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SHORT-TERM INTENSIVE INITIAL CHEMOTHERAPY FOR PULMONARY TUBERCULOSIS—PRELIMINARY REPORT

——Can the Duration of TB Treatment Be Even Shorter?——

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ABSTRACT

In order to investigate whether the duration of TB chemotherapy can be cut even shorter, a clinical trial of short term intensive chemotherapy has been carried out since May 1974 on 60 cases of newly diagnosed infectious moderately or far advanced pulmonary tuberculosis. The regimen consisted of daily INH, RMP, EMB and SM for 3 to 6 months until the target point was reached. It was followed by non-supervised INH monotherapy for one year (2nd phase treatment) for the sake of safety.

The results show:

1. The sputum conversion is extremely rapid, complete and permanent: 63.3%, 93.3%, 98.3% and 100% at 1, 2, 3 and 4 months, respectively, with no relapse up to date.
2. 65.5% and 94.8% cavity closure can be seen at 3 and 6 months, respectively. 75% or more of lesions absorption are achieved in 61.7% and 98.3% of cases at 3 and 6 months, respectively. Further chest X-ray improvements are usually the case during the early stage of the 2nd phase INH monotherapy. There has been no roentgenological relapse also.
3. Thus, intensive treatment could be discontinued in 61.7%, 71.7%, 76.7% and 93.3% of cases at 3, 4, 5 and 6 months. Four cases could not meet the target point at the end of 6 months' intensive treatment because of open negative cavities remained in 3 and multiple tuberculoma remained in 1. Yet the further improvements thereafter in chest X-ray findings during the INH monotherapy were likewise remarkable and TB bacilli never reappeared.
4. Culture from the resected tissue homogenate failed to prove tubercle bacilli in 2 cases after 3 months of intensive chemotherapy.

With this study we are inclined to believe that shortening of TB chemotherapy down to 3 months can be achieved by intensive treatment with daily INH, RMP, EMB and SM in average newly diagnosed cases. Furthermore, the intensive chemotherapy seems to have bacteriocidal effect and it remains to be seen whether the 2nd phase monotherapy is really necessary after the target point is met by the intensive treatment.

INTRODUCTION

Despite the discovery of effective antituberculous drugs, "long term administration" has been regarded as one of the main obstacles against the success of TB control especially in developing countries. With the discovery of RMP (Rifampicin), however, 6 months administration of INH (isoniazid), RMP and SM (Streptomycin) has been claimed as sufficient and satisfactory for the initial treatment cases. The curable rate is estimated as 96% and relapse rate as 2% within 18 months after discontinuation of the treatment[1].

The primary purpose of this study is to find out whether the duration of treatment can be cut even shorter, preferably 3 months, by combining the four most potent antituberculous drugs. A clinical trial of short term intensive chemotherapy has been carried out since May 1974 at the Provincial Tuberculosis Control

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Bureau in cooperation with the National Taiwan University Hospital on 60 consecutive cases of newly diagnosed moderately or far advanced active pulmonary tuberculosis and by now all are under observation after finishing the drug regimen. Although the overall result of the clinical trial has to wait a couple of years to clarify the relapse rate, the preliminary result up to now will be presented.

Materials and Methods

Our materials consist of 60 cases of moderately or far advanced pulmonary tuberculosis newly diagnosed at the National Taiwan University Hospital or at the Taipei Demonstration Center, Provincial TB Control Bureau. The background factors of them are shown in Table 1. There were 35 males and 25 females with average age of 26.8 ranging from 16 to 66. All were moderately or far advanced with cavities except 2 by NTA classification. By Oka's classification Types III or IV, that is pneumonic or infiltrative lesions with cavities consists 68.3% of cases. There were 3 cases of Type II with extensive disseminated lesions and 16 Type VII of mixed type. All were bacteriologically positive either by culture or both smear and culture before treatment. Among them, 14 or 23.3% were found to be primarily resistant to at least one of INH, SM and PAS (Para-aminosalicylic acid).

To compromise with the older concept that TB treatment has to be long term, the drug regimen adopted by us consisted of two phases as shown in Table 2. Intensive chemotherapy (the first phase) with daily INH, SM, EMB (Ethambutol) and RMP was given for 3 months. If the target point was reached that is, sputum converted, cavity closed and 75% of the lesions absorbed, it was followed by INH monotherapy or INH+EMB, in whom tubercle bacilli were found to be primarily resistant to INH, for another 12 months (the second phase). If the target point was not reached by the end of 3 months, intensive treatment was extended and evaluated on monthly basis for at most 3 months. If the target point was not reached by 6 months of intensive chemotherapy the treatment was tentatively regarded as "failure", but it was likewise discontinued and switched to monotherapy. The vast majority of cases were hospitalized during the intensive

