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NEWS & NOTES

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ABSTRACTS

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**TUBERCULOSIS RESEARCH
AND
PROBLEMS ARISING OUT OF CHEMOTHERAPY FOR
TUBERCULOSIS**

The advent of anti-bacterial drugs during the last 15 years is a landmark in the history of anti-tuberculosis movement throughout the world. These drugs have affected not only the treatment and prognosis of tuberculosis, but also the epidemiology and the method of control and prevention of the disease. The total impact of the new drugs on the world tuberculosis problem as a whole, which is nothing short of a revolution, has brought on its trail, a large number of problems for clinical, bacteriological and epidemiological research.

As in the case of any other new drug or group of drugs, many questions of interest to clinician have arisen. They relate to, the degree of activity, mode of action, toxicity, resistance, optimum dosage, best combinations, effective period of treatment, relative merits, pre and post-operative use in surgery etc.. Other problems of primary interest to the epidemiologist and public health worker have also arisen. Some of them are—the suitability of drugs, especially Isonicotinic acid Hydrazide to be used on wide community basis and as a public health measure; the effectiveness of the drugs when used under home conditions, the public health significance of the disparity between death rates and incidence rates brought about by the drugs, the effect of the drugs on immunity production, the use of I.N.H. as a preventive measure (chemoprophylaxis), State's responsibility for making the drugs available in adequate quantities and cheaply enough for community use etc.

Some of these problems are dealt with and discussed in three of the articles published in this issue of the Journal.

The problem that is of primary interest to scientists engaged in researches of a fundamental nature, is the search for even more effective drugs; drugs that are not merely bacteriostatic but bactericidal. The success that Penicillin, for example, has achieved in the field of venereal diseases, yaws etc., gives us reason to hope that the search for a drug that will wipe out tuberculosis from the face of the earth, need not be considered too optimistic.

Until such a drug is in sight, the conquest of tuberculosis in a country like India, is bound to be long and arduous. Seeing the marked fall in death rates which the present drugs have brought about in Western countries there seems to be danger in the administrative circles in India, in considering tuberculosis as a public health problem already well on the way to solution. Such an attitude of complacency at the present time is not only premature but also fraught with danger. With the armaments that we have in hand at present, and at the peak in the epidemiology of tuberculosis that we seem to be nearing, because of the rapid industrialisation in this country, only a vigorous and concerted national effort on the part of the people and the Government, is likely to bring the tuberculosis problem under control in the next few decades.

In the field of research, we have to plan, in such a way that the limited resources of funds and personnel should be concentrated in solving some of the urgent problems that are connected with the epidemiology and control of tuberculosis in the community. However it should not lead one to believe that all that Indian Science is capable of, is clinical, epidemiological, statistical research only and not research on basic problems such as the nature of resistance, the mechanism of immunity production and its measurement, why infection results in disease in some and not in others, the bio-chemical basis of drug activity, and the search for better and more potent drugs lethal to the tubercle bacillus. It is hoped that the time will not be far away when Indian Scientists can take up these problems also for research.

—*T.J. Joseph*

Relative Merits of Various Schedules in the Domiciliary Treatment of Pulmonary Tuberculosis*

By

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Antimicrobial treatment in the patients' homes, if properly taken, has been found to be as effective as in hospitals (Sikand & Pamra 1956 a, b; Tuberculosis Chemotherapy Centre, Madras, 1959; Kim et al 1959; Kay 1957). However, a drug schedule which would give best overall results under Domiciliary conditions still remains to be worked out. Under hospital conditions, superiority of daily Streptomycin and INH schedule over all other combinations, at least for first 3-6 months of treatment, has been established by the British Medical Research Council (1955). However, the drug schedule found most effective in hospitalised patients need not necessarily be of equal merit under Domiciliary conditions with its varying problems of regularity, acceptability, self-administration, cost, organisation etc. An attempt has been made in this report to present our experiences on these aspects.

METHODS & MATERIAL

A study to determine the relative merits of the various antimicrobial regimes in Domiciliary treatment was started at the New Delhi Tuberculosis Centre in December, 1956. Table 1 shows the drug schedules and dosages used. All new patients attending the Centre and found suffering from active pulmonary tuberculosis were randomly allocated to one of the schedules. Retreatment cases were included, provided the previous treatment was stopped more than six months earlier and so were cases with diabetes, pregnancy or a tuberculous lesion in any other organ of the body. Patients with miliary and meningeal tuberculosis, however, were excluded.

TABLE 1: *Treatment Schedules*

- A. Streptomycin & I.N.H. daily.
- B. Streptomycin twice a week & I.N.H. daily.
- C. I.N.H. and P.A.S. daily.
- †D. I.N.H. alone daily.

Dosage §

<i>Weight</i>	<i>Streptomycin</i>	<i>I.N.H.</i>	<i>P.A.S.</i>
Below 40 lbs.	¼ gm.	50 mgs.per day	4 gms.per day
40 to 79 lbs.	¼ gm.	100 „ „ „	6 „ „ „
80 lbs. and above	¼ gm.	200 „ „ „	10 „ „ „

*Presented at the XVIth Tuberculosis Workers' Conference, Poona, 1960.

†Alternate patients in Schedule 'D' were given double dose of I.N.H. but as the results of the two sub-groups are in no way different, they are not shown separately.

§Doses were re-adjusted according to the gain of weight during the course of treatment whenever necessary.

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Treatment in the original schedule was to be continued till the achievement of sputum conversion, cavity closure and/or complete radiological clearing, or radiological stability for 3 months, except in schedule A, where, if by 3-6 months' treatment clinical quiescence was not attained, further treatment was to be continued under Schedule C. A stipulation was also made that if any patient on Schedule D got worse or continued to have a high degree of toxæmia for more than three weeks, treatment was to be switched over to Streptomycin and PAS daily. Further withdrawals from the allocated schedule were permissible for:—

- (a) drug toxicity, which was severe enough to require change of schedule in 16 cases only, Streptomycin being the most offending drug; and
- (b) drug resistance.

Treatment, for purposes of this study, was considered as terminated if the patient was transferred to another institution or surgical intervention became necessary.

Collapse therapy, if indicated, was started only after 6-9 months of antimicrobial treatment. This was instituted in 8 patients—3 in Schedule A, 2 each in B and D and 1 in Schedule C. Such small numbers are not likely to have influenced the results one way or the other, and these cases have therefore been included in the analysis.

The Protocol also provided for 'Maintenance Therapy' for a minimum of one year after attainment of clinical quiescence, to make total duration of antimicrobial therapy at least two years. The present paper, however, deals only with the immediate results of treatment. Whether 'Maintenance' therapy influences relapse rates in any way will be the subject of a subsequent report.

BASIS FOR COMPARISON OF SCHEDULES

Normally, the comparative merits of different drug schedules are judged only from the clinical stand-point, the aim being to achieve the maximum number of cures in the minimum time. A mass treatment scheme operated from the OPD of a Clinic, however, works in different conditions than those in hospitals or in an experimental study, where cost and the staff requirements are only secondary considerations to the prime need of enforcing regularity. Therefore, besides the clinical requirements mentioned above, drug acceptability and financial aspects have to be kept in mind. A clinically 'second best' schedule may be preferred to the 'clinically best' schedule, if the latter leads to irregularities in drug administration and does not prove as good in domiciliary conditions as in hospitalised patients. Drug schedules have been compared on the basis of:

- (a) Acceptability;
- (b) Clinical Merit; and
- (c) Financial Considerations.

ACCEPTABILITY OF TREATMENT

In all, 2207 patients were initially included in the trial, their allocation to the different schedules being shown in Table 2. Of these 973 (44.1%) are excluded

from the study as they did not complete even 3 months' treatment in the allocated schedule for the following reasons:

TABLE 2: *Age-Sex Distribution and Initial Status of Total Cases included in the study*

		Schedule A		Schedule B		Schedule C		Schedule D		Total		
		Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	
Sex	Male	344	64.1	350	62.6	357	64.4	375	67.3	1426	64.6	
	Female	193	35.9	209	37.4	197	35.6	182	32.7	781	35.4	
Age	Under 15	14	2.6	9	1.6	10	1.8	12	2.2	45	2.0	
	15-30	315	58.7	330	59.0	321	57.9	316	56.7	1282	58.1	
	30-45	138	25.7	148	26.5	150	27.1	148	26.6	584	26.5	
	Over 45	70	13.0	72	12.9	73	13.2	81	14.5	296	13.4	
Extent of Disease	Minimal	30	5.6	34	6.1	37	6.7	52	9.3	153	6.9	
	Mod. Adv.	115	21.4	117	20.9	89	16.1	121	21.7	442	20.0	
	Far Adv.	392	73.0	408	73.0	428	77.2	384	68.9	1612	73.0	
Extent of cavitation	Nil	164	30.5	165	29.5	172	31.0	183	32.8	684	31.0	
	Single	249	46.4	283	50.6	266	48.0	270	48.5	1068	48.4	
	Multiple	Unilatera	36	6.7	36	6.4	28	5.1	26	4.7	126	5.7
		Bilateral	88	16.4	75	13.4	88	15.9	78	14.0	329	14.9
Bacillary Status	Positive	351	65.4	386	69.1	389	70.2	384	68.9	1510	68.4	
	Negative	186	34.6	173	30.9	165	29.8	173	31.1	697	31.6	
	Total	537	100.0	559	100.0	554	100.0	557	100.0	2207	100.0	

(i) Admitted to Hospitals etc.	245	(25.2%)
(ii) Treatment Schedule Changed	33	(3.4%)
(iii) Died within 3 months	55	(5.7%)
(iv) Left Locality	254	(26.1%)
(v) Refused Treatment	386	(39.7%)

Total 973 (100.0%)

It is worth noting that 278 patients (i) & (ii) above, i.e. 28.6% of these are known to have continued treatment. As for the others, our experience in Delhi

suggests that such losses are a normal feature of the working of a Clinic and are not necessarily related to the type of treatment but are governed by socio-economic factors, ignorance, fear, prejudice etc. A large majority of cases entered as 'Left Locality' are really outsiders who come to Delhi for diagnosis or in the hope of quick hospitalisation and therefore leave Delhi soon after.

The 1,234 cases who completed at least 3 months' treatment under the allocated schedules can be divided from the point of view of regularity of treatment into the following two broad groups, as shown in Table 3:

- (a) Fairly Regular—Those who completed 26 weeks treatment in 40 weeks' or less, and pro-rata—(925 cases).
 (b) Irregular —Those who took over 40 weeks to complete 26 weeks' treatment, and pro-rata—(309 cases).

It may be mentioned outright that judged by hospital standards, the above definition of 'Fairly Regular' may appear too liberal but it can hardly be otherwise under existing domiciliary conditions, where unlike in hospital practice a consistently regular patient is a rare phenomenon. Regularity, however, does not necessarily imply adequacy of treatment, because a patient may be 'regular' for 6 months and then stop treatment against medical advice, making a regular treatment inadequate.

TABLE 3: *Regularity of Treatment under different Drug Schedules*

Drug Schedules	Total Cases at start	Patients with no or under three months' treatment		Patients with at least three month's treatment			
				'Irregular' Cases		'Fairly Regular' Cases	
		Number	Percentage	Number	Percentage	Number	Percentage
A	537	259	48.2	82	15.3	196	36.5
B	559	220	39.4	77	13.8	262	46.9
C	554	240	43.3	78	14.1	236	42.6
D	557	254	45.6	72	12.9	231	41.5
Total	2,207	973	44.1	309	14.0	925	41.9

Regularity of Streptomycin was easy to assess as in a large majority of the cases injections were arranged by the Centre. For PAS and INH however, regularity of administration had to be judged, by and large, from the patients' own statements verified by checking of INH tablets and PAS by the Health Visitors on surprise visits to the patients' homes, and occasional examination of urine. The proportion of cases undergoing 'Fairly Regular' treatment was nearly 42% of the total cases (75% of those who had more than 3 months' treatment). Irregularity was slightly more marked in Schedule A than in other schedules, because daily injections, though welcome initially, are resented by patients as soon

as the acute phase of toxæmia has passed. There is not much to choose between the three remaining schedules in respect of regularity.

Adequacy may be judged from the number of cases reaching a stage of 'Maintenance' and those admitted to hospital as advised. At the time of compilation of this report, 317 (34.3%) out of 925 'Fairly Regular' patients have already been put on Maintenance, 335 are still continuing treatment (143 in hospitals) and 15 have died. The remaining 258 patients left the treatment against advice. In other words 667 (72.0 %) have so far cooperated fully. This proportion varies from 84.0% in Schedule A to 65.0% in Schedule C.

CLINICAL RESULTS

Table 2 and Table 4 which give the background data show that inspite of the considerable loss of cases in all schedules, the 'fairly regular' cases could in all essential respects be regarded as comparable with the initial group. Variation within

TABLE 4: Age-Sex Distribution and Initial Status of 'Fairly Regular' Cases included in the analysis

		Schedule A		Schedule B		Schedule C		Schedule D		Total		
		Num-ber	Perce-ntage	Num-ber	Perce-ntage	Num-ber	Perce-ntage	Num-ber	Perce-ntage	Num-ber	Perce-ntage	
Sex	Male	126	64.3	161	61.5	144	61.0	157	68.0	588	63.6	
	Female	70	35.7	101	38.5	92	39.0	74	32.0	337	36.4	
Age	Under 15	1	0.4	1	0.4	4	1.7	5	2.2	11	1.2	
	15-30	121	61.7	158	60.3	137	58.1	136	58.9	552	59.7	
	30-45	49	25.0	72	27.5	64	27.1	61	26.4	246	26.6	
	Over 45	25	12.8	31	11.8	31	13.1	29	12.6	116	12.5	
Extent of Disease	Minimal	15	7.7	16	6.1	16	6.8	34	14.7	81	8.8	
	Mod. Adv.	51	26.0	60	22.9	47	19.9	46	19.9	204	22.0	
	Far Adv.	130	66.3	186	71.0	173	73.3	151	65.4	640	69.2	
Extent of Cavitation	Nil	64	32.7	73	27.9	80	33.9	84	36.4	301	32.5	
	Single	92	46.9	136	51.9	115	48.7	111	48.0	454	49.1	
	Multiple	Unilateral	10	5.1	16	6.1	9	3.8	8	3.5	43	4.6
		Bilateral	30	15.3	37	14.1	32	13.6	28	12.1	127	13.7
Bacillary Status	Positive	119	60.7	187	71.4	159	67.4	163	70.6	628	67.9	
	Negative	77	39.3	75	28.6	77	32.6	68	29.4	297	32.1	
	Total	196	100.0	262	100.0	236	100.0	231	100.0	925	100.0	

limits of random sampling apart, the 'fairly regular' cases in the various schedules could also be considered as comparable to each other. Minor differences in respect of one characteristic were usually offset by differences in the opposite sense in respect of another characteristic. An exception noted was the higher proportion of Minimal cases in Schedule D as compared to other schedules. Results have, however, been presented without 'standardisation' for any pre-treatment differences.

