficient type of domiciliary chemotherapeutic service for all cases of pulmonary tuberculosis rather than on the building of additional hospitals for the care of tuberculous patients.

In developing a truly effective public health programme based on chemotherapy, the Study Group agrees that it is essential to bring under immediate treatment all cases of pulmonary tuberculosis in the community. (By "case" is meant a person with definite roentgenographic pathology characteristic of pulmonary tuberculosis, in whose sputum acid-fast bacilli may or may not have been demonstrated by the available methods and in whom no other cause of pulmonary disease can be found.) It is realized

that the extent to which this can be done depends upon the resources available in any particular local situation. The Study Group wishes to emphasize that it does not believe that the situation with respect to chemotherapy today has matured to the point at which it can recommend mass country-wide roentgenographic case-finding and mass application of chemotherapy. The Group strongly advises that primary attention should be concentrated on the patients who seek medical advice because of symptoms of disease. By the same token, as circumstances permit, as many as possible of the asymptomatic cases should receive therapy. The Study Group realizes that such asymptomatic patients may present special problems with respect to co-operation in the long-continued self-administration of chemotherapy. Consequently, special efforts should be made to devise the most effective means for obtaining a satisfactory degree of co-operation (see section 3), for the extent to which this is accomplished, especially in an area of high prevalence, will in large measure determine the ultimate success of a chemotherapy programme in a particular community.

Chemoprophylaxis

The Study Group reviewed the chemoprophylaxis studies going on in Greenland, at the Forlanini Institute in Rome, under the direction of Professor Zorini, and in the USA by the Public Health Service. In addition, a considerable discussion took place concerning what is known about the scientific basis for chemoprophylaxis, including in the term prophylaxis the administration of INH to persons with no evidence of tuberculosis except a positive cutaneous reaction to tuberculin.

It was generally agreed that whereas, on the one hand, there was a real possibility that chemoprophylaxis (using the term broadly) might ultimately represent one of the most powerful weapons in tuberculosis control, on the other hand, very little of the information necessary for definite recommendations in this field is available.

Accordingly, the Study Group strongly recommends that, in addition to the current studies, a few more and carefully designed field research projects devoted to chemoprophylaxis be organized as soon as possible. It further recommends that these additional chemoprophylactic studies be conducted on a relatively large scale and that at least one study be made in an area of high tuberculosis prevalence. In addition, the Group emphasizes that every encouragement should be given to laboratory research on the basic mechanics of antituberculous immunity as related to chemoprophylaxis.

While the essential scientific information is being obtained, the Study Group recommends provisionally, for areas of high tuberculosis prevalence,

that INH be administered to cutaneous reactors to tuberculin who have not recently received BCG and who are the associates of infectious cases of tuberculosis.

The details of this recommendation are as follows :

1. A positive tuberculin-reactor is defined as any person whose cutaneous reaction to the 5-TU test includes an area of induration of at least 10 mm in diameter.
2. INH should be given alone and in a single daily dosage of 5 mg per kg of body-weight.
3. The administration of INH should be continued for a minimum period of 6 months and in any case for so long as the index case remains infectious.
4. Before INH administration is started, a chest roentgenogram should be obtained to exclude the possibility of the presence of parenchymal pulmonary tuberculosis. Any lesions so detected should be treated according to the recommendations indicated earlier for the treatment of tuberculous cases.

3. IMPORTANT UNANSWERED QUESTIONS AND RESEARCH PROJECTS RECOMMENDED FOR THEIR INVESTIGATION

Certain of the important unanswered questions are currently under study in such WHO-assisted projects as the Madras study and in certain field studies by university groups.

Among the questions under study are (a) the relative efficacies of INH alone and INH-PAS when administered to comparable groups of patients in field conditions, and (b) the extent to which intelligent representatives of uneducated rural people can be trained to serve as capable field auxiliaries to nurses and physicians in a tuberculosis chemotherapy programme.

