RECENT PROGRESS IN TUBERCULOSIS CHEMOTHERAPY APPLICABLE TO PUBLIC HEALTH PROGRAMS[1]

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Many types of chemotherapy are effective against tuberculosis, but relatively few make efficient use of limited resources. This article discusses the advantages of intermittent regimens, multiphase treatments, and new drug combinations in this light, and recommends specific regimens for use in Latin American nations.

Introduction

In spite of measures developed to control tuberculosis, the disease continues to have a disquietingly large incidence in Latin America, which has led many to question the possibility of bringing it under control. Despite under-registration of vital and health statistics, the estimated annual figures for 1968-1969 show 68,000 deaths from tuberculosis and 180,000 new cases among a total population of roughly 265 million in Latin America and the Caribbean (*1*). This large yearly crop of new cases, added to the number already built up as a result of ineffective programs, produces a "snowball" effect which defies the operating capacity of the health services involved.

The methods for reducing transmission of the tuberculosis bacillus–the only way of producing an impact on the epidemiolgy of the disease–are effective, and fortunately do not offer a wide range of alternatives that would make it difficult to choose among them. They are essentially limited to BGG vaccination for protecting susceptible persons and chemotherapy for interrupting transmission of the bacillus.

Treatment of infectious cases not only reduces the reservoir of infection; it also alleviates the suffering of the sick and satisfies a deeply-felt social need. Thus the urgency of this priority activity should not be underestimated, nor should its execution be postponed.

The effectiveness of chemotherapy (which is capable of yielding successful results in up to 100 per cent of the cases treated) has led to substantial revision of tuberculosis control methods and procedures. In the process, the tuberculosis problem has been transformed from a complex socio-medical matter into a public health administration problem which can be solved even in conditions of underdevelopment.

These facts, although encouraging, lend added urgency to the mission of those responsible for health administration, since negligence or failure to adhere to the principles involved in modern tuberculosis control theory are translated into deaths and cases that might have been prevented.

Principles of Tuberculosis Chemotherapy

The principles of tuberculosis chemotherapy were defined as a result of controlled experiments, carried out first in England and the United States and later in specialized centers in other areas such as India, Africa, and Japan. A large number of factors were investigated with the aim of determining the action of drugs by establishing comparisons based on variations in length of treatment, number of drugs used,

[1] Paper presented at the II Regional Seminar on Tuberculosis held in Bogotá, Colombia, on 6-10 November 1972. Also appearing in Spanish in *Boletín de la Oficina Sanitaria Panamericana.*

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frequency, and dosage. Most tests used criteria based on random grouping of participating patients, which "results in the formation of groups that can be expected to be similar in all respects," so that "intergroup variations in the results obtained with the different regimens are likely to be due to differences in the regimens themselves and not to differences in the characteristics of the groups of patients under treatment." (*2*)

Analysis of the results—negative bacteriologic findings, reduced frequency of mycobacterial resistance, reduction of the rate of reactivations—showed the advantages of prolonged treatment over short-term treatment, of several drugs versus a single drug, and of the continuous use of drugs as compared to the intermittent regimens that prevailed at the time. On the basis of these observations, which identified the two most relevant factors involved in the success of chemotherapy (the size of the bacterial population and the emergence of resistance to drugs), the principles of tuberculosis chemotherapy were defined in terms of prolonged, combined, and continuous treatment.

The intense search for ideal treatment regimens which could offer 100 per cent success, low toxicity, ease of operation, and low cost eventually prompted investigation of new variables that might offer solutions appropriate for public health action in underdeveloped countries. These investigations showed that as good results could be obtained from ambulatory treatment as from treatment in sanatoria; that the use of a third drug in the initial phase was beneficial; that intermittent treatment with two drugs was effective; that PAS[3] could be replaced by thioacetazone (T); and finally, that intensive chemotherapy applied over a short period of time (the results of which are now beginning to be known) opened up a bright prospect for the future.

Despite these advances, the validity of the classical principles of tuberculosis chemotherapy should not be called into question, nor should their widespread and accepted use be downgraded. These rules are still valid. What has changed is the connotation of each concept. "Prolonged" has come to mean at least one year, although tomorrow it may mean six months; "combined" refers to the association of drugs in particular phases of treatment, not necessarily throughout the treatment; "continuous" does not necessarily imply daily use of a drug, but only its regular use at the frequency recommended for the regimen prescribed.

Standard Regimens of Proven Efficacy

Regimens with an Intensive Initial Phase

Early experiments with chemotherapy supported the idea that using a combination of drugs increased the effectiveness of treatment, producing a higher rate of bacteriologic conversion and reducing the tendency toward mycobacterial resistance. The 1950 report of the British Medical Research Council (*3*) is clear on this point. Despite discovery of a third drug, isoniazid (INH), in 1952, two-drug regimens were still preferred by most health services and continued to be a subject for research. Combinations of isoniazid-streptomycin (SM), and INH-PAS were tried in the United States, (*4*) England, (*5*) and Madras, (*6, 7*) with favorable results.