Table 1. Background Factors of 60 Patients

Sex: Male 35 Female 25
Age: Average 26.8 years Range 16~66 years
Chest X-ray classification:
by NTA's { Mod. Adv. { With Cavity 25 / Without Cavity 1 ; Far Adv. { With Cavity 33 / Without Cavity 1 }
by Oka's IIb 3, IIIa 12, IIIb 4, IVa 25, VII 16
Bacteriology:
TB bacilli { Micro. (−) / Culture (+) 24 ; Micro. (+) / Culture (+) 36 }
Primary drug resistance 14 cases (23.3%)
(Resistance to INH or SM 9, INH+SM3, INH+SM+PAS 2)

Table 2. Drug and Study Regimen

Initial intensive phase (3~6 months)	Second phase (12 months)	Third phase (24 months)
INH 300 mg/day RMP 450 mg/day EMB 800~1,200 mg/day SM 0.75~1.0 g/day until target point*	INH only 300 mg/day or INH+EMB 800 mg/day (for INH primary resistant cases)	Observation for bacteriological and/or roentgenological relapse

* Target point : sputum, TBB converted, cavity closed, 75% lesions absorbed

chemotherapy but the second phase treatment was carried out on non-supervised ambulatory basis. All cases are to be followed up for 2 years after completion of the 2nd phase monotherapy (the third phase). The efficacy of treatment was evaluated by conversion of positive sputum, improvement of chest X-ray findings, namely cavity closure and absorption of lesions, and rate of relapse. Adverse effects during the intensive therapy were also carefully observed.

RESULTS

1. Sputum conversion

The conversion rate of TB bacilli in sputum is shown in Fig. 1, and 63.3%, 93.3%, 98.3% and 100% of cases were converted within 1, 2, 3 and 4 months, respectively, after intensive chemotherapy which is apparently superior to other regimens.

2. Bacteriological study on resected tissue

In 2 cases, the lesions were resected after 3 months of intensive treatment. Culture from the tissue homogenate failed to prove tubercle bacilli.

3. Improvement of chest X-ray findings during intensive chemothrapy

a. Cavity closure (Table 3)

Among 58 cavitary cases, 38 or 65.5% closed within 3 months, 44 or 75.9% within 4 months, 50 or 86.2% within 5 months and 55 or 94.8% within 6 months. The remaining 3 cases failed to close (open negative cavities) by the end of 6 months' intensive treatment. Bullae formation was seen replacing from localties where pneumonic or cavitary lesions existed in 8 or 13.3% of cases during the intensive chemotherapy. Four of them disappeared later during the second phase of treatment.

b. Absorption of lesions (Table 4)

As to absorption of lesions, 75% or more of shadows were absorbed within 3 months in 37 or 61.7% of cases, within 4 months in 43 or 71.7% of cases, within 5 months in 46 or 76.7% of cases and within 6 months in 59 or 98.3% of cases. In the remaining one case, the target point for the X-ray absorption was not reached by the end of 6

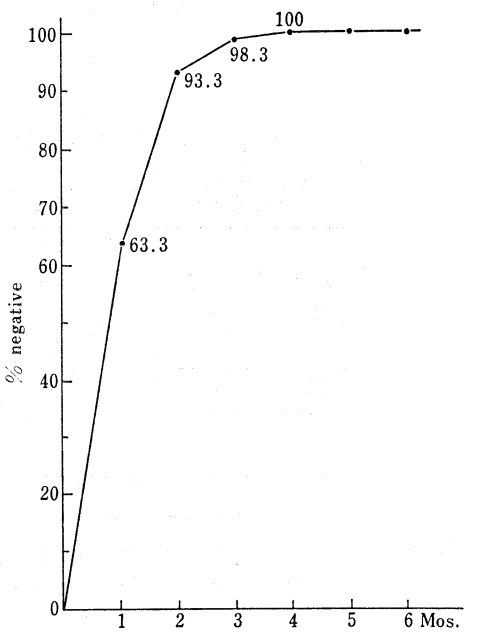

Fig. 1. Sputum conversion rate.

Table 3. Roentgenologic Improvement during the Intensive Treatment

Cavity closure:

X-ray / I.T.	Cavity closure	Open negative cavity	Bullae formation
3 months	38/58 (65.5%)	20	4
4	44/58 (75.9%)	14	5
5	50/58 (86.2%)	8	5
6	55/58 (94.8%)	3+	8

I.T.: Intensive treatment
+ : Failed to reach to target point

Table 4. Roentgenologic Improvement during Intensive Treatment
Absorption of lesions:

Duration of intensive treatment	Absorption of lesions (75% or more)	Tuberculoma formation (2cm or more)
3 months	37/60 (61.7%)	8×
4	43/60 (71.7%)	8
5	46/60 (76.7%)	8
6	59/60 (98.3%)	9*

× : 1 was resected to later
* : 1 failed to reach to target point

Table 5. Duration of Intensive Chemotherapy

	Target point reached in				Target point could not be reached in 6 mos. because of	
	3 M	3~4 M	4~5 M	5~6 M	Open nagatve cavity	Tuberculoma
No. (%)	37 (61.7%)	6 (10.0%)	3 (5.0%)	10 (16.7%)	3 (5.0%)	1 (1.7%)
	43 (71.7%)					
	46 (76.7%)					
	56 (93.3%)				4(6.7%)	

Table 6. Roentgenological Improvement during the Second Phase Treatment

Improvement observed during		Further absorption of lesions	Disappearance of bullae	Disappearance of open negative cavity
Second phase	0~3M	15	2	
	4~6	23	2	
	7~9	6	—	1
	10~12	2	—	1
No. of cases		60	8	3

months because multiple tuberculoma remained. Tuberculoma formation was seen in other 8 cases from cavities or extensive lesions during the intensive treatment.

