

## CLINICAL CLASSIFICATION OF FAR ADVANCED PULMONARY TUBERCULOSIS

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In spite of the recent progress in surgical therapy and chemotherapy the so-called far advanced pulmonary tuberculosis is still a hard nut to be cracked in the medical problem. Sunahara,<sup>8)</sup> Living<sup>10)</sup> and others<sup>1~4)9)11~15)</sup> have recently discussed about chemotherapy for the far advanced pulmonary tuberculosis; Suzuki<sup>6)</sup> and Miyamoto<sup>5)</sup> about surgical therapy, especially its limits set by pulmonary functions of patients.

There exist, however, various definitions of the far advanced pulmonary tuberculosis at present. The classification set by National Tuberculosis Association is not adequate for discussing the Far Advancedness in whose medical treatment we are now experiencing many difficulties. In Japan the governmental committee for the chemotherapy of tuberculosis has proposed the classification of tuberculosis from the standpoint of efficacy of chemotherapy, according to which the following six fundamental types are classified: A. Exudative; B. Infiltrative-Caseous; C. Fibrous-Caseous; D. Sclerotic; E. Disseminated; and F. Far Advanced and Mixed Types.

Although the "far advanced and mixed type" is defined here as showing cavitary and various other pathological components mixed diffusely on roentgenogram and unclassifiable in any other fundamental type, not all the far advanced cases we experience fall exclusively into this type. Some confusions may be seen in the definition of "far advancedness".

Authors have observed radiographically and bacteriologically the effect of chemotherapy on tuberculous patients falling into the Far Advanced type by NTA for one and a half years in sanatoria and hospitals, and studied about the limit of chemotherapy for far advanced cases of pulmonary tuberculosis with respect to the authors' original typing which is set on the basis of radiographical findings.

### MATERIALS AND METHODS

#### *I. Study groups*

Four hundred and twenty patients falling into the Far Advanced Cases by NTA were selected and have been placed under chemotherapy for 18 to 48 months (23.8 months on the average). Their age distribution and sex distinction

are shown in Table 2, the majority (62.1%) being in the age of 21 to 40. One hundred and sixty seven cases (39.9%) of them had never experienced any previous chemotherapy, and the remaining 253 cases (60.1%) had received some chemotherapy before.

The patients are grouped as shown in Table 1. Almost all of them have cavities (97.3%) falling into fibrous-caseous type with sclerotic-walled cavity or destroyed lung.

At the commencement of the observations, the percentage of patients with both sputum cultures and staining positive for tubercle bacilli was 80.0 per cent (336 cases); that of those with only sputum cultures positive 10.5 per cent (44 cases); and that of those with both cultures and staining negative 9.5 per cent (40 cases).

## II. The authors' classification of the far advanced pulmonary tuberculosis (Table 1)

The authors tried to classify the cases radiographically into five groups on the basis of findings of cavity in principal side, existence of cavities on the opposite side and extent of disease on a roentgenogram. Cavities are rated into three grades according to their size: gigantic cavity, having the interior diameter of more than 4 cm; intermediate one, having that of 4 to 2 cm; and small one, having that of less than 2 cm.

The far advanced cases by our classification are correlated with type of Classification of Japanese Governmental Committee as in Table 1; namely, 70

TABLE 1. Radiographical Classification of the Far Advanced Pulmonary Tuberculosis Proposed by Authors

Authors' classification				Classification of Japanese						Per cent	
Principal side	Opposite side	First-treated group	Re-treated group	B		C		F	Total		
				Ka..d	Kx, y, z	Ka..d	Kx, y, z				
I	Destroyed lung gigantic cavity multiple cavities	Gigantic cavity, multiple cavities. Wide lesion multiple cavities	54	109	0	2 (1.2)	1 (0.6)	46 (28.2)	114 (70.0)	163 (100)	38.9%
II	Gigantic cavity multiple cavities	Not wide lesion intermediate or small cavity, wide lesion	33	75	5 (4.6)	1 (0.9)	1 (0.9)	57 (52.8)	44 (40.7)	108 (100)	25.7%
III	Intermediate or small cavity multiple cavities	Intermediate or small cavity, wide lesion not wide lesion	56	43	8 (8.1)	10 (10.1)	1 (1.0)	61 (61.6)	19 (19.2)	99 (100)	23.6%
IV	Intermediate or small cavity	Not wide lesion	18	21	5 (12.8)	8 (20.5)	2 (5.1)	24 (61.7)	0	39 (100)	9.3%
V	No cavity	No cavity	6	5	2 (18.2)		9 (81.8)		0	11 (100)	2.6%
Total			167 (39.8)	253 (60.2)	41 (9.4)		202 (48.2)		177 (42.1)	420 (100)	