Whereas other studies on like matters, and especially on the last-named, might be desirable, the Study Group agreed that the most urgent questions not under present study are :

1. Is it true that PAS cannot be satisfactorily employed as a companion drug on a long-term basis under conditions of self-administration in the field ?
2. To what extent will uneducated and entirely asymptomatic persons continue to take any single or multiple drug regimen, irrespective of palatability, and for how long ?

3. Will the efforts necessary to ensure a reasonable degree of such long-continued co-operation prove to be administratively feasible? Will efforts to test the urine do more harm than good?

4. What is the risk of infection from chronic cavitory cases which remain infectious despite long-term chemotherapy? Can this risk be balanced by artificial immunization of household contacts or by chemoprophylaxis?

Research projects urgently needed

An urgent need is a research project designed to provide information on questions 1 to 3 inclusive. Such a project would have two principal purposes: first, to obtain information on what actually happens when groups of people who consider themselves to be well are asked to self-administer drugs daily for periods measurable in many months or years; secondly, to determine whether particular drugs or particular dosage forms are substantially different in terms of their long-continued daily acceptance in field conditions. It should be emphasized that a study of this type could not be properly conducted as an adjunct to a study primarily devoted to the evaluation of chemotherapy.

As many of the problems involved in these questions are sociologically determined, it would be most helpful if such a project could be set up so that at least two widely different societies could be included. An essential feature in studies of this sort is the use of techniques developed by the social scientists. Experience has shown that to be truly effective in a research project of this nature the social scientists cannot function merely as periodic consultants but must live with the project as integral members of the research team. It is likewise essential that the social scientists have an intimate knowledge of the particular society involved and have capable assistants from that society.

The measurement of results in a research project of this type is necessarily less precise than in studies on the value of antimicrobial drugs. In essence, the measurement consists of the evaluation of data obtained by laboratory testing (e.g., testing urine for drug products) and by evaluation of periodic interviews with key members of the community in addition to regular interviews with the patients themselves, for one of the most powerful potential forces which can be enlisted on the side of the chemotherapist is the community attitude toward the drug-taking patient.

The Study Group believes that the details of such a project could best be developed by the investigators, if necessary in consultation with outside experts. It is contemplated that appropriately selected sample groups would be employed to study several sets of introduced variables, such as the following:

- (a) various individual drugs or drug pairings ;
- (b) various dosage forms of the same drug ;
- (c) various time-dose relationships of INH (This information is urgently needed when considering "chemoprophylaxis" programmes, for it is essential to determine whether, in terms of patient co-operation, it is more efficient to employ a daily drug regimen or one in which the medication is given one or two days each week.) ;
- (d) various degrees of educational and supervisory effort, domiciliary visiting, and chemical testing of urine.

It should be emphasized that the major question concerned in such a project—the degree of human frailty involved in self-medication—is not a question limited to field conditions in so-called under-developed areas. On the contrary, the trend in modern medical care in the so-called highly developed areas is more and more to depend on the patients' responsibility. Examples of this are the use of anticoagulants in patients who have experienced myocardial infarcts and the widespread use of chemotherapy on an ambulatory basis in mental illness.

For these reasons it is believed that in addition to a pointed research project on this question, which is so urgently needed for the tuberculosis programme, research groups in more highly developed areas should likewise be encouraged to interest themselves in the question of patient attitudes with respect to long-continued self-administered drug therapy.

Finally, the Study Group agrees that consideration of the present questions has revealed the vital necessity of having a continued basic research effort to produce a continuing supply of scientific information for application in the general field of technological development. Many aspects of such a research effort could be conducted in laboratories at scientific centres in highly developed areas. By the very nature of the situation, however, a considerable body of the badly needed field research would be best conducted in those areas of the world in which adequate research facilities do not exist. Consequently, it is highly desirable that WHO continue and expand its activities in facilitating the conduct of first-class field research in these areas of the world.