Irregular treatment often being inadequate treatment, the analysis that follows is mainly in respect of the 925 'Fairly Regular' cases, although some limited analysis has also been made of the 'Irregular' cases.

Results have been analysed mainly in respect of sputum conversion and cavity closure since other criteria like weight, degree of toxaemia, B.S.R. etc. can neither be accurately assessed in an Out-Patients Department, nor are they of vital

TABLE 5: *Sputum Conversion at successive stages of treatment in different Drug Schedules ('Fairly Regular' Cases)*

	Drug Schedules	Sputum Positive Cases at Start of period	Sputum Conversions at end of period		Cases with Positive Sputum at end of period	
			No.	%	Further Treatment in same schedule stopped	Further Treatment in same schedule continued
3 months	A	119	96	80.7	5	18
	B	187	126	67.4	27	34
	C	159	88	55.3	19	52
	D	163	82	50.3	20	61
	Total	628	392	62.4	71	165
3-6 months	A	18	4	22.2	14	—
	B	34	7	20.6	9	18
	C	52	16	30.8	11	25
	D	61	14	23.0	17	30
	Total	165	41	24.8	51	73
6-9 months	A	*	—	—	—	—
	B	18	1	5.6	4	13
	C	25	6	24.0	9	10
	D	30	2	6.7	10	18
	Total	73	9	12.3	23	41
After 9 months	A	*	—	—	—	—
	B	13	1	7.7	12	—
	C	10	5	50.0	5	—
	D	18	4	22.2	14	—
	Total	41	10	24.4	31	—
Overall	A	119	100	84.0	—	—
	B	187	135	72.2	—	—
	C	159	115	72.3	—	—
	D	163	102	62.6	—	—
	Total	628	452	72.0	—	—

*Since Schedule A was seldom continued beyond 6 months, results have not been given beyond this period.

importance. Similarly, radiological improvement unrelated to cavity closure has a very minor significance, except in abacillary and non-cavitary cases, where such a change remains the only available criterion for comparing results.

(a) Sputum Conversion

Table 5 shows sputum conversion rates at various stages of treatment among the 628 originally bacillary cases in the different schedules. Since patients kept dropping off at various stages of treatment for many reasons, these rates have been combined by the life-table method on the assumption that patients stopping treatment would have fared as well or as bad as those continuing it. This assumption would probably be true of all schedules except D, where many patients were withdrawn from the schedule because of deterioration.

Cumulative conversion rates have been shown in Table 7. It is clear that schedule A is by far the best at 3 months period (80.7% conversions) and also in the

TABLE 6: *Cavity Closure at successive stages of treatment in different Drug Schedules ('Fairly Regular' Cases)*

	Drug Schedules	Cases with Cavitation start of period	Cavity Closures at end of period		Cases with open Cavities at end of period	
			No.	%	Further Treatment in same Schedule stopped	Further Treatment in same Schedule continued
3 months	A	132	83	62.9	10	39
	B	189	70	37.0	35	84
	C	156	51	32.7	30	75
	D	147	40	27.2	30	77
	Total	624	244	39.1	105	275
3—6 months	A	39	12	30.8	27	—
	B	84	20	23.8	18	46
	C	75	28	37.3	15	32
	D	77	21	27.3	20	36
	Total	275	81	29.4	80	114
6—9 months	A	*	—	—	—	—
	B	46	8	17.4	7	31
	C	32	7	21.9	10	15
	D	36	3	8.5	13	20
	Total	114	18	15.8	30	66
After 9 months	A	*	—	—	—	—
	B	31	5	16.1	—	—
	C	15	1	6.7	26	—
	D	20	3	15.0	14	—
	Total	66	9	13.6	57	—
Overall	A	132	95	72.0	—	—
	B	189	103	54.5	—	—
	C	156	87	55.8	—	—
	D	147	67	45.6	—	—
	Total	624	352	56.4	—	—

*Since Schedule A was seldom continued beyond 6 months, results have not been given beyond this period.

TABLE 7: *Cumulative* Sputum Conversion and Cavity Closure Rates at successive stages of treatment in different Drug Schedules ('Fairly Regular' Cases)*

	Drug Schedules	Cumulative Sputum Conversion Rate upto end of period	Cumulative Cavity Closure Rate upto end of period
End of 3 months	A	80.7%	62.9%
	B	67.4%	37.0%
	C	55.4%	32.7%
	D	50.3%	27.2%
End of 6 months	A	85.0%	74.3%
	B	74.1%	52.0%
	C	69.2%	57.8%
	D	61.7%	47.1%
End of 9 months	A	85.0%†	74.3%†
	B	76.1%	60.4%
	C	76.6%	67.0%
	D	70.2%	51.6%

long run (85.0% upto 6 months) and Schedule D the least satisfactory (50.3% at 3 months and 70.2% upto end of 9 months). There is not much to choose between schedules B and C at least in the long run (76.1% and 76.6% conversions respectively at the end of 9 months). Cumulative rates have been worked up to 9 months' treatment only, as thereafter the number of unconverted or open cavity cases left over were small. The rate shown for Schedule A at 9 months is the same as at 6 months since treatment under this Schedule was usually changed after 6 months.

Deaths have been entered as 'sputum positive' and 'cavity present' till the last stages of Tables 5, 6 and 7 even if the patient died earlier during treatment, for death in any case has to be considered as failure of treatment.

(b) Cavity Closure

Cavity closure at successive stages among the 624 original cavitory cases is shown in Table 6 and cumulative rates in Table 7. Once again, Schedule A maintains its clear superiority over the other schedules in the initial stages (62.9% at 3 months as against 37.0% and 32.7% in Schedules B and C respectively) although later on, Schedules B and C catch up to a certain extent. Comparing Schedules B and C at 9 months, one notes that the latter gives slightly better results (67.0% as against 60.4%).

For purposes of Tables 6 and 7, cases with residual thin-walled 'cystic' cavities with negative sputum have been counted amongst 'cavity closure' cases. The number of such cases in Schedules A, B, C, and D was 12, 6, 8 and 5 respectively.

(c) Radiological Change

Table 8 shows radiological response of 185 cases which were sputum negative and non-cavitory at start of treatment. Improvement after 3 months in Schedule A is almost the same as after 9 months in Schedules B and C with Schedule D lagging behind. Similarly Minimal cases were analysed separately to see if Schedule D could for such patients, be considered as efficacious as other Schedules. The results are shown in Table 9. Whereas Schedules A, B and C appear to be equally good,

* Calculated by the life-table method.

†For Schedule A the rate for 9 months is the same as that entered for 6 months as in almost all cases treatment schedule was changed after 6 months.

the improvement registered under Schedule D is considerably lower even in this type of cases. This would tend to show that even in less advanced cases, Schedule D is disappointing by comparison.

(d) Deaths

There were 15 deaths after a minimum of 3 months' treatment and these were almost evenly distributed i. e. 3 in Schedule C, and 4 each in Schedules A, B & D. The proportion of deaths, in general, was low.

TABLE 8: Radiological Changes among Non-Cavitary Abacillary Patients
(‘Fairly Regular’ Cases)

Drug Schedule	Total non-cavitary abacillary cases		Marked improvement		Moderate Improvement		No Change		Worse	
	No.	%	No.	%	No.	%	No.	%	No.	%
After 3 Months' Treatment										
A	46	100.0	12	26.1	24	52.2	9	19.6	1	2.2
B	43	100.0	3	7.0	25	58.1	14	32.6	1	2.3
C	52	100.0	6	11.5	32	61.5	11	21.2	3	5.8
D	44	100.0	4	9.1	23	52.3	13	29.5	4	9.1
Total	185	100.0	25	13.5	104	56.2	47	25.4	9	4.9
After 9 Months' Treatment										
A*	—	—	—	—	—	—	—	—	—	—
B	29	100.0	4	13.7	19	65.5	4	13.8	2	6.9
C	31	100.0	11	35.5	13	41.9	5	16.1	2	6.5
D	29	100.0	9	31.0	9	31.0	10	34.5	1	3.4
Total	89	100.0	24	27.0	41	46.1	19	21.3	5	5.6

*Treatment in Schedule ‘A’ was usually stopped after 6 months.

TABLE 9: Radiological Changes among Minimal Cases after 3 months' treatment ('Fairly Regular' Cases)

Drug Schedule	Total		Marked improvement		Moderate improvement		No Change		Worse	
	No.	%	No.	%	No.	%	No.	%	No.	%
A	15	100.0	2	13.4	8	53.3	5	33.3	—	—
B	16	100.0	1	6.3	10	62.5	5	31.2	—	—
C	16	100.0	—	—	11	68.7	4	25.0	1	6.3
D	34	100.0	1	3.0	16	47.0	13	38.2	4	11.8
Total	81	100.0	4	4.9	45	55.6	27	33.3	5	6.2

(e) Results in 'Irregular' Patients

Tables 10 and 11 show sputum conversion and cavity closure rates in 'Irregular' patients. As expected, the results, though not inconsiderable, are poorer than for the corresponding regular patients. It is interesting to note that the 'cumulative sputum conversion after 6 months' of irregular treatment in Schedule A (69.5%) is almost equal to that obtained after 6 months' regular treatment in Schedules B and C, and that cavity closure for the same period in the irregular A group is even higher than after 6 months' regular treatment in Schedules B and C. It would be well to remember that when Streptomycin injections are irregular and interrupted, Schedule A virtually becomes Schedule B.

TABLE 10 Sputum Conversion at successive stages of treatment in different Drug Schedules ('Irregular' Cases)

	Drug Schedules	Sputum Positive Cases at Start of Period	Sputum Conversions at end of period		Cases with Positive Sputum at end of period	
			Number	Percentage	Further Treatment in same Schedule stopped	Further Treatment in same Schedule continued
3 months	A	45	29	64.4	9	7
	B	49	21	42.9	11	17
	C	53	26	49.1	6	21
	D	44	16	36.4	16	12
3-6 Months	A	7	1	14.3	6	—
	B	17	4	23.5	11	2
	C	21	6	28.6	7	8
	D	12	4	33.3	5	3

Cumulative Sputum Conversions rate upto 6 months: A: 69.5%; B: 56.3%; C: 63.7%; D: 57.8%.

TABLE 11 Cavity Closure at successive stages of treatment in different Drug Schedules ('Irregular' Cases)

	Drug Schedules	Cavity positive cases <i>at</i> start of period	Cavity Closures at end of period		Cases with Open Cavities at end of period	
			Number		Further	Further
3 months	A	42	17	40.5	13	12
	B	53	13	24.5	13	27
	C	47	12	25.5	11	24
	D	44	10	22.7	16	18
3—6 Months	A	12	4	33.3	8	
	B	27	9	33.3	13	5
	C	24	2	8.3	10	12
	D	18	3	16.7	8	7

Cumulative Cavity closure rate upto 6 months:
A: 60.3%; B: 49.6%; C: 31.7%; D: 35.6%.

(f) Drug Resistance

Due to large load, routine sensitivity tests were carried out only on cultures found positive after six months or more of antimicrobial treatment. Cultures were considered resistant if there was any growth in 15 mcgm Streptomycin per ml and 5 mcgm

TABLE 12 Development of Resistance among Patients Sputum Positive after 6 months of Treatment ('Fairly Regular' Cases)

Drug Schedules	Total 'Fairly Regular' Patients	Patients Sputum Positive at 6 months	Sensitivity results available*	Resistant to			Sensitive to S.M. & I.N.H.	
				S.M.	I.N.H.			
					Cat. post.	Cat. neg.		Total
A	196	14	(100.0%)	(50.0%)	5	2	7 (50.0%)	(42.9%)
B	262	39	32 (100.0%)	13 (40.6%)	9	4	13 (40.6%)	12 (37.5%)
C	236	34	28 (100.0%)	—	7	2	9 (32.1%)	19 (67.9%)
D	231	42	35 (100.0%)	—	10	12	22 (62.8%)	13 (37.2%)
Total	925	129	109 (100.0%)	20 (18.3%)	31	20	51 (46.8%)	50 (45.9%)

* Patients resistant to both Streptomycin and INH have been counted under both heads.

INH per ml tubes, in accordance with standards adopted by Veterans' Administration Cooperative Study (Livings 1959). Table 12 shows results of sensitivity tests.

INH being the only drug common to all the Schedules, INH resistance may be used as the basis of comparison. It appears that the incidence of INH resistance strains is the highest in Schedule D and the lowest in Schedule C. As for Schedule A, it may be remarked that although the number of cases remaining positive after 6 months of treatment is very small, yet the risk of resistance among such cases is as high as 57%.