4. Duration of intensive chemotherapy (Table 5)

The duration of intensive chemotherapy required for reaching to the target point in this series was therefore 3 months in 37 cases (61.7%), 4 months in 6 (10.0%), 5 months in 3 (5.0%) and 6 months in 10 (16.7%). The remaining 4 cases did not reach to the target point by the end of 6 months' intensive chemotherapy because of open negative cavities in 3 cases and multiple tuberculoma in 1. The factors likely to cause the extension of intensive treatment beyond 3 months will be discussed later.

5. Further improvement during the second phase treatment

Neither bacteriological nor roentgenological relapse has been observed in all cases during the 2nd phase of treatment. Instead, as shown in Table 6, further improvement of chest X-ray findings such as more absorption of lesions, disappearance of bullae or open negative cavity was observed in the majority of cases within 6 months after the discontinuation of intensive chemotherapy. Noteworthy to mention is that it was also true even in the 4 tentatively regarded as "failure" cases.

6. Side effects

Side effects observed during the intensive chemotherapy are shown in Table 7. Abnormal liver functions in 11 cases, transient leucopenia in 4, vertigo due to SM in 6, blurring of vision in 3, and skin

Table 7. Side Effects

Side effects	No. of cases
1. Abnormal changes in L.F.T.	11
Mild elevation GOT, GPT	10
Hyperbilirubinemia	1
2. Transient leukopenia	4
3. Vertigo	6
4. Blurring of vision	3
5. Skin rash	2

L.F.T. : Liver function tests

Table 8. Follow-up Period in the Third Phase

Follow-up	Number of patients
1～6 months	19
7～12	19
13～18	19
19～24	3

rash in 2. None had gastrointestinal distress and flu syndrome. None had discontinued intensive chemotherapy because of side effects except 2 in whom RMP was temporarily discontinued for a couple of weeks because of abnormal liver functions.

7. Follow up observation in the third phase of study

By now all 60 cases have finished the chemotherapy and under follow-up study for variable length of time ranging from 1 month to 20 months as shown in Table 8. So far neither bacteriological nor roentgenological relapse has been observed.

Some representative cases will be demonstrated in the following:

Case 1. LSS

A 19 year-old boy came to us with chief complaints of cough and fever for 3 weeks. Bilateral extensive pulmonary tuberculosis with cavity was found (Fig. 2a). Tubercle bacilli were found to be primarily resistant to SM. After intensive treatment, sputum converted in 1 month, chest X-ray lesions rapidly absorbed with bilateral bullae formation. Intensive treatment was terminated after 3 months. Chest X-ray findings at that time was shown in Fig. 2b. It was followed by INH alone for 12 months which was terminated in March 23, 1976. Further chest X-ray improvement was seen during the second phase of treatment. One of the recent chest X-ray was shown in Fig. 2c. Neither bacteriological nor roentgenological relapse up to now.

Case 2. WWS

A 19 year-old single girl came to us with chief complaints of cough, hemoptysis and fever for 2 weeks. Bilateral far advanced pulmonary tuberculosis with cavities was found (Fig. 3a). Tubercle bacilli were primarily resistant to SM. After intensive treatment, sputum converted in 1 month. Lesions markedly absorbed with big bulla formation within 3 months but it was considered that the case had not reached to the target point. Intensive treatment was extended for 2 more months until her chest X-ray findings looked as Fig. 3b and was followed by INH alone for 12 months until October 1975. Bulla disappeared during the 2nd phase treatment (Fig. 3c) and she has been enjoying married life thereafter without bacteriological and roentgenological relapse.

Case 3. LWF

This is a 20 year-old university student. He came to us with chief complaints of cough, hemoptysis and fever. Bilateral extensive pulmonary tuberculosis with cavities was found (Fig. 4a). Tubercle bacilli were sensitive to all drugs. After intensive treatment sputum converted in 2 months, but fever persisted for

more than 2 months with toxic symptoms. Transient worsening of chest X-ray lesions (Fig. 4b) after intensive chemotherapy was observed but they were absorbed later. Intensive treatment was terminated after 6 months when the chest X-ray was shown as Fig. 4c; a bulla remained in the left upper lung. It was then followed by INH alone for 12 months. Further improvement of chest X-ray findings was observed and no bacteriological relapse so far. The recent follow-up chest X-ray showed that the bulla was disappeared.