4. SUMMARY

After a careful review of the situation and with due recognition of the present gaps in knowledge concerning antituberculous chemotherapy, the Study Group agrees that : (a) tuberculosis prevalence surveys should be encouraged ; (b) all known cases of pulmonary tuberculosis should receive chemotherapy, and in areas of high prevalence with inadequate hospital facilities the chemotherapy may be on an ambulatory or domiciliary basis ;

(c) because of the many complexities involved, an ambulatory or domiciliary programme at this time should be started in one or more localized areas within a country rather than on a country-wide basis ; (d) the preferred chemotherapeutic regimen for use in an ambulatory-domiciliary programme is INH-PAS administered daily (If the use of PAS is impracticable, the use of INH alone is justified, pending the results of research on certain outstanding questions.); (e) INH alone should be administered "prophylactically" to tuberculin reactors who are associates of infectious tuberculous patients ; (f) research employing the disciplines of both the medical sciences and the social sciences is urgently needed on certain questions concerning the general reliability of patients in the self-administration of drugs over a long period ; (g) it is imperative that several carefully conducted large-scale field investigations on the use of INH in chemoprophylaxis be carried out.

The Study Group wishes to emphasize that because of the rapidly changing nature of the situation with respect to tuberculosis chemotherapy, the present recommendations are necessarily provisional. In view of this and in view of the fact that certain highly important and pertinent information is to be anticipated in the near future, the Study Group believes that it would be most advantageous for the subject to be reviewed in good time.

Annex

ARGUMENTS FOR AND AGAINST THE USE OF INH ALONE

A decision whether to employ INH alone demands the weighing of two sets of arguments as set forth below.

1. The arguments which weigh against the use of a programme with INH alone are :

(a) The fact that tubercle bacilli resistant to INH *in vitro* become predominant in the sputum of patients who remain infectious despite long-continued treatment with INH. This may well result in neutralization of drug effectiveness *in vivo*.

(b) As at least some of these bacilli have the capacity to multiply in mice and to some extent in guinea-pigs, they may remain a threat to the associates of the treated persons and to the treated persons themselves.

(c) Should new infections be acquired from certain of these tubercle bacilli resistant to INH *in vitro*, they would be expected to be unaffected by the administration of INH.

(d) The patients involved in such a programme would be living in environmental conditions which would facilitate the spread of tuberculous infection to a much greater extent than would occur in areas where environmental conditions are better.

(e) The nutritional status of the patients might be in some way related to an increased susceptibility to infection from the INH-resistant bacilli.

All these statements are true, but the degree to which they obtain has not yet been defined with precision. In sum, the case against such a programme employing only INH is the fear that a temporary amelioration of the tuberculosis situation in a community will be followed within a few years by tuberculosis which would be essentially untreatable with the major antituberculous agent available today.

2. The arguments which would tend to make a programme with INH alone a reasonable action at the present time are :

(a) The use of INH even without a companion drug will eliminate the infectiousness of many persons.

(b) As tuberculosis tends to spread by small household epidemics, the reversal of the infectiousness of a single member of the family by the use of INH might have very considerable effects in reducing the morbidity in a particular community if replicated in sufficient homes.

(c) Even when infectiousness persists, at least during the early months of therapy, the quantitative aspects of the infectiousness may be considerably diminished.

(d) If infectiousness persists for a sufficiently long period, despite INH therapy, the bacilli excreted will be INH-resistant and altered in other biological characteristics. There is considerable reason to believe that these altered bacilli (which do not necessarily represent all of a particular microbial population) have lessened pathogenicity for certain animal species and may have lessened pathogenicity for man.

(e) Only a small minority of persons infected with tubercle bacilli get tuberculous disease. Consequently, even if some of the mixed microbial populations containing INH-resistant cells did cause infection in household associates, there is a tremendous public health barrier limiting the development of cases—namely, the self-healing tendency of the primary tuberculous infection.

(f) It might be possible by a potent BCG vaccine to protect close associates of the treated patients from the INH-resistant and otherwise altered tubercle bacilli.