Two-phase treatment was later proposed by Russel *et al.* (*8*) and Kass *et al.* (*9*). Canetti (*10*) recommended it on the basis of research on experimental tuberculosis at the Pasteur Institute in Paris. Justification of an initial intensive phase of treatment with three drugs depends on the size of the bacterial population, the selection of resistant mutants, and the prevalence of cases with primary resistance to the drugs involved.

In patients with large bacterial populations, such as those found when a bacilloscopy is positive, the number of resistant bacilli is very large. In such cases the use of several drugs in the initial phase reduces the risk of selective

[3]Para-amino salicylic acid. Other abbreviations used in this article:

INH—isoniazid	RAMP—rifampicin
SM—streptomycin	EMB—ethambutol
T—thioacetazone	PZ—pyrazinamide

survival of resistant bacilli and speeds up reduction of the whole bacterial population.

The British Medical Research Council (*11*) demonstrated the advantages of a third drug in the initial phase of chemotherapy by comparing the dual INH-PAS regimen with initial administration of three drugs (SM-INH-PAS) followed up with INH-PAS. The first regimen achieved favorable results in 84 per cent of the cases and the second in 97 per cent.

A 1964 experiment of the International Union Against Tuberculosis that was designed to investigate the causes of chemotherapy failures (*12*) utilized an initial three-drug regimen (SM-INH-PAS) for 28 weeks, followed by INH-PAS. This produced negative bacteriologic results in 99.3 per cent of those patients who continued the prescribed treatment for 52 weeks and whose infections had shown previous sensitivity to the drugs used.

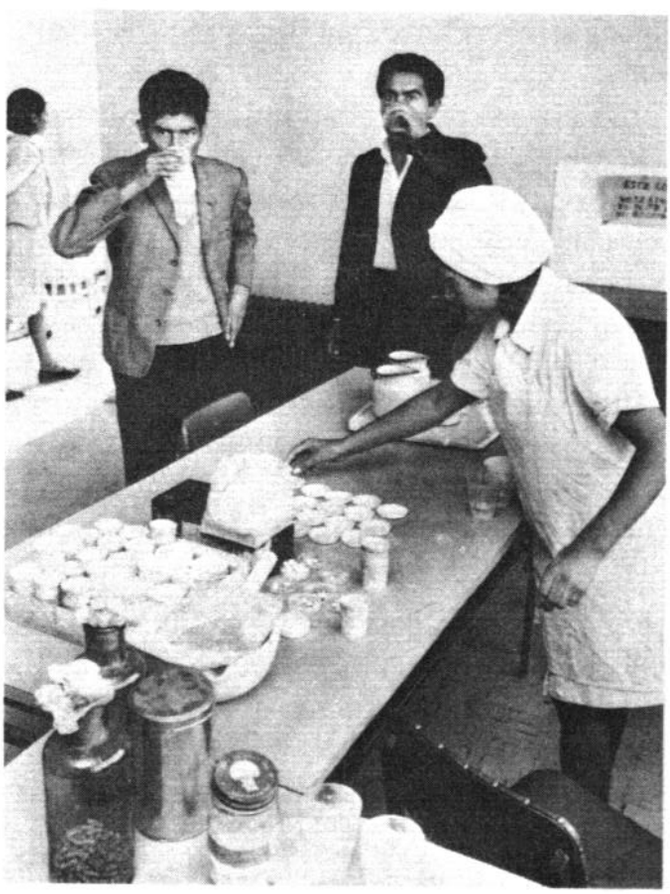
A simplified version of this initial triple regimen was described by Fraga (*13*), who in 1965 began to administer SM-INH-PAS for the first three months of treatment, INH-PAS for the next three months, and isoniazid alone for the last six months. An evaluation of 785 patients who completed the 12-month course of chemotherapy showed that 94.7 per cent were bacteriologically negative.

The advantages of using a third drug in the initial phase of treatment having been shown, an attempt was made to find an ideal duration for initial streptomycin use in terms of operational convenience, toxicity, and cost.

An experiment of the East African Tuberculosis Investigation Center and the British Medical Research Council (*14*) used an initial three-drug regimen of SM-INH-T followed by INH-T, in which streptomycin was administered for two, four, or eight weeks. The results showed that 90 per cent of the patients receiving streptomycin for two weeks became bacteriologically negative, as did 94 per cent of those receiving it for four weeks and 97 per cent of those receiving it for eight weeks. A control experiment in which INH-T without streptomycin was used in the initial phase produced negative bacteriologic results in 87 per cent of the cases. It is important to mention that the results obtained with supplementary use of streptomycin were strictly dependent on uninterrupted use of isoniazid and thioacetazone during the entire period of treatment. Since thioacetazone is a purely bacteriostatic drug, bacterial multiplication sets in as soon as its use is discontinued and its concentration in the patient drops to a sub-bacteriostatic level (*15*).