As mentioned before, among the 60 cases, 4 cases (6.7%) failed to reach to the target point by the end of 6 months' intensive treatment because of open negative cavity and/or tuberculoma. Intensive chemotherapy was likewise discontinued for these cases but follow-up study showed further improvement of chest X-ray findings and no bacteriological relapse has been observed in all these cases.

One of these 4 cases is presented as follows.

Case 4. HLC

This is a 19 year-old girl student. She came to us with cough, fever and hemoptysis. Pretreatment chest X-ray showed bilateral far advanced pulmonary tuberculosis with tuberculoma and cavities (Fig. 5a). Tubercle bacilli were sensitive to all drugs. After intensive treatment, sputum converted within 4 weeks. Chest X-ray findings after 3 months' intensive treatment could not reach to the target point. Even after 6 months' intensive treatment, some tuberculoma left behind and we thought it was a failure case (Fig. 5b). Intensive chemotherapy was likewise discontinued and followed by INH monotherapy. However, follow-up chest X-ray showed further improvement of considerable degree and recent follow-up chest X-ray is illustrated as Fig. 5c when the monotherapy was terminated.

Discussion

It has been well documented for more than 20 years that any triple drugs chemotherapy including INH +SM for one year would obtain more than 95% sputum conversion and relapse rate of around 5% for the initial treatment of pulmonary tuberculosis provided the treatment is well supervised. It is not the case, however, when they are applied in the field as an ambulatory treatment. In Taiwan, a free drug regimen of 24 months duration consisting of INH, SM and Thiacetazone in the first 12 months followed by INH alone for another 12 months, was given to registered infectious cases in the past 10 years. According to the report of the Provincial TB Control Bureau, the overall results were far from satisfactory; the sputum conversion rate after 1 year was 70.5% in 1970 and 67.5% in 1971, the chest X-ray study showed 44.1% of cases improved, 41.3% unchanged and 14.6% worsened, not to speak of relapse rate[2]. In addition to the relatively frequent primary drug resistance cases, difficulties pertaining to the long term treatment are considered to be the major factors leading to the poor results. Not only patients but also doctors in general are not confident of sufficient follow up of the long term regimen and nobody knew actually how many patients took the drugs regularly for such a long term. It is evident therefore that unless we work out some new regimens which can shorten the duration of chemotherapy, it would be difficult to obtain the same effect in the field as in the institute with the previous regimens at least in the developing countries. The future problem of TB chemotherapy should be therefore aimed at working out feasible and adequate short course treatment.

The discovery of "Rifampicin" has brought the dawn to a settlement of this problem as it was soon found that the drug converts the sputum much faster and completely than any other else[3]. Encouraged by this fact many clinical trials with regimens including Rifampicin have been carried out by various groups of investigators.

It may be summarized that they have more satisfactory effect to eliminate tubercle bacilli and have lower relapse rate, and that INH+RMP for 6 months are able to control 93~100% of initial active pulmonary tuberculosis with 0~7% of relapse rate within 2 years after the treatment[1)4)~13)]. Although the results are apparently superior to the previous standard triple drugs, yet we feel 6 months period is still a bit longer to us. Could the duration of treatment, the supervised period in particular, be cut shorter to the minimum, preferably 3 months, most of our patients are not only willing but also able to pay more for a limited period of time. Then, the emergence of treatment failure cases will be greatly reduced which will undoubtfully make a great step forward toward the final success of the overall TB control.

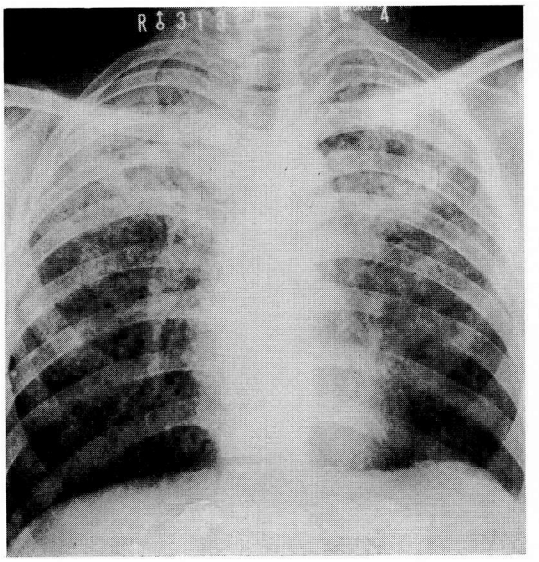

Fig. 2 a. Case 1. LSS. Before treatment.