( ): %, Ka..d: non-sclerotic-walled cavities, Kx, y, z: sclerotic-walled cavities

TABLE 2. Age Distribution and Sex Distinction of Cases

Age ↓	Sex →				Total	
	M.	F.	M.	F.		
-20	16	5.7%	24	16.6%	40	9.5%
21-30	73	26.2	65	45.1	138	32.8
31-40	88	37.5	35	24.3	123	29.3
41-50	58	20.8	9	6.2	67	15.8
51-60	23	8.3	5	3.5	28	6.7
61-	21	7.5	3	2.4	24	5.7
Total	279	100%	141	100%	420	100%
	(66.4%)		(33.6%)			

per cent of group I are occupied by destroyed lung and approximately 30 per cent by fibrous-caseous lesion with sclerotic-walled cavities, while in groups II, III and IV, type C with thick-walled cavities is found in absolute majority, and the number of type F decreases in their order, no case being found in group IV. Contrary to type F, Type B is found only in 1.2 per cent of group I, but its percentage rises in groups II, III and IV, amounting to approximately 30 per cent in group IV.

All the above-mentioned patients were placed under chemotherapy for more than 18 months in order to test the adequacy of "far advanced" in Table 1.

RESULTS

[1] Comparison among the groups by the authors' classification (Fig. 1, 2)

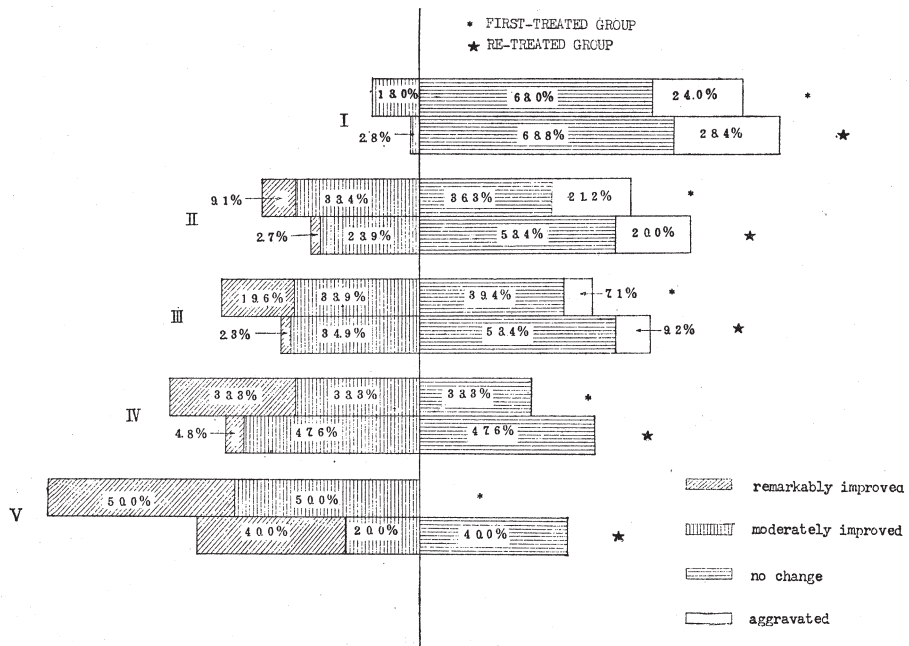


FIG. 1. Radiographical change (Authors' classification) (18 mon.)

Radiographical change: As shown in the Fig. 1, clear difference in radiographical improvement was seen among groups I, II, III, and IV in both the first-treated and retreated group. The difference in the grade of radiographical improvement was statistically significant between group I and the other groups. The aggravation rates were 24.0, 21.2 and 7.1 per cent in groups I, II and III respectively, no aggravation was observed in group IV and V.

Bacteriological change: Similar clear difference was seen in bacteriological improvement between I and the other groups as in radiographical improvement (Fig. 2).