Intermittent Regimens

The most important factor in the success or failure of chemotherapy is the patient's cooperation in taking the prescribed drugs regularly over a period of many months. Daily self-administered treatment over a long period induces a feeling of monotony which, in association with the gradual disappearance of symptoms, encourages irregularity. Observations in which chemical tests were used to assess the patient's adherence to the prescribed



Fully supervised ambulatory drug administration, such as that being provided at this center, helps guard against treatment failure.

use of drugs showed a considerable percentage of failures (*16*). In contrast, intermittent treatment meets the requirement of being completely supervised. That is, it offers assurance that the drugs have been properly administered.

Since the beginnings of chemotherapy, researchers have been aware of intermittent treatment regimens—such as those studied in the United States during the 1950's (*17*) in which isoniazid was administered daily and streptomycin twice a week. The results were comparable to those obtained by using both of these drugs daily. However, British experiments of that period (*5*) showed better results with a daily regimen of SM-INH.

The fact was that intermittent treatment lacked a scientific foundation to explain the results being obtained in man. Experimental research at the Pasteur Institute of Paris (*18, 19*) and by Dickinson and Mitchison (*15, 20, 21*) in England have since provided such a foundation for intermittent regimens. The question was investigated by exposing bacteria *in vitro* to the action of a drug for varying lengths of time and then removing the drug by filtration at the end of each period. This allowed the size of the bacterial population to be determined at given intervals in a drug-free medium.

The results showed that there is a lag period during which the bacilli are latent and have not yet resumed the process of multiplication. This lag period varies with the drug used, its concentration, and the length of exposure. These investigations also demonstrated that thioacetazone and thiocarlide are purely bacteriostatic drugs, which is to say that as soon as they are withdrawn from the culture medium the germs begin to multiply with no intervening lag period. The other drugs tested—isoniazid, ethionamide, cycloserine, ethambutol (EMB), pyrazinamide (PZ), streptomycin, and rifampicin (RAMP)—are bactericides; the lag period varies with the drug and the length of exposure. The results achieved suggest that in determining the structure of intermittent regimens, the limits are conditioned by the lag period on one hand and by toxicity (which determines the size of the dose) on the other.

Three controlled experiments carried out at different times by the Tuberculosis Chemotherapy Center at Madras, India, demonstrated the efficacy and feasibility of the intermittent regimens. The first (*22*) showed that totally supervised treatment with 1.0 g SM and 12.5 to 16.1 mg/kg INH administered together twice a week was as effective as a treatment with INH-PAS administered daily in two doses. Favorable results were achieved in 94 per cent of the cases with the intermittent treatment and in 84 per cent with the daily one.

In the second experiment (*23*) four intermittent drug regimens were studied. Three were the following weekly regimens: 0.75 to 1.0g SM and 750mg INH; 0.75 to 1.0g SM, 750mg INH, 4g PZ; and 0.75 to 1.0g SM and 400mg INH daily for four weeks, followed by 0.75 to 1.0g SM and 750mg INH once a week. A comparison of all patients taking these weekly regimens with others taking a biweekly regimen (0.75 to 1.0g SM and 750mg INH) showed that weekly administration led to an overall favorable result in 72 per cent of the cases as against 90 per cent in the group receiving drugs twice a week. Those who received drugs once a week also showed differences with respect to the rate of isoniazid inactivation, with 82 per cent of the slow inactivators and 60 per cent of the rapid ones becoming bacteriologically negative.

In the third experiment (*24*) biweekly administration of oral drugs (400 to 750mg INH and 7.5 to 10.5g PAS) was compared with a daily regimen (150 to 200 mg INH and 7.5 to 10.5g PAS); both were preceded by an initial intensive two-week phase in which three drugs (1g SM, 400 mg INH, 6g PAS) were given. The intermittent regimen yielded better results in terms of toxicity, and the bacteriologic results were similar: 88 per cent negative results in the case of intermittent treatment and 87 per cent in that of daily treatment.

These findings indicate that intermittent regimens can be highly effective. Since they are also cheaper, less toxic, and subject to total supervision, their use in public health programs should be given priority.

Causes of Failure

Observations of chemotherapeutic trials indicate that the chief causes of failure are premature interruption of treatment, irregular or inadequate use of drugs, prescription of inadequate or incorrect regimens, primary resistance, and toxicity. Of these, only the last can be attributed directly to the drugs involved; and the possibility of substituting another of the many drugs available renders this cause less important. Generally speaking, it may be said that factors responsible for failure of drug therapy can be neutralized by maintaining well-organized treatment. The failures should not be ascribed to the drugs but to their incorrect use.