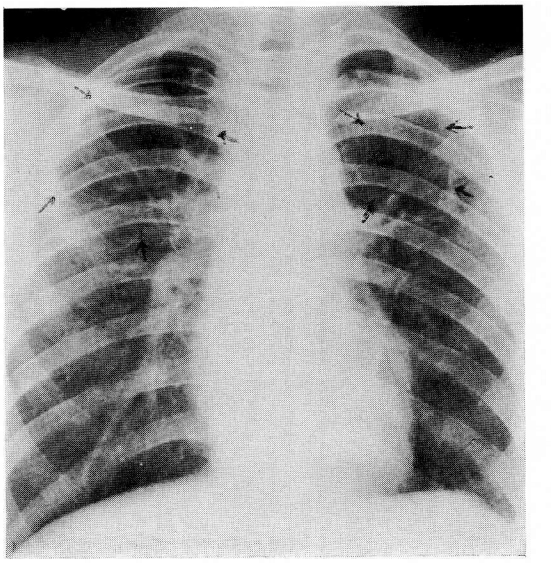

Fig. 2 b. After 3 months' intensive treatment. Bilateral bullae formation (arrows). I.T. discontinued.

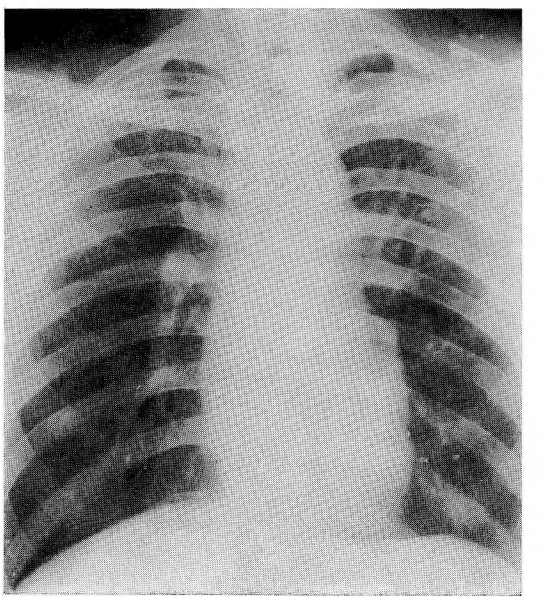

Fig. 2 c. Twelve months after completion of treatment. Bilateral bullae has disappeared.

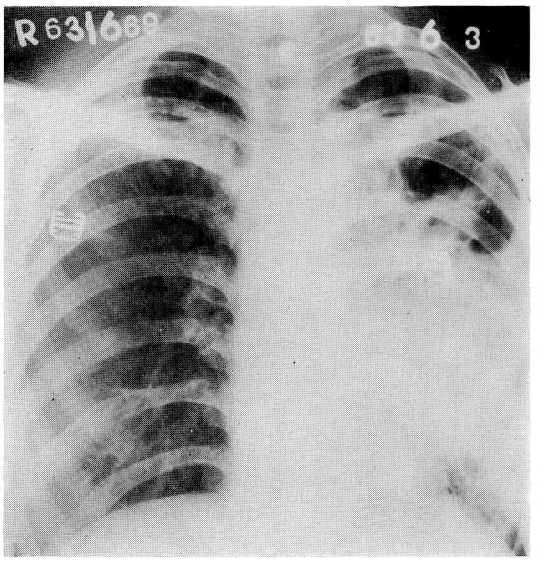

Fig. 3 a. Case 2. WWS. Before treatment. Bilateral extensive diseases with cavities.

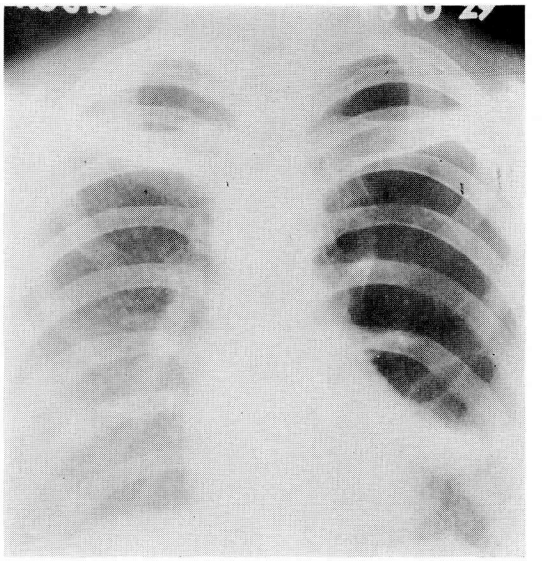

Fig. 3 b. After 5 months' intensive treatment when it was terminated. Big bulla occupied entire left lung.