Since sensitivity tests for PAS were not done, the results for Schedule C are not strictly comparable to other schedules

It will also be seen that only in 20 (39.2%) of the 51 patients showing INH resistance had the bacilli lost catalase activity, the percentage of catalase negative being highest in Schedule D. This seems to be the only extenuating factor in favour of Schedule D, if catalase negativity is accepted as an index of lower virulence.

FINANCIAL CONSIDERATIONS

On the face of it, the schedules vary considerably in respect of cost. However, if one considers the length of treatment necessary to reach a stage of Clinical quiescence, the differences narrow down to a great extent. From this study it appears that if the length of treatment in all schedules is accepted as 12 months (excluding post-treatment 'Maintenance Therapy'), roughly the following pattern of treatment would obtain in the schedules that may be considered as good treatment on the basis of immediate results :

Schedule A

- (i) Nearly 35% would need Schedule A for an average of 4 months followed by Schedule D for 8 months;
- (ii) Nearly 35% would need Schedule A for an average of 4 months followed by Schedule C for 8 months;
- (iii) Nearly 30 % would need Schedule A for an average of 4 months, then Schedule C for 4 months and finally Schedule D for 4 months.

Schedules B, C & D: Each for 12 months.

Calculating at current prices, the average cost per patient for 12 months' treatment (including cost of administration of injections at 25nP per injection) would be as follows:—

Schedule A	Rs. 150/-
„ B	„ 105/-
„ C	„ 130/-
„ D	„ 12/-

DISCUSSION

Comparison of results under various schedules is fairly easy in hospital patients or under experimental conditions, where drugs can be administered regularly for a stipulated period and withdrawals are rare. In a Domiciliary Service, large number of patients fall out at various stages of treatment, making clear percentages misleading, and the results too involved for clear understanding. Studies of a similar nature in other countries have also faced similar difficulties

(Mount *et al*, 1954; Robin *et al* 1957; McDougall *et al* 1956) and, therefore, 'calculated rates' according to life-table method, as presented in this report, are considered a better index of results (Livings 1959). Tuberculosis Chemotherapy Centre, Madras (1959) study is conspicuous for a very small number of patients falling off, but this study was based on a highly selected group of patients under experimental conditions. Under conditions obtaining in the country at present, it is extremely difficult to conduct mass-scale studies with such ideal standards. Nor indeed are such conditions obtainable in the routine working of Clinics.

Sputum conversion was achieved in 80.7% in three months in Schedule A, which is considerably higher than in all other Schedules. This is in contrast to the British MRC (1955) and the Veterans' Administration Report (Livings 1959) which do not find appreciable difference in this respect, at least between Schedules A and C. Tuberculosis Chemotherapy Centre, Madras, (1959) reports 89.0% conversion after 9 months' home Treatment as against our 76.6% in Schedule C. Even though Robins *et al* (1957) report lower conversion rates than ours i.e. 56.0% in 12 months under Schedule C an explanation has to be found for lower conversion rates in our patients on Schedule C, as against the Madras experience. It could be due to deliberate missing of one or both drugs by patients. This is not easy to control or prevent in normal clinic working conditions, and has been reported by workers in other countries also (Dixon *et al* 1957 and Wynn-Williams *et al* 1958). The higher incidence of INH resistance in our series as compared to the Madras study could also be due to this factor. In clinic practice, however, efficacy and acceptability of a treatment have to go together, and it has to be admitted that under our conditions, Schedule C seems to be inferior to Schedule A whatever the reason thereof.

Regarding hospitalisation, it was found necessary for 33 patients in Schedule A, the corresponding figures for Schedules B, C and D being 59, 44 and 49 respectively. As the total numbers treated and the initial disease were comparable, and indications, aims and procedure for hospitalisation were the same for all the schedules, the significance of this difference is obvious in countries with meagre institutional facilities.

Almost all workers are of the opinion that Schedule A is the most powerful combination and is the treatment of choice for acutely ill and advanced patients, where maximum benefit is required quickly (Ross 1958; Crofton 1955; Muschenheim 1955; Mitchell & Bower 1958; Tucker 1955). However, superiority in respect of cavity closure and sputum conversion, *per se*, do not make it the 'best' schedule. This superiority has to be judged in relation to cost, acceptability and management under domiciliary conditions. Schedule A is somewhat more costly, more difficult to arrange, and less easily acceptable to patients after the toxaemia has disappeared. But in a situation like ours at present, where quick conversion and early return to work are imperative, the minor disadvantages of Schedule A are more than offset by its advantages already referred to. The higher cost is more than compensated by lesser need of hospitalisation for patients on this schedule. Further the quicker and higher conversion rates assume immense public health and social significance when isolation is not possible in nearly 80% of the homes and facilities for hospitalisation are so insufficient. The larger and earlier conversions reduce the total risk of development of drug resistance. An additional argument for Schedule A is that even when patients are irregular, results of treatment are better than or at least as good as those of regular patients on other schedules.

Some American workers (Deuschle *et al* 1954) consider INH alone almost as efficacious as Schedules B and C even for advanced disease, and Muschenheim

(1958) goes as far as to say that Schedule A is probably the only regime unequivocally established as markedly superior to Schedule D. Our study does not corroborate this view. Even though cases who deteriorated on Schedule D have been eliminated, the results are still poorer than all other schedules, thus tending to prove that INH alone, though cheap, easily administered and acceptable, is not as good as other Schedules for open and cavitary cases. It has also been shown that even for minimal and non-cavitary cases, the results of this Schedule are poorer than Schedules B and C though Philips (1959) found Schedules D & C equally effective in such cases. As stated already, doubling the dose of INH in half the cases in Schedule D, did not in any way improve the results. This has also been the experience of Mount et al (1954) and Biehl (1954) with 10 mgm and more of INH per kg body weight.

In conclusion we feel justified in saying that :

- (1) Schedule A supplemented in later stages by Schedule C, is slightly more costly, more difficult to arrange in terms of organisation and also leads to somewhat greater irregularity. These disadvantages are, however, more than offset by the following considerations:
 - (i) Higher percentage of patients taking adequate treatment;
 - (ii) Higher and quicker sputum conversion, cavity closure and radiological improvement, allowing early return to work;
 - (iii) Lesser need for hospitalisation;
 - (iv) Lesser risk of drug resistance.

If antimicrobials are to be issued free from a Clinic, regularity and cooperation can in a way be enforced by arranging injections in the patients' homes. This will apply easily to an urban clinic where majority of tuberculosis patients are likely to be met as 'nests', so to speak, in the poorer quarters of a city.

- (2) When injections cannot be easily arranged, Schedule C is the obvious choice. One has also to fall back on this schedule for continuation of treatment if clinical quiescence is not attained within 3 to 6 months of Schedule A.
- (3) Even though conversion and cavity closure rates in Schedule B and C are of the same order, the former carries a somewhat higher risk of INH resistance and has, therefore, no merit to recommend it.
- (4) Schedule D having shown poor results by modern standards should only be reserved for situations where the other schedules cannot be given for financial or organisational reasons i.e. where 'no treatment' is the only other alternative.

ACKNOWLEDGMENT

This paper is the result of a joint effort of several members of the staff, not only throughout the conduct of the trial, but also at the time of the collection and interpretation of the data. Special thanks are due to Doctors R. Narasimhan, S.S. Goyal, G.D. Gothi and Jaswant Singh, and we take this opportunity of acknowledging their contributions.

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Pulmonary Functions before and After Thoracoplasty operation and Pulmonary resection*

By

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The value of an operative procedure must be judged not only on the basis of its ability to inactivate or remove a tuberculous process, but also on its function diminishing characteristics. Patients with tuberculosis for whom surgery is proposed often have little functional reserve and the choice of the type of operation may well be crucial in preventing any further progression towards respiratory insufficiency and Cor-pulmonale.

The effect of surgical removal of various amounts of lung or its collapse on the function of the remaining lung has been the subject of several other studies, the results of which have not always been in agreement; while some investigators have found a pattern consistent with developing emphysema in the remaining lung, others have reported over distension alone without any other evidence of disturbance of function.

The gradual increase of resective surgical work for pulmonary Tuberculosis in our Hospital stimulated our interest to determine the comparative effects of Thoracoplasty in contrast to resective surgery on the loss of pulmonary functions in patients surgically treated for tuberculosis. A group of tests is available to measure objectively both divisions of pulmonary functions (1) Ventilation i.e. mechanical component and (2) Respiration i.e. the physiochemical component. In the present study only the first component has been studied.

During a period of 18 months from July, 1958 to December 1959, 84 patients were studied with respiratory function tests pre-operatively. For one reason or the other it was possible to do post-operative studies only in 47 patients. Hence observations have been made and conclusions derived only in 47 patients, studied both pre and post operatively. Posterior staged thoracoplasties were done in 32 cases. Of these, 18 cases had this operation as primary form of surgical therapy, while the remaining 13 cases had Pneumoperitoneum for a period of 12—24 months and one had empyema and non expandible lung following Pneumothorax treatment for nearly 3 years prior to surgical interference. In the resection group, 11 cases had lobectomy and 4 had pneumonectomies. Of the 4 cases who had pneumonectomy, 2 had Pneumoperitoneum and 2 had A. P. as the treatment prior to the operation.

Method of Study

Of the patients studied, 33 were men and the rest 14 were women. The average age of the group under review was 32 years with the youngest being 18 years and the eldest to be operated being 60 years old. All the patients were with

* Presented at the XIVth Tuberculosis Workers' Conference, Poona, 1960.

moderately or far advanced tuberculosis which was not always unilateral in distribution but all were with rather relatively stable tuberculous lesions. All the patients were ambulatory and in good physical condition. The operations included pleural pneumonectomy, pneumonectomy, Lobectomy, Lobectomy with a segment or a Wedge and Thoracoplasty.

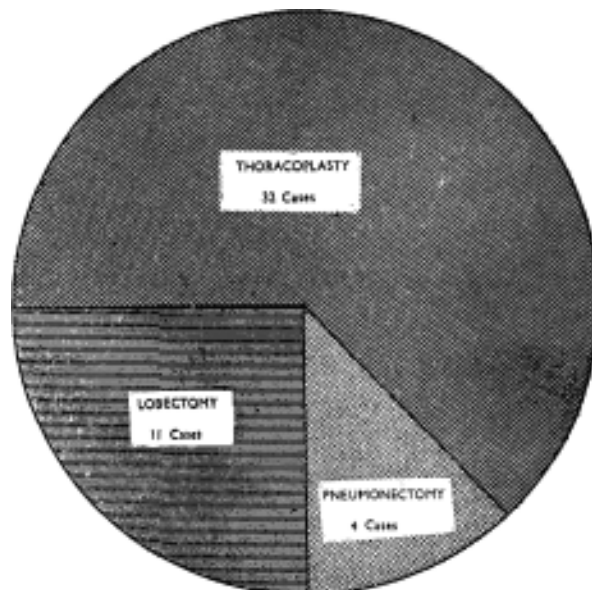
Preliminary observations of Vital Capacity, maximal breathing capacity, bronchspirometry, Bronchoscopy and fluoroscopy were obtained in all patients.

Function determinations were made within a period of 14 to 30 days before surgery particularly in a phase when the amount of secretions was less and were repeated post surgery, the average interval being 82 days.

A Collins respirometer (with nine litre bell and tubing with 3/4 inches in diameter) was employed to measure pulmonary volumina and maximum breathing capacity. *Cournand's* Regression formula was used to calculate Predicted Vital Capacity and maximum breathing capacity.

Bronchspirometry was performed using a standard Zavods double lumen-catheter introduced under direct Laryngoscopy under topical Laryngotracheobronchial anaesthesia with 1 % xylocaine solution. Preliminary seduction included a barbiturate (Sodium Sonreyl 3 grs.) plus Atropine sulphate gr. 1/100. Correct position of the Catheter in the left main bronchus was verified fluoroscopically, the Cuff balloons were inflated and the proximal Catheter Channels were attached to double recording Spirometers, containing 100 per cent, oxygen and Soda lime Cannisters. Records of oxygen consumption, tidal air, respiratory minute volume, inspiratory and expiratory reserve volume and Vital Capacity were obtained. The Broncho-spirogrammes were graded as to its appearance and quality. Tracings which were satisfactory in every way were used for comparative study.

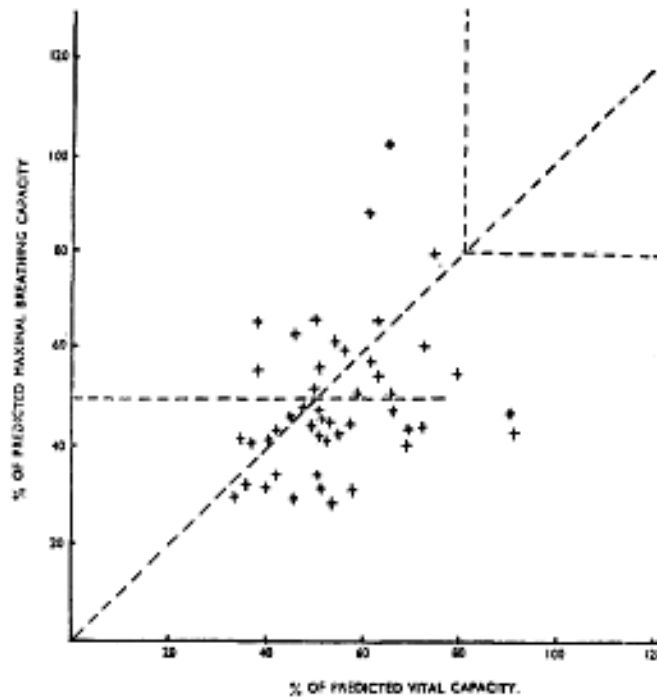
Surgical Procedure adopted :— Graph I shows the various surgical measures done in the group under review.



The trend in the choice of the operation was Thoracoplasty while resection was reserved for very definite indications including strictly localized unilateral disease, a giant or a Lower lobe Cavity or a destroyed lung.