Primary Resistance and Pre-Treatment Sensitivity Tests

The following statement appears in the introduction to a 1963 issue of the WHO *Bulletin:* "To assure the efficacy of chemotherapy, the infecting organisms from all newly diagnosed patients with active tuberculosis must be tested for sensitivity to the specific drugs before treatment is begun." (*25*).

This concept, which dates from the earliest experiments with chemotherapy, gained increasing acceptance as more knowledge of the prevalence of primary resistance was obtained. As a result of its acceptance, however, a large number of laboratories that had been performing culture tests began doing sensitivity tests before the method was brought to an adequate technical level. The consequences of this are well known: results that were unreliable because of technical deficiencies caused loss of confidence in both the method and the laboratories, and led to general disorientation regarding drug therapy.

It was later recognized that sensitivity tests require a degree of technical refinement found only in laboratories of very high technical competence. In a study made in the reference laboratory of Cardiff, Great Britain, samples classified as resistant by local laboratories were examined. Patients initially diagnosed as resistant included 82 reported resistant to streptomycin, 66 reported resistant to PAS, and 86 reported resistant to isoniazid. Subsequent investigation revealed that 50 per cent, 42 per cent, and 27 per cent of these patients, respectively, had infections that were actually sensitive to the drug in question (*26*).

In 1964 Poppe de Figueiredo (*27*), confronting the impossibility of performing routine sensitivity tests on all new cases, proposed establishing a predictive classification, based on a careful treatment history, in which patients were divided into the following categories: little or no treatment (cases not treated at all or treated for periods of up to 30 days); probably sensitive (patients treated correctly for more than one month and generally for no more than three months); and chronic cases (positive cases with a history of months or years of insufficient drug therapy). This practice, in addition to providing an imaginative substitute for pre-treatment resistance tests, made it possible to define priorities for chemotherapeutic policy in Brazil.

In an investigation made by the International Union Against Tuberculosis (*12*) which assessed the effectiveness of standard chemotherapy in 651 patients, primary resistance was diagnosed in 70 cases (10.8 per cent), of which 55 showed resistance to one drug, 14 to two drugs, and one to all three drugs. Standard drug treatment yielded a favorable bacteriologic reaction in a substantial number of these cases.

This matter was the subject of a later investigation by the Hong Kong Tuberculosis Treatment Service and the British Medical Research Council (*28, 29*), in which the role of pre-treatment sensitivity tests was examined. A total of 566 cases in which bacterial sensitivity had been demonstrated were divided into three groups and subjected to different forms of treatment, as follows:

Group A: 187 cases (18 per cent of which were resistant to one drug, 10 per cent to two drugs, and 5 per cent to three) were treated with SM-INH-PAS/INH-PAS, regardless of the results of the pre-treatment sensitivity test.

Group B: 192 cases (15 per cent of which were resistant to one drug, 5 per cent to two drugs, and 5 per cent to three) had their SM-INH-PAS/INH-PAS treatments modified according to the results of indirect sensitivity tests.

Group C: 187 cases (20 per cent of which were resistant to one drug, 5 per cent to two drugs, and 9 per cent to three) were treated with three selected drugs to which their bacilli were sensitive, as revealed by rapid slide cultures.

The findings a year after treatment showed favorable results for 89 per cent of Group A, 92 per cent of Group B, and 94 per cent of Group C. Out of the 394 members of the three groups who had shown sensitive bacilli and were treated with SM-INH-PAS, 95 per cent had become bacteriologically negative; this represented a failure rate of 5 per cent.

The information cited here enabled Mitchison (*29*) to estimate the role of primary resistance in chemotherapy failure. He found that with a 4 per cent rate of primary resistance, the failure rate was 0.7 per cent; with resistance at 10 per cent, the failure rate was 1.7 per cent; and with resistance at 30 per cent, the failure rate was 5.1 per cent. These findings prompted Fox (*30*), in ranking the factors responsible for unfavorable results of chemotherapy, to put primary resistance at the bottom of the list.

The New Drugs and Re-Treatment

During the period in which the standard treatment drugs were being tested, many other anti-mycobacterial drugs were discovered. Some of them, such as thioacetazone, viomycin, and pyrazinamide, were found concurrently with the three major drugs. Others were found later, including ethionamide, cycloserine, kanamycin, and more recently ethambutol and rifampicin. Drugs originally considered second-line, minor, or subsidiary treatment agents (with the connotation of being less effective, more toxic, and more expensive than first-line drugs) are not necessarily still regarded that way. The advent of ethambutol and rifampicin changed the prevailing opinion as to the efficacy and, to some extent, the toxicity of these drugs. However, all of them are still considered costly, with the exception of thioacetazone, which was never really considered a reserve drug but rather one that was put aside because of the success of isoniazid.

The success achieved with rifampicin and ethambutol, especially the former, suggests their use for initial treatment of tuberculosis—rifampicin in association with isoniazid and ethambutol to replace PAS. The RAMP-INH regimen is especially interesting because of the bacteriologic results it has achieved and its ease of administration.