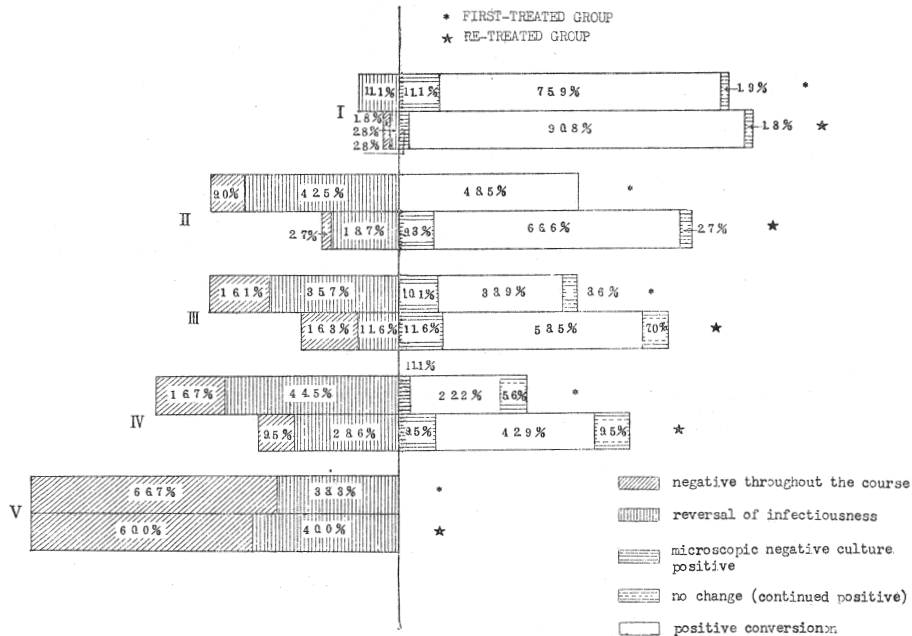


FIG 2. Bacteriological change (Authors' classification) (18 mon.)

Analyses of Improved and Aggravated Cases

Analyses were made of radiographical changes brought by 18 months chemotherapy for the improved and the aggravated cases.

I. Improved cases (Table 3)

i) Remarkably improved cases: Remarkably improvement was obtained in 29 patients (6.9%) among 420 far advanced cases. The numbers of them according to the authors' classification were: no case in group I, 5 in II, 12 in III, 7 in IV, and 5 in V; and 23 for the group of first-treatment and 6 for that of re-treatment.

Their age distribution was as follows; 4 cases, less than 20 years; 14 cases, 21 to 30; 7 cases, 31 to 40; 4 cases, 41 to 50; and no case, more than 51. Twenty-four patients of them had cavity at the start of therapy. The inci-

TABLE 3. Analyses of Remarkably Improved Cases

	First treatment	Re-treatment	Cavity			Required period for cavity closure				Required period for bacteriological improvement			Resistance	No resistance	Required period for target point achievement				
			New	Moderately new	Old	6 Mon.	12 Mon.	18 Mon.	Negative at first	6 Mon.	12 Mon.	18 Mon.			6 Mon.	12 Mon.	18 Mon.	21 Mon.	
I	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0
II	3	2	5	0	0	2	1	2	0	2	3	0	(SM 10r)	4	0	2	3	0	5
II	11	1	10	1	1	1	6	5	3	3	5	1	(P 10r)	8	0	1	7	4	12
V	6		6	0	1	1	2	4	0	4	3	0	(P 10r)	6	0	1	2	4	7
√	3	2							3	1	1	0	0	2	0	4	1	0	5
tal	23	6	21	1	2	4	9	11	6	10	12	1	3	20	0	8	13	8	29

dences of cavity closure were 4 cases in 6 months, 9 in 12 months, and 11 in 18 months after the start of therapy.

Of the 29 remarkably improved cases 6 had been negative for tubercle bacilli in sputum cultures from beginning, 10 were rendered non-infectious by 6 months, 12 by 12 months, and 1 by 18 months after the start of therapy. Almost all of them were rendered so within 12 months after the start of treatment.

There were only three patients whose bacilli developed drug-resistance during therapy.