Results

Ventilatory function profile of the Entire Group :— Graph II indicates the pre-operative Ventilatory functions of every patient with maximum breathing capacity on the ordinate and the vital capacity on the abscissa, as the per cent, of the predicted normal.



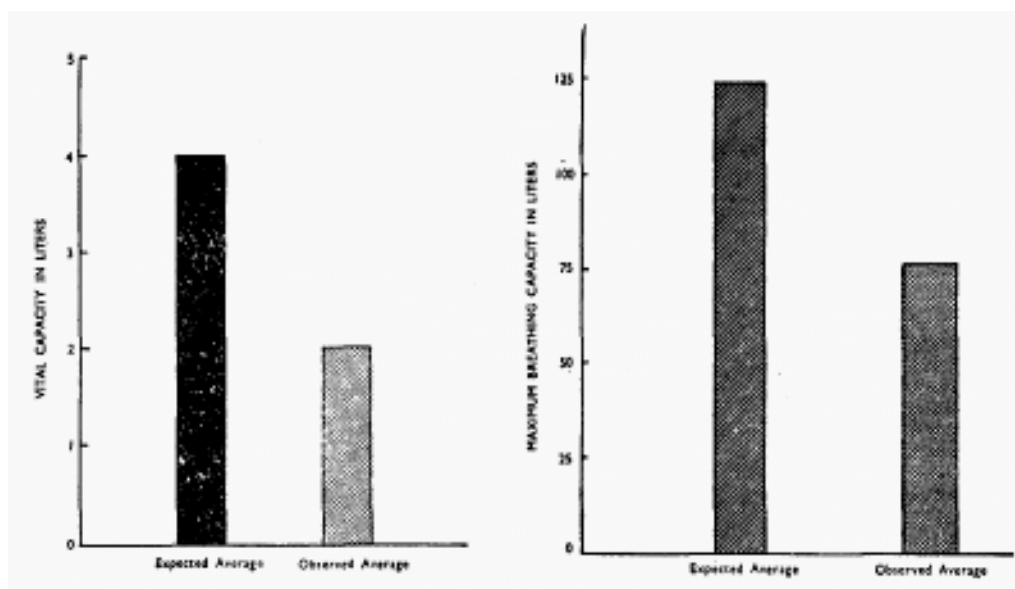
The regression equation for calculation of the predicted normal values have a standard error of about 20 per cent, therefore a performance of 80 per cent, or better must be regarded as possibly being within the normal limits of the whole group.

Points falling on a line drawn at fortyfive degrees to the Coordinate axes show equal impairment of M. B. C. and V. C. That is, the fraction $\frac{\text{per cent. Of Predicted M.B.C.}}{\text{per cent. Of Predicted V.C.}}$ (air velocity index) is equal to 1.0

As is evident from the graph, none of the patients had normal M.B.C. and V.C.

Almost all patients had moderate impairment of Ventilatory functions. Most patients had air Velocity indices within the normal limits of 0.8 to 1.2 suggesting that a Ventilatory defect demonstrable was of restrictive type.

Graphs III & IV show comparison of the average Vital Capacity and maximum breathing capacity observed with the expected average in the 47 cases under review.



The average observed Vital Capacity was 2.14 litres as compared with 3.96 litres expected Vital Capacity. Similarly the observed Maximum Breathing Capacity was 98.2 litres as compared with the average 121.5 litres expected Maximum Breathing Capacity.

A. Thoracoplasty Group :—

Graph V shows the results of comparative study of the total Vital Capacity, maximum breathing capacity and Vital Capacity of the individual lung, oxygen intake per minute and C. C. per breath.

Graph V—THORACOPLASTY GROUP

	Average before Operation	Average after Operation	Total number of cases studied	Functional Loss
Total Vital Capacity	2.14 Liters	2 Liters	25	0.14 Liters
Vital Capacity (R)	1.2 Liters	0.7 Liters	15	0.3 Liters
Vital Capacity (L)	1.2 Liters	0.9 Liters	15	0.3 Liters
Maximum Breathing Capacity	60.3 Liters	48.1 Liters	25	12.2 Liters
Ventilation (R)	5.9 Liters per mt.	5.2 Liters	15	0.7 Liters
Ventilation (L)	5.3 Liters per mt.	5.1 Liters	15	0.2 Liters
Oxygen Intake per Minute (R)	334.4 c.c.	262.7 c.c.	6	71 c.c.
Oxygen Intake per Minute (L)	368 c.c.	224 c.c.	5	144 c.c.
C.C. per Breath (R)	22.6	17.3	6	5.33
C.C. per Breath (L)	29.6	29.5	5	0.1

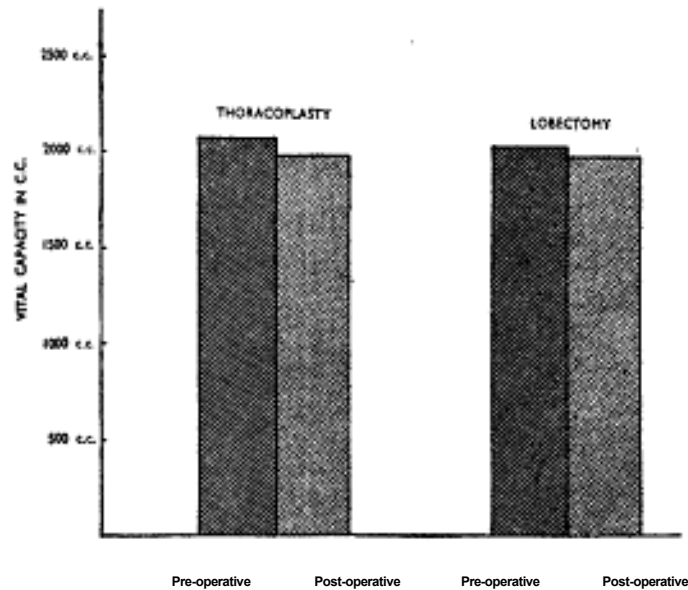
B. Resection Group:—

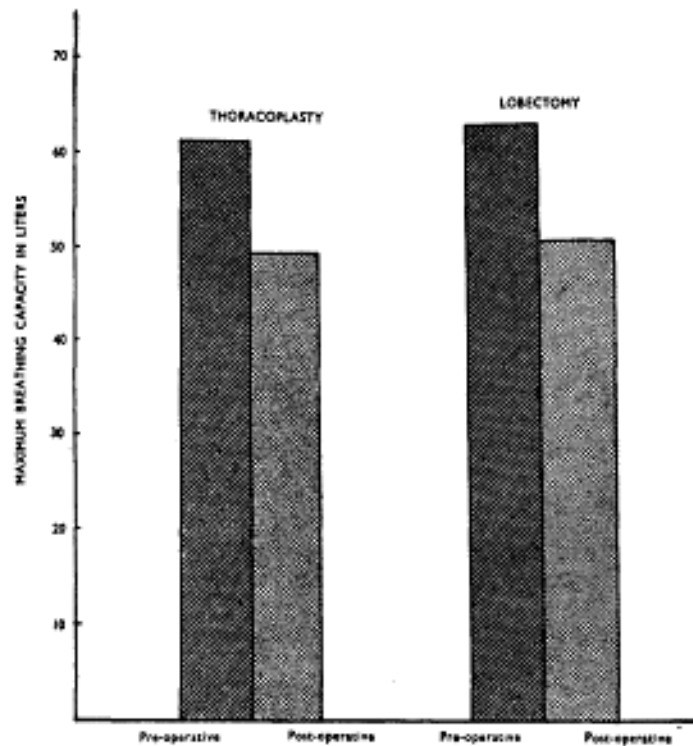
(i) Lobectomy Group:— Graph VI shows the results of comparative study of the total Vital Capacity, Maximum Breathing Capacity, Vital Capacity of the individual lung, oxygen intake per minute and C. C. per breath.

Graph VI:—LOBECTOMY GROUP

	Average before Operation	Average after Operation	Total number of cases studied	Functional loss
Total Vital Capacity	2.1 Liters	2.0 Liters	11	0.1 Liters
Vital Capacity (R)	1.2 Liters	1.1 Liters	6	0.1 Liters
Vital Capacity (L)	1.1 Liters	0.9 Liters	5	0.2 Liters
Maximum Breathing Capacity	61.6 Liters	49.0 Liters	11	12.6 Liters
Ventilation (R)	7.4 Liters per mt.	5.7 Liters per mt.	6	1.7 Liters
Ventilation (L)	10.1 Liters per mt.	5.5 Liters per mt.	5	4.6 Liters
Oxygen Intake per Minute (R)	334.4 c.c.	262.7 c.c.	6	71 c.c.
Oxygen Intake per Minute (L)	368 c.c.	224 c.c.	5	144 c.c.
C.C. per Breath (R)	22.6	17.3	6	5.33
C.C. per Breath (L)	29.6	29.5	5	0.1

(ii) *Pneumonectomy Group*:— Graph VIII shows the results of comparative study of the total Vital Capacity, maximum breathing capacity, vital capacity of the individual lung, oxygen intake and c. c. per breath.





Discussion

Pre-operatively the Vital Capacity was abnormally low and immediately after operation there was further reduction in most of the cases.

In every case the preoperative values for the maximum breathing capacity were low. The reduction was frequently very marked and quite out of proportion to the extent of the lesion. Following operation there was a fall in the maximum Breathing Capacity.

Previous experience with bronchspirometry in the measurement of functional loss due to thoracoplasty are relatively few. The main purpose of the Bronchspirometry was to measure oxygen consumption and Vital Capacity of the operated lung.

Pinner and associates carried out Bronchspirometry post-operatively in 11 patients who had Thoracoplasty operation. The operation varied in extent. The oxygen uptake of the operated side ranged from 23-46 per cent of the bilateral value (mean of 32%).

Leinner investigated twenty six cases with resection of 4-8 ribs. He found a slight decrease of oxygen uptake, minute volume, tidal air and Ventilation equivalent.

Gaensler and Watson studied 22 cases of right sided six rib apical thoracoplasty. The study showed that right lung's participation in the total oxygen uptake diminished from a pre-operative value of 56 per cent to a post operative value of 22 per cent. The right lung's vital capacity portion of the total went down from 38 to 22 per cent.

The results of consecutive bronchspirometry in 23 cases by the same workers are presented from one to thirty days pre-operatively, immediately pre-operatively, immediately post-operatively and 3 months post-operatively. It was shown that the mean pre-operative change in per cent of oxygen uptake is slight.

The total loss during surgery of oxygen uptake may vary from 3 to 100 per cent subject chiefly to the technical factors involved and the extent of the disease. An occasional patient may even show a gain in oxygen uptake. Mean loss was 20 per cent.

Although the post-operative gain was striking in numerous cases this was not always so, some patients showing a continuous loss, the mean post-operative gain from 1—3 months post operatively was 6 per cent.

Kaltrieder found a greater reduction in Vital Capacity than is to be expected from the extent of lung tissue compressed. He noted a reduction of 50 per cent in the Predicted normal value of Vital Capacity (This being due to interference with the mechanics of respiration by reducing the lateral expansion of the chest excursion of the diaphragm and rib rotation).

Leinner noted that following thoracoplasty, there is diminution of total pulmonary volume, reserve air showing the greatest reduction.

Warring noted lowering of the maximum breathing capacity.

Cournand and Richards noted a constant co-relationship between the number of ribs resected and the decrease in maximum breathing capacity. The important factors disturbing such a co-relation in individual cases were the development of scoliosis, further disturbance in diaphragmatic function or collapse of valuable amounts of normal lung tissue.

At variance with these opinions Wright and Woodruff concluded that when collapse is confined to diseased lung tissue no significant reduction in respiratory Capacity on the surgical side occurs. They stated that after sufficient time had elapsed for return of mobility and comfort, the maximum breathing capacity is increased often by as much as 50 per cent. This increment being due to strengthening of respiratory muscles in an exercising patient compared to his former status as a bed patient.

In the present series under review despite the poor functions preoperatively, the reduction in the vital capacity and maximum breathing capacity was there, though there was slight decrease of oxygen uptake, minute volume, tidal air and the ventilation equivalent.

The total oxygen uptake diminished by 2% on an average from its pre-operative value to its post operative value. Similarly the vital capacity diminished by 33% from its pre-operative to post operative value. The maximum breathing capacity showed a loss of 20%.

Knowledge of the amount of the functional loss resulting from different types of resection for Pulmonary Tuberculosis is limited but Ventilatory functions lost as a result of resection, co-relate well with the extent of lung tissue removed.

Although the Bilateral Pulmonary function is of interest in this problem, the changes in function on the operated side obtainable from Bronchspirometry is even more pertinent.

Hirdes found a depression following lobectomy to the extent that the operated lung decreased its participation in the bilateral function by mean value of 12 per cent for oxygen and 9 per cent for Vital Capacity in a series of 36 cases.

Vander Drift in selected group of upper Lobectomies (6 right and 6 left) all of which were considered to be perfectly successful the mean decrease in percentage of the bilateral oxygen uptake for the right sided procedure was from 47 percent preoperatively to 40 percent post operatively and for the left sided operation group the unilateral function was 40 percent before and 25 percent after operation.

Gaensler in a series of 29 lobectomies found a decrease of oxygen consumption from a mean of 47 percent of the bilateral function preoperatively to 35 percent post operatively. The corresponding figures for Ventilation were 51 percent before and 41 percent after operation.

Limburg in a group of 14 patients who had undergone right upper lobectomy, the right lung suffered a mean loss of 47 percent of its normal value for oxygen uptake and 35 percent of its normal Vital Capacity.

In five patients with right sided lower lobectomy, the right lung lost a mean of 51 percent of its normal oxygen uptake and 49 percent of its Vital Capacity.

2 additional patients who had both right middle and Lower lobes removed resulting in a mean loss to the right lung of 67 percent of its oxygen uptake and 61 percent of its normal Vital Capacity.