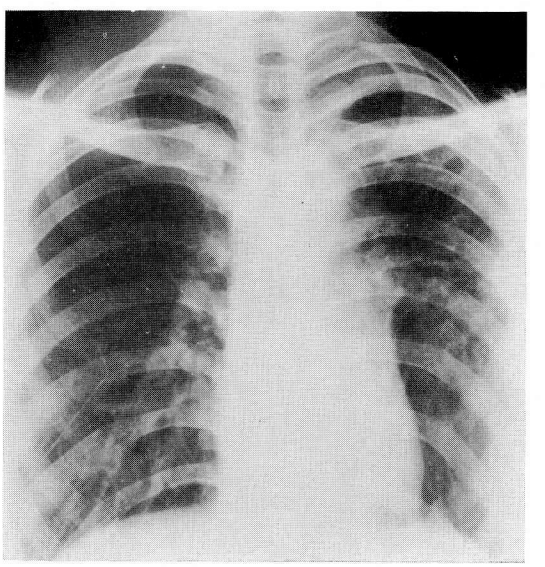

Fig. 3 c. Second phase monotherapy for 10 months. Bulla has disappeared.

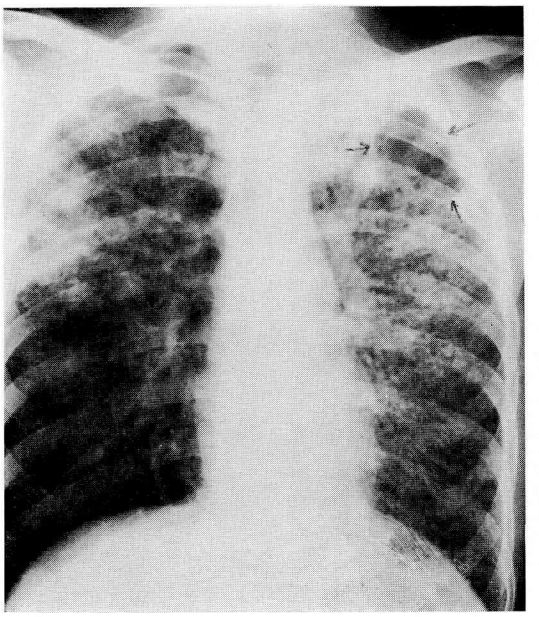

Fig. 4 a. Case 3. LWF. Before treatment. Bilateral extensive diseases with cavities (arrows).

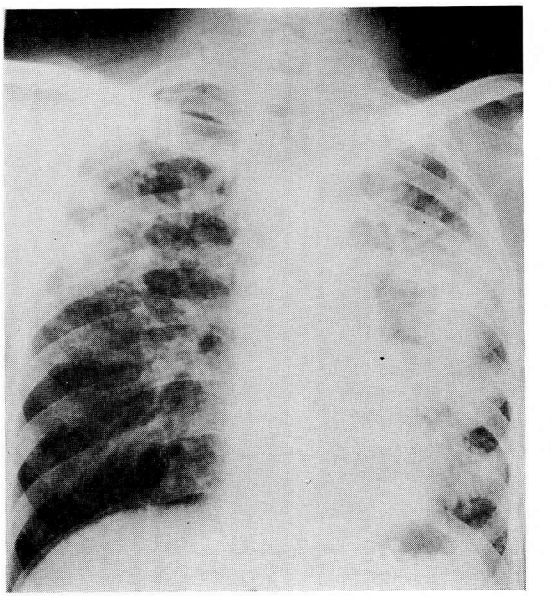

Fig. 4 b. Transient worsening of X-ray shadows after intensive chemotherapy.

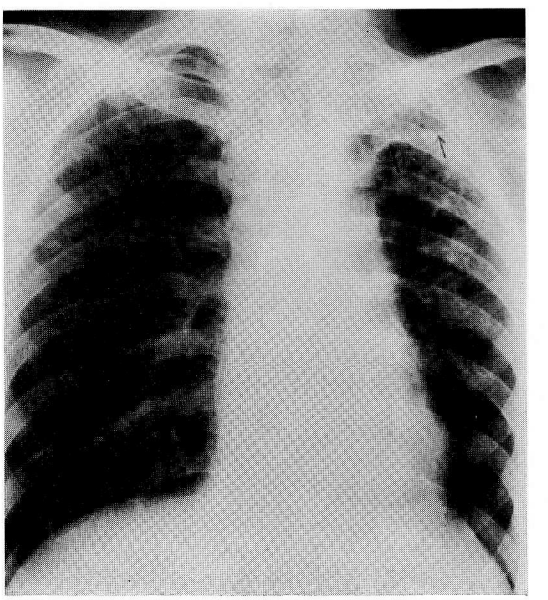

Fig. 4 c. After 6 months' intensive treatment when it was terminated. Bulla in left upper lung (arrows).