It took 12 months for 8 cases, 18 months for 13, and 21 months for 8 to reach the target point at which cavity disappeared, sputum cultures were rendered negative for tubercle bacilli, and radiographical findings remained unchanged for more than 3 months.

ii) Moderately improved cases: Moderate improvement was obtained in 93

TABLE 4. Analyses of Moderate Improved Cases

	First treatment	Re-treatment	Cavity			Required period for bacteriological improvement				Resistance					Indicative for operation		Inoperable	Negative conversion after more than 18 mon. chemotherapy			
			New	Moderately new	Old	Negative at first	6 Mon.	12 Mon.	18 Mon.	Positive	SP	SI	S	I	P	Not operated				Operated	
	7	3	2	4	5	1	0	1	2	6	2	0	1	2	0	2	0	8	0	0	10
	11	18	6	5	1	1	8	7	2	11	3	1	3	1	0	17	6	6	0	0	29
	19	15	2	6	7	6	3	4	2	19	1	2	7	3	0	15	8	7	4	4	34
	6	10	0	1	3	3	4	1	1	7	0	0	1	0	1	9	5	0	2	2	16
	3	1				2	1	0	1	0											4
al	46	47	10	16	16	13	16	13	8	43	6	3	12	6	1	43	19	21	6	6	93

S: streptomycin P: p-aminosalicylic acid I: isonicotinic acid hydrazide

cases, 22.1% of whom 10 belonged to group I, 29 to II, 34 to III, 16 to IV, and 4 to V by the authors' classification (Table 4).

The first-treated patients were 46, and the re-treated ones 47. Their age distribution was similar to that of the whole series of patients.

Of the 89 patients with cavities at start 27 cases showed cavity reduction to less than half in interior diameter.

Of 93 cases 10 had been negative for tubercle bacilli in sputum cultures from beginning, and 32 were rendered non-infectious by the therapy. Reversal of infectiousness was found in 84.7 per cent within 12 months.

Of the 33 patients who developed drug-resistant bacilli, none showed three-drug resistance, 5 cases two-drug resistance, and 24 cases one-drug resistance (15 against SM, 2 against PAS and 7 against INH).

### *II. Aggravated cases*

Seventy-four cases (17.6%) aggravated, 44 of which were included in group I, 22 in II, 8 in III, and none in IV and V.

Twenty-four cases were the first-treated and 50 the re-treated ones. Their age distribution is similar to that of the whole series of patients. All the cases showed positive on smear for tubercle bacilli; and no case was found which was rendered non-infectious within 18 months of chemotherapy.

Drug-resistant bacilli were found in 72 of the 74 cases, of which 30 cases (40.5%) developed resistance against three-drugs, 28 cases (37.9%) against two-drugs, and 14 (18.8%) against one drug (10 against SM, 3 against INH and one against PAS).

Complications were found in 11 of the 74 aggravated cases: diabetes mellitus 2, lung gangrene 2, silicosis 1, nephritis with articular rheumatism 1, hepatitis 1, ankylostomiasis 1, influenza 1, asthma bronchiale 1, and spondylitis tuberculosa 1.

Radiographical aggravations were classified as follows: enlargement of cavity (mostly accompanied by growth of infiltrative lesion) 44, extension of infiltrative lesion 11, development of new cavity 22, and appearance of new infiltrative lesion 1.

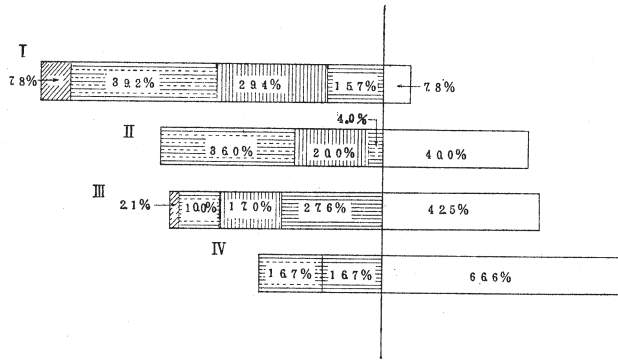
### *III. Cases which showed no change*

Of far advanced 420 cases, 234 cases (55.7%) were no change. The number of them by groups of the authors' classification were: 116 cases of 163 cases for group I (71%), 52 cases of 108 cases for group II (48.1%), 46 cases of 99 cases for group III (46.4%), 16 cases of 39 cases for group IV (41.0%) and 2 cases of 11 cases for group V (18.4%). Of these 234 cases, 74 cases belonged to the group of first-treated group and 160 cases to that of re-treated group.