Experimental work with rifampicin has shown it to be at least as active as isoniazid (*31*) and capable of sterilizing lesions (*32*), while prompting only a very small proportion of resistant mutants (1 in 10^8) (*33*). In addition, it reaches very high concentrations in the blood (10 to 60 times the minimum level needed to inhibit the disease) and remains above the minimum level for about three hours (*34*).

Clinical experiments reported by Nitti (*35*), Gyselen (*36*), Brouet (*37*) and Dubra (*38*), using rifampicin in association with isoniazid on a daily basis for initial treatment of tuberculosis, showed a bacteriologic conversion rate of 100 per cent for patients on whom evaluation was completed. Poppe de Figueiredo (*39*), who experimented with a short course of treatment using 600 mg RAMP, 500 mg INH, and 1,200 mg EMB, also obtained 100 per cent conversion. Investigations by Decroix *et al.* (*40*) yielded a conversion rate of 92 per cent, and those of Raleigh (*41*) attained a rate of 98 per cent.

Investigations by Dubra (*38*), utilizing a biweekly regimen of 600 mg RAMP and 15 mg/kg INH, and by Decroix *et al.* (*40*), using a biweekly regimen of 900 mg RAMP and 750 mg INH, yielded results similar to those obtained with daily use—100 per cent bacteriologic conversion.

In re-treatment, rifampicin is almost always associated with ethambutol. Intermittent administration of this combination has yielded

100 per cent bacteriologic conversion, with or without an initial daily phase (*40, 42*), and 96 per cent conversion in another instance where a daily regimen was used (*43*). These results in man confirm levels of efficacy revealed by experimental research. However, there are some conflicting findings regarding the nature and frequency of toxic reactions.

Many reports on the use of rifampicin state that daily administration of this drug in doses of 450-600mg is not accompanied by signs of toxicity or intolerance (*35, 36, 41*). On the other hand, some investigations indicate that in addition to side-effects of lesser importance, cases of jaundice may occur–mainly in alcoholics (*37, 44, 45*).

Also, some reports on intermittent treatment refer to toxic reactions of an immunologic type that can sometimes be extremely serious (*46, 47*). In 1970 Farga (*48*) described a fatal case of thrombocytopenia associated with the intermittent use of rifampicin. Kreis *et al.* (*49*), comparing one group given a daily regimen with another given an intermittent regimen, observed the onset of 12 cases of jaundice in the former group and one in the latter, confirming earlier reports that jaundice was most frequent when rifampicin was administered daily.

Poole *et al.* (*46*), using an intermittent regimen with a daily initial phase, reported that no serious problems were encountered in the initial phase, but that treatment had to be discontinued for 22 per cent of the cases in the intermittent phase, during which one case with renal insufficiency and three with thrombocytopenia were observed. In 16 of the 49 patients (33 per cent) antirifampicin antibodies were detected in the blood, and a significant relationship was noted between toxic manifestations and the presence of antibodies.

Fraga *at al.* (*50*) found that a biweekly intermittent regimen for re-treatment (1,200mg RAMP and 50mg/kg EMB) achieved bacteriologically negative results in 93.5 per cent of 90 cases treated, and involved only one case of toxicity leading to interruption of treatment. This latter was a case of hemolytic anemia in which antirifampicin antibodies were present.

Verbist *et al.* (*51*) used 1,800 mg of rifampicin in association with ethambutol once a week for primary drug treatment and also for re-treatment, attaining negative bacteriologic results of 100 and 94 per cent, respectively. There were no cases in which toxicity caused treatment to be discontinued.

Ethambutol has also been studied as a substitute for PAS in primary drug treatment. Huggin (*52*) compared SM-INH-PAS with SM-INH-EMB and found the latter to be superior in terms of tolerance and efficacy. Pilheu (*53*) obtained a bacteriologic conversion rate of 97.3 per cent without toxic side-effects in initial treatment with INH-EMB.

Citron (*54*) reports that ethambutol is probably not as effective as PAS in treating advanced cavitary forms, and that toxicity depends on the dose administered–occurring very rarely at 15 mg per kg of body weight but reaching incidence rates as high as 15 per cent, usually after the first six months, if the dosage is raised to 25 mg/kg.

These conflicting findings show that much is still to be learned about the metabolism and action mechanisms of these two drugs. The lengthy period of clinical and laboratory observation required for their use, in addition to their high cost, makes it impractical for developing countries to employ them in public health programs, even for re-treatment of tuberculosis. The same holds true for treatments which are effective but highly toxic and expensive, such as the ethionamide-pyrazinamide-cycloserine combination.

The alternative for re-treatment in countries with limited means has been shown by observations indicating that streptomycin resistance does not occur when the drug is used as an initial supplement to INH-T in primary treatment of patients with isoniazid-sensitive infections (*55*).