Taylor and associates studied 35 cases of segmental resection and 39 patients with tailoring thoracoplasty. All patients suffered a loss of 20 percent of total vital capacity, the variations between the individual groups being remarkably few in this respect. The only group which had a larger Vital Capacity loss was that, undergoing pneumonectomy. In the group under Review there was reduction in Total Vital Capacity from 2.1 liters preoperatively to 2.0 liters postoperatively. Similarly the M.B.C. showed a loss of 12.6 liters from its preoperative value of 61.6 liters to 49.0 liters.

The total oxygen uptake showed a diminution of 71 c.c. and 144 c.c. respectively on the operated side.

Conclusion :—The mean loss of Pulmonary functions resulting after Lobectomy is less than after thoracoplasty. Moreover the loss encountered in thoracoplasty increases steadily with the number of ribs removed after operation.

Several authors have pointed out that the amount of functioning lung removed determines the degree of impairment of function and have stressed the importance of preserving as much normally, functioning pulmonary parenchyma as possible in various chronic conditions.

SUMMARY

1. The Results of Pulmonary function studies in a group of 47 patients before and after Thoracoplasty operations have been reviewed.

2. The mean loss of Pulmonary function resulting after Lobectomy is less than after Thoracoplasty.

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3. The loss encountered in thoracoplasty increases steadily with the number of ribs removed after operation.

Of the measures associated with the best clinical and functional results, the following are stressed:

A. Preoperative measures

1. Energetic efforts to reduce the amount and bacterial content of the sputum and to avoid bacterial resistance by using combined chemotherapy controlled by drug susceptibility studies.

2. Encouraging light to moderate amounts of physical activity as well as diaphragmatic breathing exercises before operation.

B. Intra operative measures

1. Lysis of all the pleural adhesions including the inferior pulmonary ligament.

2. Thorough decortication including freely 'Curld Under' edges of the lower lobe resulting from previous pneumothorax and removing the soft fibrin strands so often seen, the immediate gain in pulmonary expansibility is always striking.

3. Pleurizations of as much lung surface as possible after the completion of resection.

4. Saline irrigation of the entire pleural Cavity prior to closure to wash out pleural irritants.

5. Pleural drainage with two large catheters; one directed apicoposteriorly, the other Ventrally.

C. Postoperative measures.

1. Immediate and continued use of breathing exercises, coupled with the use of the Contra-lateral recumbent (non-operated side down) position.

2. In the presence of good expansion, early removal of drainage tubes (third to fourth post operative day) in order to minimise pleural reaction.

3. Early re-thoracotomy in case of extensive clothing even though the general condition of the patient appears satisfactory.

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Success and Results of Chemotherapy alone without collapse Therapy In Pulmonary Tuberculosis*

By

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Introduction

Circumstances compelled the senior author to treat fairly advanced cases of pulmonary tuberculosis with chemotherapy alone since 1955 in two hospitals which he visits regularly as consultant where there are no trained medical officers to undertake collapse therapy but there are arrangements to transfer them to larger tuberculosis hospitals for surgery. While waiting to be called for surgery a number of cases improved so much that even with tomograms cavities that were present after one year of chemotherapy disappeared in another six months to 1 year's time. But usually in the cases either in the Sanatorium (S) or in the hospitals (H) who ultimately recovered if the cavities closed within 9 months to 1 year time mainly with intensive chemotherapy as described below. Some of these cases who were put to postural recumbancy (Dillwyn Thomas) and also reported separately by the senior author (S. K. Ganguli 1958—All India Tuberculosis Workers' Conference, Madras).

Materials :—This paper is to report our experiences gained from 677 proved cases of pulmonary tuberculosis treated during the last four years (1955 to 1958) from three different hospitals viz., M. R. Bangur Sanatorium, Digri, Police Hospital, Midnapore, and Eastern Frontier Rifles Hospital, Salua. The non-tuberculosis cases and irregular discharged cases have been omitted from the series. As the facilities available in these hospitals are different and the treatment provided to the patients has been modified accordingly, the patients in this series may be grouped into two. In the first group "S" out of 553 cases of M. R. Bangur Sanatorium, 363 cases have been discharged closed quiescent, 33 cases died and the result of the remaining are compiled separately in the post-script. In the second group "H" out of 124 cases treated at police hospital, Midnapore and E.F.R. Hospital, Salua, 104 cases have been discharged closed quiescent, 2 cases died and the result of the remaining who are still in the hospitals is included in the post-script. Of the remaining cases of group "H" & "S" about 30 cases there is little chance of recovery and the rest mostly admitted within a year is expected to recover.

Age of the patients:	17 to 70 years in the 1st group. 25 to 50 years in the 2nd group.
Sex:	In the 1st group—Male —468 Female — 85 In the 2nd group—Male —121 Female — 3
Occupation:	Diverse in group S. But in group H the patients were all Police cases except 3 female cases who were wives of the police service men.
Stage of the disease:	Table I below shows the stage to which belong total 467 cases discharged closed quiescent from different hospitals.

* Paper presented at worker's Conference, Poona, 1960.

The table also shows that 230 cases of group S and 44 cases of group H are moderately and far advanced cases.

Table—I

<i>Group</i>	<i>Stage I</i>	<i>Stage II</i>	<i>Stage III</i>
S	133	80	150
H	60	32	12

Group S patients were selected for admission by Selection Committee. These patients had to wait for hospitalisation till beds were available, while the group H patients were admitted as soon as the disease was diagnosed.

Associated disease—Diabetes mellitus in 10 cases of group S and in 2 cases of group H.

Peptic Ulcer— 8 cases in group S (proved by X'ray, Fractional test meal, occult blood in stool). There was frank malaena and haematemesis in one case.

Complicated with bone tuberculosis (spine and hip) — 10 cases.

Miliary cases — 6 including 1 meningial.

Sputum for A.F.B.—Positive in ordinary smear in 249 of group S and 42 of group H.

Major surgical intervention — In 56 of group S i.e. 4.8% of the regular discharge of the group.

Temporary collapse therapy— In 149 cases of group S .ie. 41%. None in group H cases.

Chemotherapy alone — 158 cases i.e. 43.6% of the discharged cases of group S. 98 cases or 94.5% cases of group H (six cases required surgery in addition to Chemotherapy).

Treatment — All these patients (group S and group H) received diet costing Rs. 2/8/- per day, consisting of very adequate quantities of protein, fat carbohydrate, vitamins and minerals. The total calories exceeded 3,600 per day.

As regards rest, except for the very ill patients all of group H cases were up and about in the wards and due to paucity of nursing staff enforcement of bed rest was not possible and also due to the fact that the patients of both the hospitals (Police Hospital, Midnapore and Eastern Frontier Rifles, Salua) belong to semi-military and police forces, it was difficult to enforce bed rest and to our surprise we observed that compared to cases of group S in the Sanatorium where bed rest was enforced, the result of treatment among the group H cases in the police hospitals in the same stage without proper rest even did not show any appreciable difference. Our experience confirms to that of Wynn Williams and Douglas Young (1957). The only symptoms which put the police cases to rest was during haemoptysis. Fortunately haemoptysis except as the presenting symptoms at the commencement of the disease was rare amongst the group H patients whereas haemoptysis amongst the group S cases in the similar stages of the diseases was much more frequent in group S. The reason cannot be explained. As regards environmental hygiene and climate, both the hospitals and the Sanatorium were ideally situated in open lands without any building within a furlong or more. The buildings were especially constructed for the purpose. Both the hospitals and the Sanatorium are situated within the

same district with almost similar climatic condition with moderately low humidity. Maximum temp, in Summer 115° F minimum in Winter 48° F.

Chemotherapy — The course of antimicrobial treatment prescribed to the majority of these patients were, what we call cyclical or rotation courses of chemotherapy. A course continued for three months according to the following schedule:
1st Month: Dihydro Streptomycin Sulphate or Streptomycin —1/2 to 1 gm. daily.

Sulphate according to body weight

Isoniazid tablets—(4-7 mg./kg. of B.W.)
(300 mg. per day average).

2nd Month: Dihydrostreptomycin sulphate or streptomycin sulphate Sodium P.A.S. —1 gm. 3 times a week

3rd Month: Isoniazid— 300 mg. a day.
Sodium P.A.S. —12 gms. a day.

In addition, the patients received vitamin B complex tablets 6 tab. per day containing (vitamin B1—10.0 mg., B2—2.0 mg. Niacianamide 10.0 mg., B6—1.0 mg., Cal. Pantothenate 3.0 mg. in each tablet). Vit. C—500 mgs. daily in stage II and stage III cases. A few received vitamin A & D capsules as well.

The idea of cyclical course of chemotherapy was that by administering not more than two months at a time any one of the three chemotherapeutic drugs along with another it was presumed that chances of emergence of resistant strains to any particular drugs was definitely less than when two drugs were continued months together. Most of the patients tolerated the drugs as administered by cyclical schedule.

As already stated that the ancillary method of treatment including temporary collapse therapy is available in the Sanatorium and not available in other two hospitals, the group "H" patients have been treated with chemotherapy alone. The end results of chemotherapy in two groups of cases at different stage of the disease have been shown below:-

Table II

		Group "S"	Group "H"
Stage I	Total No.	97	60
	% of the total discharged	73%	100%
Stage II.	Total No.	29	24*
	% of the total discharged	36%	75%
Stage III.	Total No.	32	6*
	% of the total discharged	22%	50%

It is observed that the success of chemotherapy alone in group "H" patients is more than in group "S" patients of the same stage of the disease. But if the duration of treatment and amount of chemotherapy required in these two groups are compared it was found that the group "H" patients required a little longer duration of treatment and more amount of chemotherapy than the group "S" patients. Most of the Sanatorium patients had chemotherapy outside before admission and as such period of stay in the Sanatorium was shorter than police

* The remaining 8 stage II and to stage III cases were given postural recumbancy treatment from six weeks to six months as well, so they have been left out of the category of success by chemotherapy alone.

in 1958 amongst stage I cases, from 29% in 1955 to 70% in 1958 in stage II cases and from 11% in 1955 to 35% in 1958 amongst stage III cases.

(4) The chemotherapeutic treatment regime was continuous and was administered according to what is known as cyclical or rotational method as given below :

1st month—(i) Di-hydro Streptomycin sulphate or Streptomycin Sulphate— $\frac{1}{2}$ —1 gm. daily according to body weight.

(ii) Isonicotinic acid hydrazid—5—7 mg/kg of body weight. Average 300 mgm. a day.

2nd month—(i) Di-hydro streptomycin sulphate or Streptomycin Sulphate—1 gm. on alternate days.

(ii) Sodium P.A.S.—12 gm. a day.

3rd month—(i) Isonicotinic acid hydrazid—average 300 mgm a day.

(ii) Sodium P.A.S.—12 gm. a day.

Other medicines—Vit. B. Complex, Vit. C were administered in adequate doses and other vitamins S.O.S.

(5) Toxic symptoms in a few cases due to chemotherapy and methods adopted to alleviate those symptoms have been described.

(6) The experience gained is that temporary collapse therapy administered even under expert management has been relegated to an insignificant place in the management of Pulmonary Tuberculosis but still has some place in our country (India) till the opportunities for resectional surgery are universally available.

(7) Experience was also gained that strict bed rest is no longer essential with adequate chemotherapeutic treatment except in acutely ill toxic patients and in patients with haemoptysis or those who have large necrotic or tension cavities with bilateral advanced disease.

Post-script :—Results of remaining 157 “S” cases and 18 “H” cases during the year 1959.

Of the 157 cases in the Sanatorium i. e. those who were in the Sanatorium on 1st January, 1959, 64 have been discharged closed quiescent after treatment with chemotherapy alone, 15 cases with chemotherapy and collapse, chemotherapy and surgery 6 cases, and 4 cases were transferred to other Hospitals. There were 14 deaths majority of whom was admitted as bilateral advanced cases in whom intensive prolonged chemotherapy with or without collapse had no appreciable effect except prolonging their lives in the Sanatorium for more than 2 to 3 years and in some cases even longer. The remaining 54 patients are still in the Sanatorium and undergoing treatment amongst whom 34 are being treated with chemotherapy alone and 20 with P. P. chemotherapy. Majority of the 34 chemotherapy cases are expected to recover as they have improved both clinically and radiologically since admission during the latter part of 1958 and a few of them will require surgery either thoracoplasty or resection if there is no further improvement within the next 3 months.

Here it will not be out of place to mention that we have discharged 47 patients more during the year 1959 who were admitted during the same year and 40

Further Experience with Viomycin, Pyrazinamide and Cycloserine in the treatment of Pulmonary Tuberculosis*

By

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At the XIV Tuberculosis Workers' Conference at Madras in January, 1958, we reported our preliminary studies on 24 patients who had received treatment with one of the three new anti-tuberculosis drugs: viomycin, pyrazinamide or cycloserine. (Banerjee and Fletcher, 1958). At that time we expressed our opinion that these drugs had a definite place in the treatment of pulmonary tuberculosis, especially for re-treatment of patients with drug resistance and for surgical coverage for such patients. The object of the present paper is to evaluate our total experience with 115 patients who have been treated with one or the other of these drugs during the last 3 years, including the 24 patients previously reported. Most of these patients were suffering from far-advanced pulmonary tuberculosis and had been treated for prolonged periods with the usual anti-tubercular drugs without success. In 45 cases the new drugs were used to provide anti-microbial drug coverage for surgical intervention when there was evidence of drug resistance to conventional therapy.

Further experience has generally confirmed our previous conclusions, particularly as to the value of these agents for surgical coverage. There have also been some examples of serious toxic reaction, which had not been noted at the time of these preliminary reports.

Material and Methods

One hundred and fifteen patients with chronic and advanced pulmonary tuberculosis were selected for the study. With the exception of 13 patients, all had sputum positive on smear before these drugs were started. All had been previously treated with SM, INH and PAS for an average of 3-4 years and there was clinical evidence of resistance to these drugs, although actual sensitivity determination could not be done.