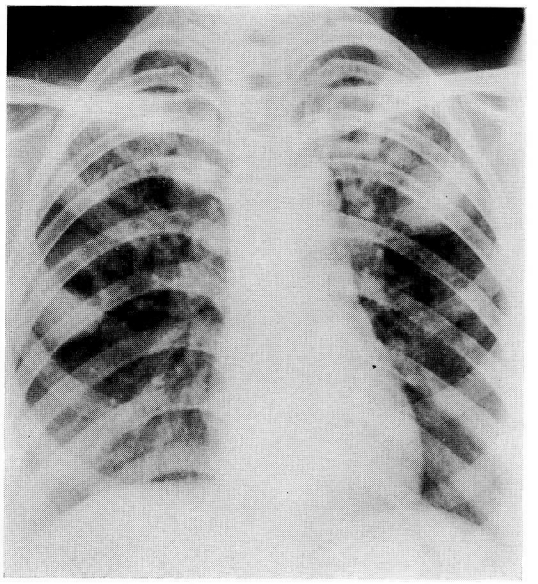

Fig. 5 a. Case 4. HLC. Before treatment. Bilateral extensive lesions with cavities and tuberculoma.

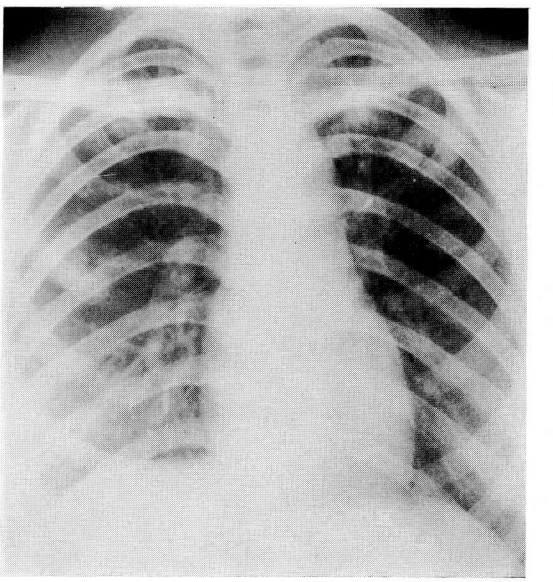

Fig. 5 b. After 6 months' intensive chemotherapy. Multiple tuberculoma remained with open negative cavities. I. T. discontinued.

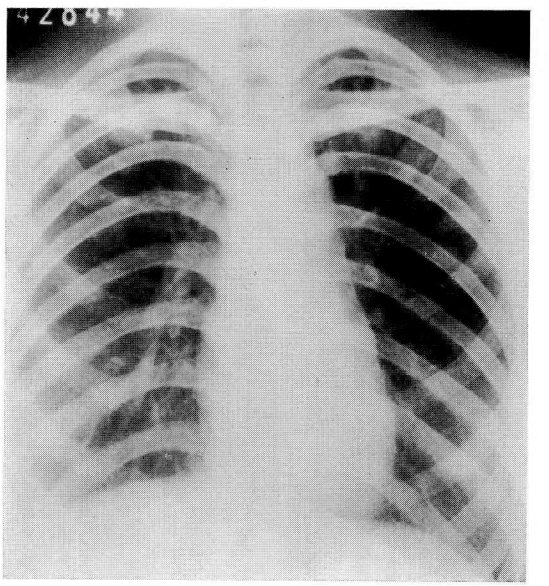

Fig. 5 c. Further improvement during INH monotherapy for 10 months.

Table 9. Background Factors Influencing the Duration of Intensive Treatment

Factors		I.T. for 3 Mos. (37 cases)	I.T. for 4~6 Mos. (23 cases)	Statistical significance
Sex	Male	20 (54.1)	15 (65.2)	N.S.
	Female	17 (45.9)	8 (34.8)	
Age	Less than 20	13 (35.1)	4 (17.4)	N.S.
	20~40	20 (54.1)	17 (73.9)	
	More than 40	4 (10.8)	2 (8.7)	
Extent of disease				
Moderately advanced		18 (48.6)	8 (34.8)	N.S.
Far advanced		19 (51.4)	15 (65.2)	
Type of disease				
IIb		1 (2.7)	2 (8.7)	N.S.
IIIa+IIIb		9 (24.3)	7 (30.4)	
IVa		16 (43.3)	9 (39.2)	
VII		11 (29.7)	5 (21.7)	
Cavity				
Size	No cavity	2 (5.4)	0	$p<0.05$
	Smaller than 4 cm	27 (73.0)	12 (52.2)	
	4 cm or larger	8 (21.6)	11 (47.8)	
Nature	Fresh	37 (100.0)	21 (91.3)	N.S.
	Old	0	2 (8.7)	
Sputum smear for AFB				
Positive		18 (48.6)	18 (78.3)	$p<0.01$
Negative		19 (51.4)	5 (21.7)	
Drug susceptibility				
Sensitive to 3 drugs		32 (86.5)	14 (60.9)	$p<0.025$
Resistant to 1 or more		5 (13.5)	9 (39.1)	
Diabetes mellitus		0	1 (4.4)	N.S.
No diabetes		37 (100.0)	22 (95.6)	
Extrapulmonary tbc.		3 (8.1)	2 (8.7)	N.S.
No extrapulmonary tbc.		34 (91.9)	21 (91.3)	