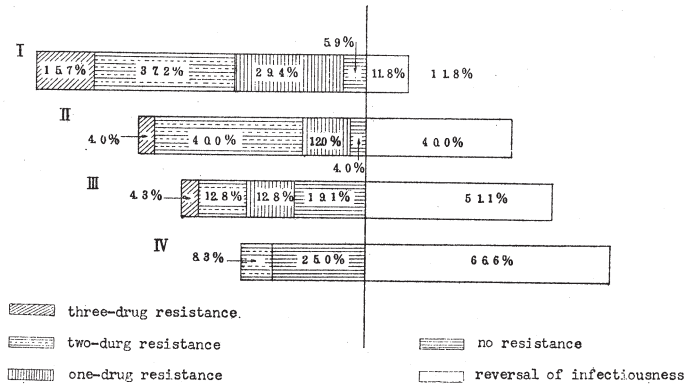
### [2] *Incidence of drug-resistant bacilli (Fig. 3)*

135 cases of non-drug-resistant patients showing positive for tubercle bacilli at the start of therapy have been taken as object of study.

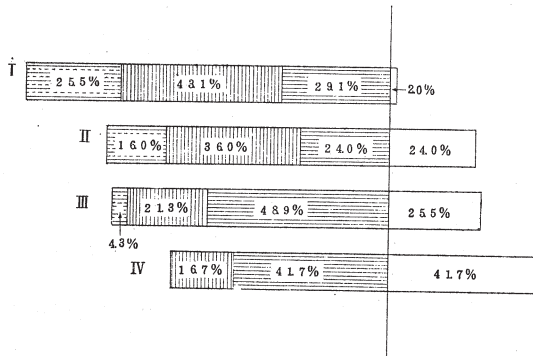
Drug-resistant bacilli were found in 239 cases (70.3%) of the 380 patients whose sputum cultures had been positive for tubercle bacilli at the start of



Incidence of drug-resistant bacilli (six months)



Incidence of drug-resistant bacilli (twelve months)



Incidence of drug-resistant bacilli (eighteen months)

FIG. 3

therapy.

As clearly shown in Fig. 3 in which the incidence of drug-resistant bacilli are correlated with the groups by the authors' classification, there were found significant differences among groups I, II, III and IV. Drugresistance was observed in 68.6 per cent after 6 months and in 82.3 per cent after 18 months in group I, and in 52 per cent after 6 months and in 56 per cent after 18 months in group II, while in only 29.9 and 8.3 per cent after 18 months in groups III and IV respectively.

### [3] Rehabilitation (Fig. 4)

As stated above, only a few cases enjoyed cavity closure and reversal of infectiousness with chemotherapy only; approximately 7 per cent could be rehabilitated after 18 months of treatment. The greater majority remained cavity-loaded and infectious notwithstanding systematic chemotherapy.

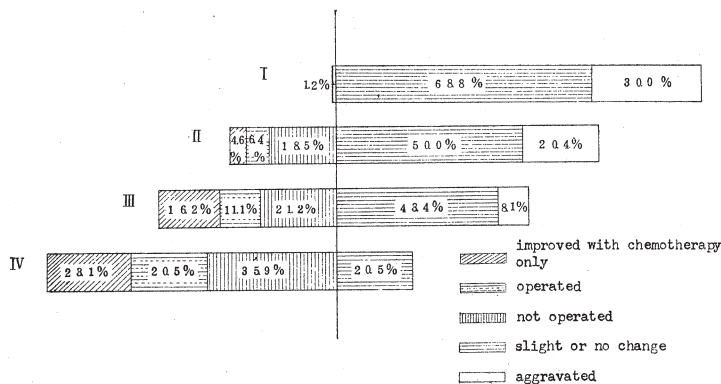


FIG. 4. The effects brought by 18 to 48 (average 23.8) months' chemotherapy from the standpoint of rehabilitation

In order to rehabilitate, surgical treatment such as thoracoplasty or lobectomy is indispensable, but this treatment will be found indicative for only an extremely small number of cases of far advanced pulmonary tuberculosis.

Analyzing the effects brought by 18 to 48 (23.8 on the average) months' chemotherapy from the standpoint of rehabilitation, the following results were obtained; of the 409 patients who showed cavitory components on roentgenogram at the start of therapy, (1) 30 cases (7.3%) improved with chemotherapy only so far to cavity closure and reversal of infectiousness and could be rehabilitated; (2) 83 cases (20.3%) improved so much enough to be endurable to surgical treatment, 26 of which received actually surgical operation with the result of reversal of infectiousness and are about to be rehabilitated; (3) 217 cases (53.1%) remained unchanged or improved so unsatisfactorily that cannot be expected to be rehabilitated; and (4) 79 cases (19.3%) aggravated.