The division of these patients into various groups for purposes of treatment and analysis is indicated in Table I. It will be noted that 18 patients were treated with viomycin, 38 with pyrazinamide and 59 with cycloserine. Seventy patients were in the "Non Surgical Group" and 45 were in the "Surgical Group".

TABLE I
Division of Patients in Treatment Groups

Drug	Non-Surgical Group	Surgical Group	Total
Viomycin	14	4	18
Pyrazinamide	20	18	38
Cycloserine	36	23	59
Total	70	45	115

* Presented at the Worker's Conference, Poona, 1960.

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The Non-Surgical Group consisted of 70 patients who were beyond the scope of surgical treatment because of the extent and distribution of pulmonary lesions, limited pulmonary function or poor general condition. The average duration of previous treatment with SM, INH and PAS was 50 months, or just over 4 years. All had far advanced, bilateral, active pulmonary tuberculosis with a down-hill course of the disease before starting the new drugs. In all except 10 cases the sputum was positive on smear, and all were considered to show clinical evidence of bacterial resistance to the conventional drugs. Fourteen of these patients were treated with viomycin, 20 with pyrazinamide and 36 with cycloserine, for average periods of 16 weeks, 10 weeks and 12 weeks (Table II). Such relatively short treatment periods of 3-4 months were dictated partly by the short supply of the drugs and partly by the fact that further improvement was not usually noted after about three months of treatment.

TABLE II
Non-Surgical Group

Drug	Number of Patients	Average Previous Treatment in months	Average Period of Treatment in weeks	Toxicity	RESULT	
					Good	Failure
Viomycin	14	35	16	Albumin-urea-2 Sensitivity—2	3 (21%)	11
Pyrazinamide	20	61	10	Jaundice—1 Menorrhagia—2 Hemoptysis—1	3 (15.0%)	17
Cycloserine	36	54	12	Severe Psychosis Mild Mental Symptoms—2	7 (19.4%)	29
Total	70				13 (18.6%)	57

The Surgical Group consisted of 45 patients who had had prolonged previous treatment with the usual anti-tuberculosis drugs and had developed resistance to them. The average period of previous treatment was 40 months or nearly 3 years. All had positive sputum on smear except for 3 patients who, on serial roentgenograms and clinical examination, showed active disease.

Surgery was the only hope for these patients but the attending risk was considered high because of the infectiousness of the sputum, the extent of the lesions and the evidence of drug-resistance. For these reasons, the newer drugs were employed for surgical coverage for these patients. Viomycin was used for four patients, pyrazinamide for 18 patients and cycloserine for 23 patients (Table III). Therapy was usually commenced 2-4 weeks before operation and continued for 4-12 weeks (1-3 months) after operation.

TABLE III
Surgical Group. Type of Operation

	Pleuro— Pneumo- nectomy	Pneumo- nectomy	Lobecto- my	Segmen- tal Resection	Thoraco- tomy	Thoraco- plasty	Total
VIOMYCIN	—	1	2	—	—	1	4
PYRAZINA- MIDE	1	10	6	—	1	—	18
CYCLOSER- INE	1	13	4	—	3	2	23
TOTAL	2	24	12	—	1	3	45

The types of operation performed are also indicated in Table III. It will be noted that pneumonectomy or pleuropneumonectomy was required in 26 of the 45 cases (61.9 per cent). Of the 15 patients who had lobectomy or segmental resection, 3 had bilateral resections and one had a thoracoplasty on the contralateral side. Three patients were treated by thoracoplasty alone and one patient had only a thoracotomy. Pleuropneumonectomy was contemplated for this patient but was abandoned when pathological bleeding developed after mobilization of the lung. The above figures will confirm the fact that this was a group of patients with far-advanced disease for whom salvage by surgery was attempted with the aid of the new drugs.

Dosage Schedule: Viomycin, pyrazinamide and cycloserine were each used in combination with the usual dosage of isoniazide (150-300 mgm. daily). The larger doses of isoniazid which had been tried by some investigators (Wolinsky and Kapur, 1959) were not used. Viomycin was given in a dosage of 2Gms. twice weekly in divided dose, 1 Gm. in the morning and 1 Gm. in the evening. For pyrazinamide the dosage was 1.5 to 2.0 Gms. daily, depending upon body weight. This is similar to that employed by other workers (Small, 1959; Kaida and Sugiyama, 1959). Cycloserine was given in a dosage of 250 mgm. twice daily, or 500 mgm. per day, except for the first few patients, who received 1 Gm. daily. This is the usual recommended dosage, though some workers have given 750 mgm. daily. (Ryder, 1959; Wolinsky and Kapur, 1959).

As already indicated, the usual period of treatment was not more than 3-4 months although a few patients were treated continuously for as long as six months with one of these drugs. The longer treatment period of 6 to 24 months used by some investigators (Wolinsky and Kapur, 1959; Small, 1959) were not practicable in this series.

Results in the Non-surgical Group

The data are summarized in Table II. It will be seen that out of a total of 70 patients who had treatment with one of the three drugs, the result in 13, or 18.6 per cent, was considered "Good" and in 57 as "Failure". A good result means that the patient is clinically well, the x-ray is stable (though cavities may still be apparent), the sputum is negative on concentrated smear or culture for at least six months, and the patient is considered fit for discharge from the sanatorium. The

follow-up period in these cases is variable and is not sufficient for us to state that the disease actually is arrested. No doubt some of these patients would suffer relapse within a few years. The patients classified as "Failure" had persistently positive sputum and progressive disease after treatment, though many of these patients had a temporary period of clinical improvement, weight gain, x-ray improvement and even temporary conversion of sputum, during the treatment period. Thus, the actual rate of salvage in cases of this type, using any one of these three drugs, is not more than 15-20 per cent. The results with each of the three drugs will now be discussed in further detail.

Viomycin: Out of 14 patients treated with viomycin for an average period of 16 weeks, only 3 patients (21.4 per cent) had real benefit. One of them showed marked clinical improvement, sputum conversion and cavity closure. Another patient showed moderate clinical improvement and sputum conversion, and 11 lbs. weight gain, though there was not much radiological change. She had a thoracoplasty later on. In a third patient, with bilateral far advanced lesions, the down-hill course of the disease was checked by viomycin and apparently he was salvaged by pulmonary resection. All these three patients were finally discharged as arrested cases.

Toxicity was noted in two patients who had persistent albuminuria after prolonged treatment with viomycin for 20 to 24 weeks. In two cases treatment had to be stopped because of toxic symptoms. One patient developed a severe sensitivity reaction after 4 weeks of treatment and the other developed jaundice and dermatitis after one week of treatment. It is difficult to say whether viomycin actually caused the jaundice and dermatitis or not.

Pyrazinamide: Twenty patients were treated with pyrazinamide for an average period of 10 weeks. Three patients (15 per cent) had a good result. Two of them had sputum conversion and showed radiological improvement. One of these has already been discharged as an arrested case and the other is still under sanatorium treatment, but should be discharged soon. The third patient had a right pneumectomy under coverage of pyrazinamide about one year previously and was re-admitted with a fresh lesion in the remaining lung, but with negative sputum. She showed marked and rapid regression of her lesion with a second course of pyrazinamide and was discharged as an improved case.

One patient showed signs of severe liver damage. He had pyrazinamide treatment for three months and soon after the drug was stopped, developed jaundice and ascites from which he ultimately recovered. This case was reported in detail in our previous communication (Banerjee & Fletcher, 1958). One patient, who was treated for 14 weeks with pyrazinamide, died of massive haemoptysis two months after the discontinuation of the drug. Another patient had haemoptysis during treatment with pyrazinamide and became worse. Some increased menstrual flow was noted by most of the female patients treated with pyrazinamide, and two patients experienced menorrhagia of moderately severe degree. It seems clear that pyrazinamide, especially when administered over a prolonged period, has some definite effect on the clotting mechanism.

Cydoserine: Thirty six patients were treated with cycloserine for an average period of 12 weeks. A favourable result was obtained in 7 cases (19.4 per cent). In five cases the arrest of the disease was due to cycloserine therapy alone. Two patients improved and stabilized under cycloserine and the control of the disease was later completed by surgery under cover of pyrazinamide. One patient, who had cycloserine for 20 weeks, first improved both clinically and radiologically and gained 13 lbs. in weight. She then became worse, lost 25 lbs., cavities reopened and she

died while still under treatment. This was a very chronic case in which there was obvious clinical evidence of the development of resistance to cycloserine and isoniazid. A similar case was reported in our previous communication (Banerjee & Fletcher, 1958).

There were three patients who developed severe psychoses after one or two weeks of treatment with cycloserine. Two more patients developed mild mental symptoms, one after the first week of treatment and the other after the fourth week. These mild symptoms cleared up promptly after treatment was stopped. However, in the case of the patients with psychoses, abnormal behaviour persisted for 2 to 3 months, in spite of the fact that cycloserine was discontinued immediately and treatment with tranquilizers and electric shock therapy was instituted. None of these patients had any neurological symptoms. After recovery from the psychosis, two of these patients were later salvaged by pulmonary resection under cover of pyrazinamide. One of them is still under treatment and is scheduled for excisional surgery in the near future. Because of the importance of toxic manifestations, a case report of one of these patients is presented herewith.

Case Report

Ramchandra (Hospital No. 7782), a 22 year old male, was admitted in January 1957 with far advanced bilateral pulmonary tuberculosis and positive sputum. Chest X-ray showed a larger cavity in the right upper zone and scattered infiltrations on both sides. Initially he was treated with SM, INH and pneumoperitoneum, and PAS was added after 3 months because of reactivation on the left side. After one year of treatment, there was evidence of resistance to these drugs and the sputum remained positive without much radiological improvement. In January 1958, cycloserine was started to provide anti-microbial coverage for a contemplated right pneumonectomy. After 2 weeks the patient suddenly developed a severe psychosis and cycloserine was immediately discontinued. The patient was completely disoriented and was at times quite boisterous. He talked incoherently and at times showed a paranoid tendency. He responded slowly to treatment with tranquilizers and E.C.T., which was administered in 8 sittings. Within 3 months his mental condition had returned to normal. His general condition, which had deteriorated during the psychosis, gradually improved, although sputum remained positive. In November 1958, right pneumonectomy was successfully performed under pyrazinamide-INH coverage and the patient was discharged in July, 1959 in good condition with tuberculosis apparently arrested.

Results in the Surgical Group

The results in the Surgical Group are indicated in Table VI. It will be noted that surgical coverage was provided by viomycin for 4 patients, pyrazinamide for 18 patients and by cycloserine for 23 patients. It is our impression that the results do not vary significantly among the 3 drugs, although it should be noted that there were no complications in the viomycin group and all four patients had good results. This is probably not statistically significant, due to the small size of the group. Therefore, it seems more useful to consider the over-all results in the entire group, rather than to consider separately the result with each of the drugs.

The Complications of Surgery were remarkably few, when one considers that this is a group of "Salvage Cases", with far-advanced disease, positive sputum and resistant organisms. Broncho-pleural fistula did not occur in this series, although there was one case of an asymptomatic residual air space after upper lobectomy, which was controlled by post resection thoracoplasty. The absence of

fistula is the more remarkable in view of the fact that 26 of the patients had pneumonectomy. There was only one case of post-operative empyema, in a patient who had pneumonectomy under cover of cycloserine. The complication was successfully managed by drainage and total thorociplostry. Six patients (13.3 per cent) had a spread, or reactivation of disease post-operatively. Three of these patients were in the pyrazinamide group and three in the cycloserine group. Three patients had contralateral spread, that is, fresh lesions appearing on the opposite side at intervals of 1-7 months after operation. In 2 cases the operation was a right pneumonectomy and in one it was a resection of the right upper and middle lobes. All three of these spreads were controlled by further periods of drug therapy. Two of the patients were discharged in good condition and one is still under treatment in the sanatorium with sputum negative and x-ray clearing. One patient had a spread on the same side one year after resection of the left apicoposterior segment under cycloserine coverage. This was controlled by a further course of drug therapy and post-resection thoracoplasty. The patient is still in the sanatorium with sputum negative, general condition good and x-ray clearing. Two patients had a reactivation of pre-existing contralateral disease following operation—a right upper lobectomy under cycloserine in one case and a left pneumonectomy under pyrazinamide in the other. The first patient was managed by resection of the left upper lobe under pyrazinamide, with a good result. The other patient has not responded to treatment and still has active disease in the remaining lung, with positive sputum. He represents the one treatment failure in this group of 45 surgical cases.

There were two Post-Operative Deaths in this series of 45 operations, a mortality rate of 4.4 per cent. As far as could be ascertained, neither of these deaths was due to drug toxicity or to failure of the drugs to control the infectious process. One patient, a 45 year old female, died suddenly on the third post-operative day after an uneventful pneumonectomy under cover of pyrazinamide. There was no evidence of broncho-pleural fistula, haemorrhage, atelectasis or pneumonia. The death was attributed to coronary occlusion or pulmonary embolus, but permission for post-mortem examination was not obtained. The other patient, a 36 year old male, had a thoracotomy and mobilization of the lung with a view to performing pleuropneumonectomy under cover of pyrazinamide. Blood loss was quite severe and was replaced by multiple blood transfusions. When mobilization was complete, pathological bleeding from all the raw surfaces suddenly began and the patient went into shock. The operation was terminated without resecting the lung. Eventually, bleeding and shock were controlled, but the patient expired 24 hours later, apparently due to pulmonary edema resulting from over-transfusion. Urine examination and post-mortem examination confirmed the diagnosis of transfusion reaction and this seemed to be the cause of the pathological bleeding, rather than any toxic effect of pyrazinamide. The mortality rate of 4.4 per cent compares favourably with the rate of 5 per cent noted in a series of pulmonary resections of all types performed in this institution during the 3 years 1957 to 1959.