Number in parenthesis indicates percentage.
I.T.: Intensive treatment
N.S.: No significance

The present study which was carried out with this intension since May 1974, showed that intensive chemotherapy by combining the four most potent drugs, INH, RMP, SM and EMB, may achieve this purpose. The result clearly showed that it converted the sputum more rapidly, completely and permanently than any other regimens, and the target point was reached after 3 months in 61.7% of 60 cases with moderately or far advanced infectious pulmonary tuberculosis. The background factors likely to cause the extension of the intensive chemotherapy beyond 3 months are analysed in Table 9 dividing into 3 months' and 4~6 months' groups. Age, sex, extent or pathological type of disease and presence of extrapulmonary tuberculosis have apparently no significant relation with the duration of intensive chemotherapy. Cavities smaller than 4 cm, negative tubercle bacilli by sputum smear and no primary drug resistance are seen in significantly greater number in 3 months' group. Although statistically not significant because of the small number, older cavity and complication of diabetes are likely the factors to extend the duration of intensive chemotherapy. Furthermore, early response in bacteriological or radiological improvement was related to the duration of intensive treatment. As shown in Table 10, if sputum converted within 1 month, cavity closed, more than 50% of

Table 10. Early Bacteriological or Radiological Response and Duration of Intensive Treatment

Response	I.T. for Mos. (37 cases)	I.T. for 4~6 Mos. (23 cases)	Statistical significance
Bacteriological status			
1 Mon. after I.T.			
Microscopy			
Negative	30 (81.1)	18 (78.3)	N.S.
Positive	7 (18.9)	5 (21.7)	
Culture			
Converted	27 (73.0)	11 (47.8)	$p<0.05$
Not converted	10 (27.0)	12 (52.2)	
X-ray findings after			
2 Mos. I.T.			
Cavity			
No cavity or closed	33 (89.2)	4 (17.4)	$p<10^{-6}$
Not closed	4 (10.8)	19 (82.6)	
Absorption of lesions			
50% or more	36 (97.3)	5 (21.7)	$p<10^{-6}$
Less than 50%	1 (2.7)	18 (78.3)	
Tuberculoma formation			
Yes	1 (2.7)	8 (34.8)	$p<0.001$
No	36 (97.3)	15 (65.2)	

Number in parenthesis indicates percentage.
I.T.: Intensive treatment
N.S.: No significance

the lesion absorbed within 2 months and without tuberculoma formation, the intensive chemotherapy can be most likely terminated after 3 months.

The concept that TB chemotherapy should be continued for at least one and half year, is based on the experimental and/or clinical study showing that the chemotherapeutic drugs are mainly bacteriostatic rather than bacteriocidal and relapse rate is definitely higher if the treatment is terminated earlier. Compromised with this concept the intensive chemotherapy was followed by non-supervised INH monotherapy for one year (2nd phase treatment) in this study. Is this really necessary? Theoretically speaking, if the therapeutic regimen can achieve bacteriocidal effect at a certain period of time (when the target point is reached), the 2nd phase monotherapy will not be necessary. The fact that our intensive regimen is highly likely to achieve bacteriocidal and bacteriosterile[3] effect is supported by the following:

1. Our four drug combination are superior to 6 SHR regimen in regard to the rapidity and completeness of sputum conversion.
2. In the two resected cases, no tubercle bacilli could be proved from the tissue homogenate.
3. No relapse case has been observed. Even in the "failure" cases, in whom target point was not reached after 6 months, not only no bacteriological relapse but also further improvement in chest X-ray findings was observed after discontinuation of 6 months' intensive treatment.

Further improvement of chest X-ray findings observed in general during the early stage of the 2nd phase treatment is not necessarily the effect of INH monotherapy as tissue repairing process usually take time after the microorganisms are eliminated.

Though many investigators reported that various side effects, such as serious hepatic toxicity, generalized hypersensitivity, cutaneous reaction, purpura, abdominal pain, pancreatitis, flu syndrome and respiratory syndrome[14][15] during the use of RMP containing drug regimens, yet many large scale controlled studies indicated drug toxicity was infrequent and rarely serious[4]~[13]. Recent publications[16][17] have emphasized that

disordered liver function at a purely biochemical levels is unlikely to be of significance and that the raised transaminase and bilirubin levels tend to return to normal even though RMP is continued. In the present study, the systemic reactions were not observed. Nor was there any patient with purpura or flu syndrome. None discontinued the assigned regimen because of adverse reactions. They do not seem to be a major drawback in short-term intensive chemotherapy.

In summary, we believe, for the majority of newly diagnosed infectious pulmonary tuberculosis, as we did not include cases with minimal or moderately advanced lesions without cavity, 3 months' intensive chemotherapy with daily INH, RMP, EMB and SM will effectively control the disease. For the exceptional cases, it may be necessary to extend the duration of intensive treatment for a couple of months but never exceed 6 months. It is highly likely that the 2nd phase treatment is not necessary but this question is remained to be clarified.

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