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THE ROLE OF PREVENTIVE TREATMENT (CHEMOPROPHYLAXIS)  
 IN TUBERCULOSIS CONTROL

by

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INTRODUCTION

Preventive treatment (chemoprophylaxis) for tuberculosis became a practical possibility only with the availability of a safe, inexpensive, oral drug bactericidal for tubercle bacilli. Isoniazid possesses these characteristics. The demonstrated effectiveness of isoniazid in treatment led to the idea that the drug would also be effective as a prophylactic agent. Presumably, preventive treatment with isoniazid acts by diminishing or eliminating a relatively small bacterial population in new or healed lesions. Such treatment is, in reality, single-drug chemotherapy for subclinical tuberculosis.

After the prevention by isoniazid of experimental tuberculosis in guinea pigs had been demonstrated, trials in human subjects were initiated. The effectiveness of prophylactic isoniazid was measured by direct observation of the frequency of new cases of tuberculosis among those who received placebo and those who received isoniazid. Trials have repeatedly shown a reduction of cases in treated groups of infected persons; the protective effect persists for many years beyond the treatment period, perhaps indefinitely.

Because the intake of isoniazid could not be assured in the clinical trials, the results did not really measure the maximum ability of the prescribed regimens to reduce subsequent disease. Instead, the trials provided information on a more practical point, namely the reduction in tuberculosis that could be achieved under field conditions. Clearly, isoniazid is able to prevent the development of progressive clinical disease, probably in almost all infected persons who take it as prescribed.

INDICATIONS AND CONTRAINDICATIONS

Only in very unusual circumstances, when there is a high risk of infection for a relatively short time (e.g., in a laboratory experiment), does the use of isoniazid to prevent infection appear to merit consideration; in such situations, the protective effect of the drug is derived only while it is being taken.

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Usually, preventive treatment refers to preventing the development of overt clinical disease after tuberculous infection has occurred. Thus, except to the extent there is competition for resources, a preventive treatment program would not conflict conceptually with a BCG vaccination program aimed at protecting the uninfected.

Although each person who is infected with tubercle bacilli is at some risk of developing disease, there is no country where it is practical to identify and treat all positive tuberculin reactors. Treatment decisions must be based on factors such as the estimated risk of developing clinical disease, the risk of adverse reactions, the opportunity for transmission of tubercle bacilli if disease is not prevented, patient motivation, and of course, availability of resources. Prophylactic isoniazid can be recommended for several categories of infected patients--contacts; persons with past untreated tuberculosis, or with fibrotic lesions on chest radiograph; persons with special concomitant clinical problems--in whom the risk of developing adverse reactions to isoniazid, present only while the drug is being taken, is smaller than the risk of developing tuberculosis, which lasts a lifetime.

Preventive therapy is contraindicated for persons with a history of isoniazid-associated hepatic injury or allergic reactions and with acute liver disease of any cause. Preventive therapy can be used, but with caution, in persons who are pregnant, who regularly consume alcohol, who have chronic active liver disease, or who are taking any other medications with which isoniazid may interact. The presence of progressive, overt, clinical tuberculosis must always be ruled out before prescribing prophylactic isoniazid, since such disease is an indication for multiple-drug therapy.

Adverse reactions are uncommon among healthy persons receiving isoniazid for treatment of tuberculous infection. Those that do occur tend to appear more frequently with increasing age. Pyridoxine (vitamin B6) can be used to prevent or treat the uncommon peripheral neuropathy. Progressive liver damage, rarely observed in children, may occur in 1 to 2 percent of persons over age 35. Liver injury can occur at any time during treatment and is an absolute indication to stop the drug, in which case the reaction is generally reversible; if isoniazid is continued in the face of symptoms, hepatic damage can be fatal.

Experience has shown that isoniazid resistance is not often a problem when preventive treatment fails and disease subsequently develops. Because of the low frequency of isoniazid-resistant mutants in small bacterial populations, this finding is not unexpected. Furthermore, most failures of preventive treatment are probably the result of failure to take the drug, so that selection of resistant mutants is not an important factor.

Special considerations for a preventive treatment program concern duration of treatment and policies for treating tuberculin-negative contacts (who may be in the earliest stage of infection), contacts of isoniazid-resistant cases, and persons who cannot tolerate isoniazid.

#### FEASIBILITY

The WHO Expert Committee on Tuberculosis, in its Ninth Report (1974), considered that "preventive treatment was not suitable for mass application in a community health programme." The Committee did not rule out more selective use of preventive treatment although they wisely stated that "a policy of preventive treatment..... is irrational, even for special risk groups, unless the treatment programme for patients suffering from infectious tuberculosis is widespread and well organized, and achieves a high rate of cure."