This finding has led to use of a SM-PAS combination in areas where thioacetazone has replaced PAS in standard regimens, and to use of another reserve drug–pyrazinamide–for re-

treatment of the disease. This regimen (SM-PAS-PZ) is relatively inexpensive, involves tolerable toxicity levels, and has produced favorable bacteriologic results in 94 per cent of the cases treated. Its success has probably been due to the fact that streptomycin is active against bacteria in a neutral or alkaline medium, while pyrazinamide is active in an acid medium (*21*).

Tuberculosis Chemotherapy in the Health Programs of Developing Countries

The discovery of drugs for treating tuberculosis gave public health authorities a control method with the essential characteristics needed for large-scale use: a high degree of efficacy, ease of operation, and low cost. Thus it became feasible to make regular use of chemotherapy in general health services, so that all the benefits could be made available to each patient in his own area of residence.

Selection of a strategy for extending the benefits to the greatest number of persons presented no problem, after it was shown that home treatment was as effective as hospital treatment (*56*). Once the supposed advantages of treatment in an institution were found to be a myth, ambulatory treatment became the ideal policy for controlling tuberculosis and the only adequate one for developing countries. In short, tuberculosis has been shown to be a disease that can be treated at home. The limited number of beds needed for acute cases, complications, and emergencies should be located in general hospitals.

Standardization of Treatment Regimens

Standardization of treatment regimens for the nation or local health region is a basic measure which makes a program more operative, promotes the use of a regimen whose efficacy has been proved, and helps to bring expenses more into line with budgetary resources. From among the many regimens provided by controlled experiments in drug treatment, a choice should be made of those which, in terms of efficacy, convenience, acceptability, low toxicity, and low cost, are best suited to conditions in the area where they are to be applied.

Highly Effective Low-Cost Regimens

The most widely used standard regimens are the combinations SM-INH-PAS, SM-INH, and INH-PAS. Of the three drugs involved, PAS is the least active, most expensive, least tolerated, and most likely to be rejected by the patient. Using thioacetazone as a replacement for PAS offers the advantage, among others, of considerably reducing the cost of standard drug treatment.

Thioacetazone is a thiosemicarbazone derivative whose anti-tubercular activity was first taken into account around 1950. Later, as a result of its toxic effects and the spectacular success of isoniazid, it was practically forgotten. References to post-1950 use of thioacetazone, however, can be found in Latin American literature, notably in the reports of Vargas Machuca, (*57*) Larocea *et al.*, (*58*) Orrego Puelma *et al.*, (*59*) and Gómez *et al.* (*60*).

With the advent of isoniazid, Silveira *et al.* (*61, 62, 63*), who had been working with thiosemicarbazone, experimented with INH-T. Based on 95.6 per cent favorable results in children and 74.2 per cent in adults, routine use of this combination was proposed. The same combination has been employed by Purriel and Muras, (*64*) Feldman, (*65*) and Schiffrin *et al.* (*66*).

At the present time thioacetazone is being used in place of PAS by many Latin American countries, including Bolivia, Chile, Colombia, the Dominican Republic, Ecuador, Haiti, Paraguay, and Peru. The incidence of adverse reactions has been comparable to that obtained with PAS, and there has been no reduction in efficacy.

In Lima, Mayuri *et al.* (*67*) used two regimens of SM-INH-T, one with daily streptomycin and the other with biweekly streptomycin, obtaining favorable results in 94 and 93 per cent of the cases, respectively. Toxicity

caused the treatment to be changed in 4.1 per cent of the former cases and none of the latter.

The first controlled experiments on the performance of thioacetazone as a substitute for PAS were sponsored by the East African Tuberculosis Investigation Center and the British Medical Research Council. The results of this research were published in 1963 (*68*). The most effective combination was 300mg INH and 150mg T, which produced negative bacteriological results in 83 per cent of the cases. In 1966 it was reported that a treatment regimen using 300mg INH and 150mg T had been compared with another in which 1.0 g of streptomycin was added daily during the first two months. With the latter regimen the percentage of bacteriologically negative results increased significantly, from 79 to 90 per cent (*69*).

Subsequent research showed that increasing the period of streptomycin administration from two to four weeks and then to eight weeks, while continuing the treatment for 18 months, yielded bacteriologically negative rates of 87, 93, and 97 per cent, respectively (*70*). Another experiment indicated that no increase in efficacy was attained by increasing the dosage of isoniazid from 300 mg to 450 mg (*71*).

In India a comparison of PAS-INH with 300 mg INH plus 150 mg T showed the efficacy of both to be similar (*72*). An investigation by the International Union Against Tuberculosis (*73*), conducted in seven developing countries where thioacetazone had replaced PAS, indicated that results there were comparable to those obtained from regimens using PAS. It also indicated that daily administration of 1 g streptomycin over a four-week period during the initial phase improved the results of the unsupervised INH-T regimen.