The Final Results in the surgical group are also encouraging (Table IV). Of the 45 patients, 32, or 71.1 per cent, were classified as having a good result. This means that the patient was discharged from the sanatorium in good condition, with sputum negative and without evidence of active disease by chest x-ray. Most patients were not discharged until 4 to 6 months after operation, so there was ample opportunity to observe any early complications, spread or relapse. Some patients have had further follow-up examinations a year or more after operation, but others have not been seen since discharge. Obviously, some of these might have had a relapse later on unknown to us. Ten patients, or 22.2 per cent, are still under treatment in the sanatorium, having been operated upon 3 to 12 months previously, but in good condition, with sputum negative and prognosis favourable. There is only

TABLE IV

T *Surgical Group—Complications and Results*

Drug	Number of Patients	Complication of Surgery			Surgical Mortality	Results		
		Broncho-Pleural-Fistula	Empyema	Spread or Reactivation		Good	Still Under Treatment Sputum Negative. Prognosis Good	Failure Disease Uncontrolled
Viomycin	4	—	—	—	—	4	—	—
Pyrazinamide	18	—	—	3	2	9	6	1
Cycloserine	23	—	1	3	—	19	4	—
Total	45	—	1 (2.2%)	6 (13.3%)	2 (4.4%)	32 (71.1%)	10 (22.2%)	1 (2.2%)

one patient (2.2 per cent) who has to be classed as a failure, due to persistent, uncontrolled disease. He is a 35 year old male who had a left pleuropneumectomy under cover of pyrazinamide. Within 2 months after operation, sputum again became positive, due to reactivation of lesions in the contralateral lung. Post-resection thoracoplasty on the side of pneumonectomy and drug therapy have been ineffective in controlling the disease.

DISCUSSION

Toxicity:

All three of these drugs are potentially toxic. According to our experience, Viomycin is perhaps the least toxic. In two cases we had a sensitivity reaction necessitating the stoppage of the drug, and there were 3 cases of mild albuminuria which cleared up after completion of the treatment.

Hepato-Toxicity of pyrazinamide is a serious problem, the more so since it develops without warning and may be serious or even fatal. This problem has been reviewed in detail by Small (1949), who collected reports on 1629 patients treated with pyrazinamide. Thirty-nine of these patients (2.4 per cent) developed jaundice and there were 3 deaths. In 88 additional cases the treatment was discontinued because of the detection of abnormal liver-function tests. Ideally, liver-function tests, preferably the B.S.P. or Bromsulphonphthalein test should be carried out at intervals of 1 to 2 weeks, to detect impending liver damage. In practice, this is difficult and was not done in our series. We had one case of jaundice among 38 patients treated with pyrazinamide, or an incidence of 2.9 per cent, which is similar to that quoted above.

Pyrazinamide may produce a bleeding tendency in some patients. Most of our female patients noted mild to moderate menorrhagia under pyrazinamide. Severe haemoptysis occurred in two patients and one patient exhibited pathological bleeding during operation, though this was probably due to a transfusion reaction. Since such a bleeding tendency seems to appear after prolonged treatment, possibly due to impairment of liver function, we feel that it is advisable to institute pyrazinamide therapy not more than 2 to 3 weeks before contemplated surgical intervention, and to further protect the patient by administration of Vitamin K.

Neurotoxicity, manifested by mild to severe mental symptoms, psychosis or convulsions, may present a serious problem in connection with cycloserine therapy.

This complication had not been experienced at the time of our previous report (Banerjee & Fletcher, 1958), though it has been described in most of the literature on cycloserine. In this present group of 59 patients, 3 developed a severe psychosis. A distressing feature was the fact that the psychosis in each case persisted for 2 to 3 months after discontinuing cycloserine, in spite of treatment with tranquilizers and electro-convulsive therapy. However, all patients eventually made a complete recovery. Wolinsky & Kapur, (1959) observed that the neurotoxicity of cycloserine is potentiated by isoniazid, particularly if the latter is given in high doses. It has been suggested by Barclay (1957) that the combination of the drug with phenobarbitone or dilantin will appreciably reduce the incidence of neurotoxicity. We have not had experience with this combination. It is obvious that patients with a history of epilepsy, neurological disorders, psychosis or marked emotional instability, are unsuitable for cycloserine therapy.

In summary, toxic potentiality of each of these drugs is sufficient to justify the conclusion that they should not be used in place of safer drugs for the routine primary treatment of pulmonary tuberculosis. When they are used in selected cases, it should be on an institutional basis, with the patient under close and continuous observation.

Indications for Treatment: The effect of these newer drugs in the treatment-failure group of patients, who are unsuitable for surgery, are not very encouraging, though any favourable result in such a group is welcome. It has been claimed (Small, 1959) that pyrazinamide-isoniazid has a qualitative superiority over other drug regimes because of the eradicated action of this combination, which brings about a higher percentage of open healing and sputum conversion, provided the patient is still sensitive to isoniazid. But in patients with far-advanced, chronic tuberculosis, who have developed resistance to all the usual drugs, the results of other workers are similar to our own. In a series of 35 such patients treated with cycloserine and isoniazid for periods of 9 to 13 months, Wolinsky and Kapur (1959) found that only 8 were substantially improved and none was arrested or rendered sputum-negative. In our series of 70 patients, improvement was maintained in only 13 or 18.6 per cent, and these were the patients whose disease was less extensive at the start of treatment. We have therefore concluded that the indications for treatment with the new drugs in this type of case are based on the extent and activity of the disease and the general condition of the patient. The patient with far-advanced, progressive, cavitory tuberculosis, who is going downhill in spite of treatment, will very rarely respond to the introduction of one of the new drugs. On the other hand, the patient with chronic disease, resistant organisms and positive sputum, but without much toxicity or progression of the disease, may show a gratifying response to treatment with viomycin, pyrazinamide or cycloserine.

In contrast to the non-surgical group, there is no doubt as to the value of these drugs in the Surgical Group. The low incidence of bronchopleural fistula and empyema, and the relatively low mortality rate, in a group of far-advanced salvage cases, with positive sputum and drug-resistant organism, is convincing evidence of the effectiveness of these agents in providing surgical coverage. It is a great advantage to the surgeon to have at his disposal one or more of such drugs which can be brought into play when there is evidence of resistance to the usual drugs and surgery must be undertaken. Furthermore, by judicious pre-operative use of these drugs, it may be possible to prepare for successful operation some patient who would otherwise be beyond the scope of surgery. In short, coverage with viomycin, pyrazinamide or cycloserine is indicated for any patient with positive sputum and/or organisms resistant to the usual drugs, upon whom major thoracic surgery is undertaken.

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Choice of Drugs:

The choice of the three new drugs to employ in a given case is likely to be governed partly by availability and expense, Viomycin is at present the only one of the 3 drugs available in India and it is also the most costly. It has the advantage of less dangerous toxicity than the other two, and it has been our impression that there is less tendency for the early emergence of resistance. Thus, it may be better-suited to the long-term treatment of non-surgical cases, if expense does not stand in the way.

Pyrazinamide is contra-indicated in any patient with cirrhosis, chronic alcoholism or evidence of liver damage. Cycloserine is contra-indicated for patients with a history of epilepsy, mental abnormality or neurological disorder. Otherwise, there seems to be little to choose between the two. Generally, we have preferred cycloserine for longer-term treatment, because of the threat of liver damage with pyrazinamide. Mental symptoms due to cycloserine will usually appear early if they are going to appear at all, while the possibility of liver damage increases with prolonged treatment. Under cycloserine treatment, the feeling of well-being and gain in weight, at least for a period of a few months, are striking features which are not noted to the same extent with other drugs. For surgical coverage, we have generally preferred pyrazinamide or cycloserine, although our results with viomycin in a small group of 4 patients were very good. In the series, the results with cycloserine were somewhat better than those with pyrazinamide, but most reports indicate that pyrazinamide is the more powerful drug and it is generally favoured for surgical coverage.

SUMMARY AND CONCLUSIONS

A treatment-failure group of 115 patients were re-treated with either viomycin, pyrazinamide or cycloserine in combination with isoniazid. In 45 cases, these drugs were used to provide anti-microbial coverage for surgical intervention, with excellent results and a low incidence of operative complications. Among 70 patients who were not suitable for surgical intervention, only 13 had good results. There was one case of hepato-toxicity in the pyrazinamide group, 5 cases of mild or severe psychosis in the cycloserine group, and one case of severe drug sensitivity reaction in the viomycin group.

As a result of our own experience and that reported in the literature, the following conclusions seem warranted. (1). Viomycin, pyrazinamide and cycloserine are effective agents in the treatment of pulmonary tuberculosis. For best results, they should be used in combination with isoniazid. (2). All three drugs exhibit definite and sometimes serious toxicity in a small proportion of cases. (3). None of these 3 drugs should be employed for the primary, or long-term treatment of pulmonary tuberculosis. (4). These drugs have a place, though a limited one, in the re-treatment of patients with advanced, chronic tuberculosis, who are resistant to conventional therapy. However, where surgery is not possible, not more than 20 per cent of such patients are likely to be salvaged. Viomycin is perhaps more effective in this group than pyrazinamide or cycloserine. Such patients should be carefully selected and treated under institutional care. (5). All 3 drugs, and especially pyrazinamide and cycloserine, are extremely valuable to provide effective anti-microbial coverage for patients with positive sputum and resistant organisms undergoing major thoracic surgery. Their use will result in a significant decrease in morbidity and mortality. (6). The Tuberculosis Association should use its influence to make these valuable anti-tuberculosis drugs available in India, where their use should be restricted to tuberculosis specialists, sanatoria and thoracic surgery centres.

NEWS AND NOTES

XXI Annual Meeting

The XXI Annual General Meeting of the Tuberculosis Association of India will be held in New Delhi on April 18, 1960 in the conference hall of the Association at 11.15 A.M.

The Central Committee of the Association will also meet on the same day.

The Conference of Secretaries will be held at 9-30 A.M. on 19th April, 1960. The Standing Technical Committee of the Association will meet in New Delhi on April 19th & 20th, 1960.

Health Visitors' Course

The 1960 Tuberculosis Health Visitors' Course commenced in the New Delhi TB Centre on 2nd January, 1960. Eleven candidates deputed by various states are under training.

Health Visitors' Course, Calcutta

The West Bengal Tuberculosis Association will institute Tuberculosis Health Visitors' Course in Calcutta from 1st April, 1960. Those desirous of attending the course may apply to the Honorary General Secretary, Bengal Tuberculosis Association, P.21, Scheme 49, C.I.T. Road, Entally, Calcutta-14.

Film on Home Treatment of Tuberculosis

Information Films, New Delhi, have produced for this Association a documentary film on the Home Treatment of Tuberculosis. It was previewed by the Tuberculosis Association of India and changes in the film are being effected and it is hoped that the film will be released shortly.

Library

The Tuberculosis Association of India has been developing a library which has, at present about 600 medical books and periodicals.

Eastern Regional Committee of the IUAT

The next regular meeting of the Eastern Regional Committee will be held in Sydney, Australia, on the 19th and 20th May, 1960. This will be held at the time of the W.H.O. Seminar in Sydney. The meeting will discuss among other things various aspects of fight against tuberculosis in the Eastern Region.

Sixteenth International TB Conference

The General Assembly of the International Union against Tuberculosis at its meeting held in Istanbul in September last decided that the Sixteenth International Tuberculosis Conference be held in Toronto, Canada from the 10th to 14th September, 1961.

This biennial Conference is being sponsored under the joint auspices of the International Union against Tuberculosis, Paris and the Canadian Tuberculosis Association,

IUAT Membership

The Tuberculosis Association of India has to recommend to the International Union against Tuberculosis, Paris names of those who wish to become ordinary members of that Union from India for the year 1960. Members of the Union will receive, free of cost, copies of the quarterly bulletin and newsletter published by the Union. Those wishing to enrol themselves as ordinary members may write to the Secretary, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-2.

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The Indian Journal of Tuberculosis

ABSTRACTS

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Abst. No. 2

Studies of Pulmonary Function Before and After Pulmonary Surgery in 450 Tuberculous Patients

Vital Capacity and Maximum Breathing Capacity: Four hundred and fifty tuberculous patients received pre-operative and post-operative pulmonary function tests at an average interval of six months.

There was co-relation between the extent of disease and the loss in vital capacity and maximum breathing capacity. Likewise there is co-relationship between the amount of lung tissue removed and loss of ventilatory function. In general segmental resection for localized disease caused little loss of function.

Even lobectomy does not cause sufficient loss to be significant.

Bilateral resection and Pneumonectomy may cause large loss of vital capacity and maximum breathing capacity except in the case of removal of destroyed lung.

(John, K. Curtis; Helene Bauer, Howard, K. Rasmussen and John T. Mendenhall. *J. Thorac. Surg.*, Vol. 37, No. 5, May, 1959.)

Studies on the Gaseous Content of Tuberculous Cavities

Gas samples were obtained from 19 tuberculous cavities by direct transparietal needling and examined for their Carbon Dioxide and Oxygen content.

Cavities were classified into three groups:

1. *Open Cavity:* in which air and fluid flowed freely through the communicating bronchi. The intra cavitory pressure fluctuated around zero and the gas composition varied between ordinary and alveolar air.

2. *Partially Blocked Cavity:* with the gas content varying between the values of open and blocked cavities. The blockade of communicating bronchi was either incomplete or ephemeral [The initial pressure was either clearly negative or clearly positive (Tension Cavity)].

3. *Blocked Cavity:* with initial negative pressure with low oxygen content and a high carbon dioxide content. There was a total blockade of

communicating bronchi at the time of the needling, and this could not be broken by the withdrawal of the air from the cavity or by injection of Propyl-iodine (Dionosil) into the cavity.