If preventive treatment has a role to play in tuberculosis control, it is primarily in more affluent, low prevalence countries. Such countries should be able to allocate resources to a preventive treatment program, if they wish, without compromising their ability to provide curative treatment for virtually all tuberculosis cases.

Nevertheless, the use of preventive treatment is not widespread in most such countries, largely because of fears of drug toxicity and questions concerning its practicality. The infrequent toxicity, the inconvenience, the possible stigma, and the lack of motivation for an apparently healthy person to accept long-term medication pose obstacles to a preventive

treatment program but do not make the program impossible. The attitudes of health care providers may be as significant as those of patients in determining success or failure in implementing a preventive treatment program. Experience in the United States and in Eastern Europe has demonstrated that individuals can be persuaded to take preventive treatment.

Unfortunately, preventive treatment is an imprecise technique. Because there is no way to identify those infected persons in whom tuberculosis will eventually develop, many individuals will be treated unnecessarily. Even among selected high-risk groups, only a fraction of the infected individuals in the group will ever develop disease, with or without preventive treatment. Nevertheless, it may be justified at least to offer to infected individuals in high-risk groups, as a personal health measure, the opportunity to prevent the development of tuberculosis. The individual should be informed of the short-term risks of taking isoniazid and of the lifetime risk of tuberculosis, and be allowed to make a choice. Such an approach may be preferable to the not uncommon practice of "following" such persons, usually with serial radiographs. Followup is inconvenient, consumes resources, has no definite end point, gives radiation exposure, and does not prevent tuberculosis.

A preventive treatment program appears difficult to justify in terms of public health benefits because the impact of such a program may be virtually imperceptible. It is a practical impossibility to identify and preventively treat all infected persons in a country's population, or even to identify and treat all infected persons in high-risk groups. Even if it were possible, it would be difficult to demonstrate much immediate public health impact. Silicosis, for example is a high-risk condition for development of tuberculosis, but the total number of silicotics in a country is relatively small so that even if they could all be identified and treated, there would be very little effect on subsequent tuberculosis morbidity. In certain localities, however, such as mining communities, treatment of silicotics as a group could possibly have a significant effect on local tuberculosis morbidity.

Since only a small fraction of individuals in the reservoir of infected persons will develop tuberculosis in any given year, and since only a fraction of the infected population will have received preventive treatment, there is a high probability that a preventive treatment program will have missed a person whose disease may develop soon. Thus, no immediate impact of the program on morbidity will be evident.

However, there may be long-term impact, especially if preventive treatment is directed to the young infected population. With time, older infected individuals will die, most without ever developing tuberculosis. If they are not replaced by newly infected individuals, the size of the infected reservoir will diminish. This is the situation in countries where the risks of exposure, transmission, and infection are low; older persons are leaving the infected reservoir at a faster rate than younger persons are entering it. If a preventive therapy program directed at younger persons has been operating, there will be a cumulative increase in the number as well as the proportion of preventively treated persons in the shrinking reservoir. Since the benefit of preventive treatment may persist indefinitely, treatment of the young is a long-term investment in the prevention of tuberculosis morbidity. Fortunately, isoniazid-associated hepatitis and other adverse effects of isoniazid are uncommon in the young, so drug toxicity should not be an obstacle to this strategy.

The group in which preventive treatment is likely to have the greatest impact is contacts, i.e., individuals who have a high probability of being recently infected. In this group, there should be an immediate personal health benefit because of the high risk of early development of disease in newly infected persons. However, disease in newly infected contacts is not usually of an infectious type and such cases may comprise only a small fraction of total cases, especially in low prevalence countries; therefore, the magnitude of any immediate public health benefit will be small. On the other hand, all future tuberculosis cases will arise among persons who were past contacts, so preventive treatment of contacts can be expected to have a long-term public health benefit. Prevention of these late developing cases will have an effect on transmission as well as morbidity, because such cases are more likely to be of the infectious pulmonary type. Since contact examination is often a component of tuberculosis control programs anyway, and since both cases of disease and infected persons will be found among contacts, it should be possible to treat families or households as a unit.

Although it is the conventional wisdom that preventive treatment has no role in high prevalence or developing countries, a limited role might be explored. Certainly, a preventive treatment program would have a low priority in such a country's overall tuberculosis control strategy. Nevertheless, it might be considered, if only for infected, young, close contacts of infectious cases. Determining who has been infected with M. tuberculosis may be difficult where nontuberculous mycobacteria are prevalent or where BCG vaccination has been given, but reaction size to a 5TU dose of tuberculin can be used as a criterion for treatment. Absence of a BCG scar, or failure to elicit a history of BCG vaccination, or both, would increase the likelihood of a reaction being the result of M. tuberculosis infection. There are now some countries in the World which have a high prevalence of tuberculosis and are developing, but which are also relatively affluent; limited preventive treatment might be tried in such places.

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