All these results indicate that in terms of efficacy thioacetazone is a suitable companion to isoniazid in standard regimens. The conflict arises with respect to the incidence of toxic reactions. Results from East Africa indicate low toxicity. Out of a total of 420 patients, adverse reaction to thioacetazone were observed in six (1.4 per cent) and to isoniazid in two (0.5 per cent). Adverse reactions to streptomycin were observed in 12 cases out of 211 (5.7 per cent) (*69*).

However, certain results from other areas contradict those observed in East Africa (*74*). Research in Hong Kong showed a high frequency of side-effects, especially cutaneous ones (notably in Chinese patients) (*75*). Antihistamines and Vitamin B complex did not succeed in preventing side-effects of thioacetazone (*76*) and raised the drug cost for a year of treatment from US$1.80 to US$7.60.

A second investigation, conducted by Miller (*77*) to study the frequency and geographic distribution of thioacetazone side-effects, showed that race was apparently not an important factor in explaining different effects observed in different countries. The conclusion is that differences in the frequency of thioacetazone regimen side-effects probably result from variations in supervision, recording and interpretation of reactions, and environmental factors–including prior use of other drugs or exposure to sensitizing substances.

Regimens Best-Suited for Public Health Programs in Latin America

Regimens based on use of first-line drugs have been shown to be effective, cheap, and capable of routine application by general health services. In the case of Latin America, an effort to obtain the maximum benefits from these drugs is imperative, in view of the high-quality results they can produce and the limited resources available for health activities in most Latin American communities. Though many physicians are fascinated by newer drugs, their use in Latin American public health programs is not recommended for initial treatment of tuberculosis. Rather, they should be reserved strictly for re-treatment of cases in which standard chemotherapy has failed.

Even so, re-treatment should only be planned when there are sufficient resources for treating all new cases. Under the conditions prevailing in most countries of the Region, it is obvious that every patient requiring treatment

with second-line drugs is a patient who lost the opportunity to be cured with standard drugs. This indicates organizational shortcomings and inability to get the patient's cooperation in taking the prescribed drugs regularly. It has rightly been said that the main problem in tuberculosis chemotherapy does not lie in discovering new regimens or introducing new drugs, but in being aware of how to make successful use of knowledge already gained (*78*).

In developing countries it seems improper to select a drug regimen costing 10 or 100 times what other equally effective regimens cost simply because the patient finds it more pleasant. A public health service should adhere to the principles of distributive justice; and in the particular case of tuberculosis this means meeting the obligation to extend control activities as far as possible—so that all infectious cases can be identified and offered the correct treatment, free of charge, in their own areas of residence. As Hitze (*79*) made clear, it is not enough simply to have effective, efficient, and sufficiently workable control measures at hand; these measures need to be applied in a system-

TABLE 1—A two-phase, intermittent, fully supervised regimen.

	Drug	Dosage	Duration of treatment (in weeks)	Total quantity of drugs required		
				SM	INH (100 mg tablets)	INH-T (300 mg INH plus 150 mg T in each tablet)
Phase I. Specified dosage administered six times a week.	SM	1 g	4-8 weeks	24-48 g		
	INH-T	1 tablet	4-8 weeks			24-48 INH-T tablets
Phase II. Specified dosage administered twice a week.	SM	1 g	44-48 weeks	88-96 g		
	INH	8 tablets	44-48 weeks		704-768 INH tablets	

Drugs needed to treat a case for one year: 120-136 g SM, 704-768 INH tablets, and 24-48 INH-T tablets.
Cost of drugs: from US$7.52 to US$8.57.

TABLE 2—A daily two-phase regimen supervised in the first phase.

	Drug	Dosage	Duration of treatment (in weeks)	Total quantity of drugs required	
				SM	INH-T (300 mg INH plus 150 mg T in each tablet)
Phase I. Specified dosage administered six times a week.	SM	1 g	4-8 weeks	24-48 g	
	INH-T	1 tablet			24-48 INH-T tablets
Phase II. Specified dosage self-administered daily.	INH-T	1 tablet	44-48 weeks		308-326 INH-T tablets

Drugs needed to treat a case for one year: 24-48 g SM, 350-356 INH-T tablets.
Cost of drugs: from US$2.95 to US$4.18.

atic, convenient, and coordinated fashion so as to avoid a waste of human energy, funds, facilities, and resources. The regimens shown in Tables 1 and 2, which are cheap and highly effective, are recommended above all others for standard use in Latin American countries.

The regimen in Table 1 is designed for patients who can come to the health services during the entire period of treatment, so that administration of the drug can be fully supervised. It should be given preference because of its good results.

The regimen in Table 2 is indicated for patients who cannot come to the health services during the entire period of treatment but who can do so during the first phase, at which time they can be given intensive instruction about the treatment. During the second phase the patients collect their drugs at intervals of 15 days.