Blockade or intermittent closure of an active tuberculous cavity is viewed as an obstacle to antimicrobial therapy. Sterilizing drugs such as Isoniazid and Streptomycin with effects that are exerted only against active metabolising tubercle bacilli under aerobic conditions might be expected to have a slower antimicrobial action in blocked or partially obstructed cavities than in cavities with free bronchial communication and, therefore, high concentration of oxygen.

(Jaakko H. Haapanen, Irving Kass, Goffredo Censini and Gardner Middlebrook. *Amer. Rev. Resp. Dis.*, Vol. 80, No. 1, Part 1 of two parts, July, '59.)

Patterns of Disturbed Lung Function in Patients with Chronic Obstructive Vesicular Emphysema

The lung volumes, the mechanical and ventilatory functions of the lungs, and the pulmonary diffusing capacity were measured in 19 patients with chronic obstructive vesicular emphysema.

The patients in whom emphysema developed rapidly without a preceding history of chronic bronchitis (Group B) showed severe damage to the diffusing surface of the lung as measured by the diffusing capacity for carbon monoxide.

In the patients in whom emphysema developed after many years of chronic bronchitis (Group A) the ventilatory disability and the incidence of cardiac complications were even greater than in Group B, but diffusing capacity was normal or only moderately impaired. Thus at least two separate factors are concerned in the pathogenesis of the disease:—

1. One associated with chronic bronchitis can produce the clinical and physiological picture of emphysema and cor pulmonale without detectable damage to the alveolar and capillary tissues of the lung.

Chronic bronchitis alone takes many years to produce the clinical and physiological state of

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emphysema and does not cause damage to the diffusing surface of the lung.

2. The factor concerned in the impairment of diffusion is associated with a much more rapidly developing form of emphysema.

The prognosis is graver in those patients, usually older men, in whom emphysema develops rapidly with little antecedent history of the chronic bronchitis.

(*Colin Ogilvie. Thorax, 14, 113, '59.*)

Partitional Respirometry in Cardio-Pulmonary Disease

Partitional respirometry gives useful information concerning ventilation, perfusion relationship and effective diffusing capacity.

In congenital heart disease there is diminution of diffusing capacity associated with pulmonary hypertension.

In emphysema there is decrease of diffusing capacity. Well compensated patients maintain a normal effective pulmonary flow at the expense of hyper-ventilation and inefficiency of ventilation.

In industrial diseases it helps in finding alveolar capillary block syndrome.

Ageing is associated with a progressive decrease of both diffusing capacity and ventilatory efficiency.

(*Roy J. Shephard. Thorax, 14, 153, 1959.*)

The Forced Expiratory Volume After Exercise, Forced Inspiration, and the Valsalva and Muller Manoeuvres

In patients with obstructive airway disease F.E.V. (Forced Expiratory Volume) increased immediately after forced inspiration and immediately after increase in lung blood volume by the Muller manoeuvre. This did not occur in healthy subjects or in the patients without obstructive airway disease. Increase in F.E.V. after exercise in patients with obstructive airway disease was probably due to an increase in lung blood volume and increase in the rate of respiration.

In patients with obstructive airway disease with heart disease and healthy subjects the F.E.V. was reduced immediately after reduction in lung blood volume by the Valsalva manoeuvre.

(*L. H. Capel and J. Smart. Thorax, 14, 161, '59.*)

A Comparison of Two Methods of Sputum Collection in the Diagnosis of Pulmonary Tuberculosis

A comparison is presented between the results of examining immediate (spot) and overnight (collection) specimen of sputum from 348 patients with bacteriologically proven tuberculosis using

theresults of direct examination by fluorescence microscopy and culture on Lowenstein-Jensen medium.

If culture facilities are available a 'spot' specimen can detect almost the same proportion (90.8 per cent) of positive cases as a 'Collection' specimen (93.1 per cent).

Hence 'spot' specimen examination is recommended for patients reporting from a distance and unable easily to attend on consecutive days.

Direct examination of single 'spot' specimen detected 66.1 per cent of cases with positive sputum, while two spot specimens gave 76.4 per cent positive results and of two 'collection' specimens 83.0 per cent positive results, so that a high proportion of cases presenting with symptoms and having a radiographic abnormality can be confirmed as tuberculous infections without recourse to culture.

Direct examination of two 'spot' specimens and one 'collection' specimen detected 83.9 per cent of cases with positive sputum.

Thus examination of 'spot' specimen is simple and has an advantage for diagnostic and survey work in field conditions.

(*Andrews, R. H. and Radha Krishnan, S. Tuber., Land. (1959), 40, 155.*)

The 'Bluing' Phenomenon—A source of Contamination in Cultures of Tubercle Bacilli

Tubercle Bacilli would not grow at PH less than 4.5. The 'bluing' phenomenon, a drop in PH to 3.5 of egg medium which was associated with the growth of gram-positive coccal contaminants was relatively more frequent in gastric lavage specimens than in sputum. It was caused by the large amount of acid formed in the metabolism of gamma streptococci and micrococci, normal inhabitants of the nasopharynx and the oropharynx. Such organism could withstand alkali treatment used for the treatment of specimens in the isolation of tubercle bacilli, could remain viable, could produce the acid metabolically and subsequently grow.

(*David Gale and Elizabeth, A. Loch Hart. Am. Rev. Resp. Dis., Vol. 80, Part I of No. 1, July, '59.*)

Scalene Node, Parietal Pleura, and Lung Biopsy in the Diagnosis of Intra Thoracic Disease

Biopsy of the scalene lymph node, parietal pleura and of the peripheral parts of the lung tissue are the procedures for diagnosis of pulmonary diseases in addition to laboratory X-ray and scopic procedures.

Of the 50 cases of scalene node biopsy, positive results were obtained in 38 per cent cases on histologic study.

It is useful in diagnosis of sarcoidosis, lymphoma and metastatic malignancy and for determining operability in carcinoma of the lung.

Of the 25 cases of pleural biopsy with tuberculous pleuritis, only one case gave a false negative report. This technique is of value in the case of idiopathic pleural effusion or thickened pleura. It shortens the time required to make a diagnosis even though such diagnosis could be made by slower

Lung biopsy is of help in diffuse pulmonary infiltration and for suspected presence of a compensable disease.

(*John W. Smith, Harry G. Parson and Albert C. Daniel, J. Thor. Surg., Vol. 37, No. 5, May, 1959.*)

Tuberculous Meningitis

Factors which affect the prognosis unfavourably in tuberculous meningitis are:

1. infancy and advanced age.
2. advanced stages of meningitis (particularly coma and severe focal neurologic signs).
3. duration of disease prior to initiation of treatment.
4. cerebro spinal block.
5. high protein and low sugar in cerebro spinal fluid.
6. Negative skin reaction to tuberculin in the face of advanced disease.

In addition to Isoniazid, all the patients received Streptomycin or P.A.S. or both. Seventeen patients had also received Corticosteroid hormones and one Corticotropin. The overall survival rate was 78.5 per cent.

(*B. F. Voljavec, S. P. Orton and R. F. Corps. Am. Rev. Resp. Dis., Vol. 80, No. 3, Sept., '59.*)

Tuberculosis in Childhood, Part III, IV and V

1. Regressive pulmonary condensations represent chronic pneumonic processes caused by the discharge of softened, caseous lymph nodes into the bronchial system. This may involve a lobe or a segment.

2. This may occur in a child or in adult in the initial period of fresh primary tuberculosis or in the course of chronic process following new lymphonodo-bronchogenic episodes.

3. These are generally of two types:

(a) Chronic Pneumonic Condensations, macroscopically characterized by rubber eraser like consistency and microscopically by macrocellular intra alveolar infiltrations in which necrosis is rather inconspicuous.

(b) Predominantly caseo-pneumonic due to abundant discharge of voluminous necrotic lymph nodes.

4. Three stages may be differentiated morphologically in the development of regressive pulmonary infiltrates.

(a) a short proliferative phase, in which intra alveolar syncetial joint cells predominate;

(b) stage of consolidation in which intra-alveolar infiltrate is primarily composed of mononuclear alveolar histiocytes;

(c) long period of cleansing and healing.

5. Both rubber eraser like and caseous pneumonic regressive condensations may be accompanied by extensive cavitation.

Disintegration dissolution of the infiltrated pulmonary tissue signify, in general, the acceleration of the cleansing and healing process.

6. In the initial stage of lymphonodoregressive aspiration infiltration, there are large numbers of tubercle bacilli in cells and necrotic areas of condensations, indicating the occurrence of an inflammatory fixation phenomenon.

7. While the rapid development and lobar extension of lymphonodogenic regressive infiltrations reflect an increased inflammatory susceptibility, the disappearance of histologically detectable germs signifies the effect of a vigorous post infectious immunity.

8. There exists no regressive pulmonary process of tubercular origin, occurring without any parenchymal destruction. The seemingly ideal restitution of clinical radiological condensations accompanying pulmonary tuberculosis which perhaps persisted for many years may be simulated by progressive diffuse devastation, or by the collapse and cicatrical shrinkage of pulmonary lobes, severally affected by lymphonodogenic involvements.

9. The healing of such a process is accompanied by diffuse or sacciform bronchial dilations, which later on may end in chronic bronchiectasis due to secondary infection.

10. This type of pathology may be produced in rabbits appropriately pre and super infected.

11. Atelectatic pulmonary collapse accompanying intra thoracic lymph-node tuberculosis has to be discriminated from regressive lymphonodogenic aspiration infiltrations.

12. There is no regressive inflammatory pulmonary condensations in the course of tubercular disease developed independently of tubercle bacilli. Thus term epituberculosis remains without formation and should not be used for cases in which following intra thoracic lymph-node tuberculosis, the collapse of pulmonary part occurs.

Pure atelectasis by lymphonodogenic compression is an exceptional phenomenon in tuberculosis while aspiration infiltrations predominate.

(*Ph. Schwartz. Arch. Pediatric., Vol. 76, No. 7, 8 and 9. July, August & Sept., '59.*)

Bronchial Abnormalities After Primary Tuberculosis

1. Bronchiectasis develops in 40.8 per cent of children after Primary Tuberculosis which gives rise to pulmonary collapse. A further 14 per cent show bronchial irregularity. Stricture formation is rare.

2. At least 2.1 per cent of children with a pulmonary primary tuberculous complex develop bronchiectasis, a percentage approximating to that after whooping cough.

3. The younger the child affected with pulmonary collapse and the longer the duration of such collapse, the more likely is bronchiectasis to develop.

4. The right upper and middle lobes are most frequently affected and the anatomical distribution of bronchiectasis after primary tuberculosis thus differs from that of bronchiectasis from other causes.

5. In the majority, the symptoms will develop in adult life. This is thought to be due to the predilection of the Primary Complex for the upper lobes so that bronchiectasis in this situation remains dry on account of self drainage.

6. The factor responsible for the production of bronchiectasis is bronchial obstruction by a tuberculous gland, whether by extrinsic pressure or by erosion through the bronchial wall with the development of endobronchial granulations. Tuberculosis infection of the bronchial tree plays a part but only in conjunction with the obstructive element.

7. At least 5.7 per cent of all established bronchiectasis with symptoms are due to tuberculous etiology.

(*Lisa E. Hill and J.E.G. Pearson. Brit. J. Dis. Chest., 53, 278, 1959.*)

Strepto Varicin and Isoniazid in the Treatment of Pulmonary Tuberculosis

Strepto Varicin and Isoniazid were given to a group of 55 untreated patients with moderately advanced and far advanced tuberculosis for 6 months.

92 per cent showed substantial roentgenographic improvement, 51 per cent had their cavities closed and 67 per cent became noninfectious.

The results of reversal of infectiousness were inferior to Isoniazid-Pyrazinamide with the

dosage used. The combination of Strepto Varicin and Isoniazid is no more effective than Isoniazid alone.

(*Roger DesPrez, Clarence Jordahl, Kurt Deuschle, Carl Muschenheim and Walsh McDermott., Am. Rev. Resp. Dis., Vol. 80, No. 3, Sept., '59.*)

Cycloserine-Isoniazid in the Ambulatory Treatment of Active Tuberculosis After Failure of Previous Chemotherapy

56 patients were given 500-750 mgm of Cycloserine daily in two divided doses, and 300 mgm of isoniazid daily. The results were evaluated at the end of one year. Toxic reaction was observed in 4 patients.

11 of 52 patients (21 per cent) who completed at least six months of cycloserine-isoniazid treatment showed reversal of infectiousness; 23 per cent showed roentgenographic improvement.

Improvement of one or more clinical symptoms occurred in over one-half of the patients. Eleven patients (21 per cent) showed either roentgenographic or clinical deterioration.

(*Vera Leites. Amer. Rev. Resp. Dis., Vol. 80, Part I of No. 1, July, '59.*)

Strepto Varicin and Isoniazid in the Treatment of Pulmonary Tuberculosis

Strepto Varicin and Isoniazid was given for eight months in 40 patients. Strepto Varicin does not delay the emergence of resistance to Isoniazid. In one-fifth of the patients toxicity due to Strepto Varicin was severe enough to discontinue drug. Further, the combination was not more efficacious than Isoniazid alone.

(*Arthur Nathan. Amer. Rev. Resp. Dis., Vol. 80, No. 3, Sept., '59.*)

Strepto Varicin Alone in the Treatment of Active Pulmonary Tuberculosis

Strepto Varicin was given to 28 patients with moderately and far advanced Pulmonary Tuberculosis, 20 had the drug for four months, three left the hospital before treatment was completed. In 2, drug was discontinued because of G.I. disturbance, in 2 because of roentgenological worsening and in one because of appearance of lymphocytes in C.S.F.

The sputum became negative in 5.

No change in roentgenographic appearance was seen in 3 patients, slight clearing in 8, moderate improvement in 8 patients. Extension of disease in one.

Except for 2 patients with progressive disease, there was symptomatic improvement in the rest.

(*Edgar A. Riley, David G. Simpson & John F. Sown. Amer. Rev. Resp. Diseases; Vol. 80, No. 3, Sept. '59.*)