Comparing the results in terms of the groups by the authors' classification, there are clear difference among I, II, III and IV. In detail, no case of marked improvement was found in group I and those which improved so far that could be treated surgically were in only 1.2 per cent in the same group; that is, any hope of rehabilitation can hardly be expected for this group. In the other groups, on the contrary, rehabilitation can be expected in 2.95 per cent for group II, in 48.5 per cent for III and in 79.5 per cent for IV.

From the above results the authors propose a definition of far advanced pulmonary tuberculosis in narrow sense as group I and II.

#### DISCUSSION

Concerning definitions and classifications of the far advanced pulmonary tuberculosis at present, there exist various theories. There is little knowledge on the classification of far advanced cases for analyzing the limit of chemotherapy and surgical treatment, and some confusion may be seen in the definition of far advancedness. We would like to show the comparison of the previous typing of lesion with the authors' classification.

Radiographical change. As stated above, the patients under study are classified into type B (9.7%), C (48.2%), and F (42.1%); of the 202 patients falling into type C, 188 cases have sclerotic-walled cavities. Ninety per cent of all the patients, therefore, consist of type C with sclerotic-walled cavities and type F. Regarding these cases, if radiographical and bacteriological changes are commented from the standpoint of the authors' far advanced groups, some difference in radiographical changes is seen among groups I, II, III and IV; especially between group I and the other groups there exists marked distinction. As discussed above, however, no difference is found in the effect of chemotherapy on radiographical findings between type C with sclerotic-walled cavities and type F. From these results it follows that the effect of chemotherapy on radiographical findings of the far advanced pulmonary tuberculosis is better judged by the authors' classification than by the previous typing.

Bacteriological change. Analyzing the bacteriological changes found in these cases from the standpoint of the authors' classification, clear distinction is observed between group I and the other groups, while no difference is seen between type C with sclerotic-walled cavities and type F. The effect of chemotherapy on bacteriological findings on the far advanced pulmonary tuberculosis is also better judged by the authors' classification than by the previous typing.

#### CONCLUSIONS

Four hundred and twenty cases of pulmonary tuberculosis falling into the "Far Advanced Cases" by NTA classification were observed under chemotherapy for more than 18 months, and their radiographical and bacteriological changes were correlated with the types of the disease which were proposed by the authors on the basis of radiographical findings, especially those of principal cavitory lesion and the pathological pattern on the opposite side.

- i) Significant difference was found in the radiographical and bacteriological

changes brought by chemotherapy among groups I, II, III, IV and V; especially between group I and the other groups marked difference was observed.

ii) Ninety per cent of the observed patients were included in fibrocaceous type with sclerotic-walled cavity or destroyed lung type and between these two types no difference was found in the effect of chemotherapy. However, when the radiographical and bacteriological changes are analyzed with relation to the disease groups by the authors' classification, distinct difference can be found between group I and the other groups. In other words, the authors' classification is more useful than the other typing of lesion for foreseeing the prognosis of far advanced pulmonary tuberculosis under chemotherapy.

iii) The rate of appearance of drug-resistant tubercle bacilli was the highest in group I and lower in groups III and IV, and no incidence was found in group V.

iv) Regarding drug-resistant patients, no effect will be expected in group I, and some effect will be hoped for one-drug resistance in group II, while fairly good effect is anticipated for one-drug resistance in groups III and IV.

v) Analyzing the results from the standpoint of rehabilitation, no case improved with chemotherapy only so much enough to be able to rehabilitate, only 1.2 per cent did so far enough to be endurable to surgical operation, and 30 per cent aggravated in group I. Hereupon the authors propose a definition of far advanced pulmonary tuberculosis as follows: 1) those with destroyed lung on one side, 2) those with a gigantic cavity on one side and with tuberculous lesion including gigantic or multiple cavities or over more than two-thirds of the whole field of the other side; 3) those with multiple cavities on both sides".

In order to prevent aggravation to far advanced state, sufficient chemotherapy and rest life are indispensable at the very time of discovery, and complication with any other offensive sickness must be kept in mind at the same time.

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