SUMMARY

A historical review of tuberculosis chemotherapy shows how the basic concepts of prolonged, continuous, and combined drug treatment first evolved. Though still essentially valid today, these concepts have been modified somewhat since they were first formulated. For example, instead of treatment with one drug combination, current regimens often call for different combinations at different phases of treatment. Nor does the term "continuous" treatment necessarily imply daily treatment as it once did, as a result of the greatly increased use of regular but intermittent regimens.

The most important factor in the success or failure of tuberculosis chemotherapy is the patient's cooperation in taking prescribed drugs regularly for a period of many months. There are strong indications that a considerable percentage of failures is due to this problem, especially where daily self-administered regimens are involved. Intermittent biweekly regimens can be directly supervised by public health personnel and are therefore less likely to lead to failures of this type.

An important reason for the success of intermittent treatment is the existence of a lag period between the time bacteria stop being exposed to a bactericide and their resumption of multiplication. Many anti-tuberculosis drugs, including isoniazid (INH), streptomycin (SM), rifampicin, ethionamide, cycloserine, and pyrazinamide produce this sort of lag period.

Another possible cause of treatment failure is primary resistance of the infection to one or more of the drugs used. It has been found, however, that this is only an important factor in a very small percentage of cases. Also, patients can be classified as presumably sensitive, probably sensitive, or probably resistant on the basis of past medical history. Such classification eliminates the need for sensitivity tests in most cases.

Recent successes with the non-standard drugs rifampicin and ethambutol indicate that they can be effectively used for treating tuberculosis. However, their high cost, plus the long period of clinical and laboratory observation required for their use, makes it impractical for developing countries to use them in public health programs—either for initial treatment or re-treatment of the disease.

The most widely used standard regimens for initial treatment are combinations of SM-INH-PAS, SM-INH, and INH-PAS. Of the three drugs involved, PAS is the least active, most expensive, and most likely to be rejected by the patient. Extensive studies indicate that it can be effectively replaced by thioacetazone (T), and that the effectiveness of the INH-T combination can be markedly enhanced by administering streptomycin in the early stages of treatment.

Public health services in developing countries should meet the obligation of extending tuberculosis control as far as possible, in an effort to identify all infectious cases and offer correct and free treatment to all patients. Newer drugs, which are more expensive than the standard ones, should be strictly reserved for re-treatment of cases where standard chemotherapy has failed, and re-treatment should only be planned when there are sufficient resources for treating all cases.

Today effective, efficient, and workable control measures are available. Therefore, the urgent task in developing areas is to apply them in a systematic, convenient, and coordinated way that will make the best possible use of the limited available resources. Two regimens which the author believes are particularly well suited to these purposes are presented on page 43.

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TETANUS IN THE UNITED KINGDOM

Forty cases of tetanus were officially notified in the United Kingdom during 1972,[1] and laboratories reported culture of *Clostridium tetani* from nine patients. Five of the nine patients were women in whom *Cl. tetani* was cultured from a penetrating wound; in two instances the injury was acquired while gardening. The youngest of the women was 29 years of age. It is noteworthy that injuries acquired while gardening accounted for over half the isolations from females during the years 1966-1971. This observation is probably attributable to fewer industrial injuries occurring among females, so that gardening injuries formed a larger proportion of the total. Females in the older age-groups are also less likely to have been immunized against tetanus.

One of the reports for 1972 concerned a 13-year-old Indian boy who developed tetanus following a blow to the head. *Cl. tetani* was recovered from an ear swab, together with *Staphylococcus aureus.* The patient had previously suffered from infection of the middle ear. Such cases of otogenic tetanus are not commonly recognized in the United Kingdom, but in India they may represent as much as 20 per cent of the cases. Active immunization against tetanus is a sensible precaution for patients suffering from chronic otitis media.

Another case involved a male, 25 years of age, who developed an infected abdominal wound following bowel surgery; *Cl. tetani* was recovered from the wound. Although it is uncommon to recover the organism from such sites, it is worthwhile recalling that *Cl. tetani* may frequently be recovered from feces. Post-operative tetanus is rare in the United Kingdom and, when encountered, has a tendency to occur in small outbreaks, thus suggesting exogenous rather than endogenous infection as the cause. A similar pattern is evident in other countries.

Cl. tetani was also isolated from wounds on the hands and knees of a 54-year-old truck driver who developed tetanus after his truck fell into a river. It is possible that tetanus spores are regularly present in river water in the United Kingdom, since rivers are commonly subject to fecal contamination. Tetanus spores are, however, widely distributed and may have been introduced into this patient's wounds from his clothing or from dirt or earth in his skin. [*Weekly Epidemiological Record* of the World Health Organization, 48(11)125, March 1973.]

[1] Tetanus cases reported as of 1 December 1972.