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RESEARCH

Advances in medical science are the result of painstaking, diligent and pertinent search and systematic investigations i.e. research. What was taken for granted yesterday may appear equivocal today and may even be proved incorrect tomorrow. Man's inquisitiveness poses problems and the urge to be rational provides the motive force for seeking their solution. But problems seldom have perfect solutions. When one problem is solved, others get unfolded. Thus research becomes a continuous and never-ending process and each successfully solved problem helps to extend the frontiers of knowledge.

Notwithstanding the tremendous advances in the field of tuberculosis during the last few decades, there still remain considerable gaps in our knowledge of the disease. There is very little known about the 'host' factor, its nature and importance in the causation of disease. "No diagnostic test which is both specific and sensitive is yet available. Why does treatment in one case succeed inspite of its being irregular and inadequate ? And why does the same treatment in another similar case fail even though regular and adequate ? What is the exact clinical significance of bacterial drug resistance ? Why does resistance to INH emerge more quickly and more frequently than to some other drugs ? Is the phenomenon of drug resistance attributable primarily to the microbial species or is it the property of a particular drug or both ? These and a spate of other similar problems still bedevil our understanding of the disease.

The outstanding problems are either fundamental or operational. Fundamental research, even though important, is costly and complicated and quick returns are rare. Operational research on the other hand is comparatively simpler. And when problems are many and stupendous and available resources disproportionately meagre, operational research should get precedence over fundamental research. The fruits of operational research are more tangible and of immediate benefit. Its contribution to proper planning, strategy and evaluation of control is immense.

Heretofore, practically all fundamental research and some operational and applied research has been sponsored and subsidized by the Indian Council of Medical Research. Lately the National Tuberculosis Institute, Tuberculosis Chemotherapy Centre and Madanapalle Research Unit and earlier than that, several workers and institutions have made significant contributions in the field of operational research. Recently, the Tuberculosis Association of India decided, very rightly, to plan, organize and conduct research through a special sub-committee. This is a welcome and perhaps over-due development. With

so many agencies involved in research, coordination of their endeavours becomes essential to avoid over-lapping and duplication. It is necessary that the various agencies should supplement rather than supplant each others' efforts. A clear demarcation of the field for each agency may even be possible such as ICMR taking up mainly fundamental research and the other agencies applied and operational research.

Co-operative studies, being resorted to recently, have added a new dimension to research activities. Variations in environmental factors from place to place are only too well known. The conclusions drawn from a study carried out simultaneously from different centres with a common protocol are likely to be nearer the truth and of a much wider application. Moreover, cooperative studies foster greater interest in research amongst workers and can also help to bring about enlistment of the participating institutions and betterment of the standard of work therein. The gain from these by-products would not be inconsiderable.

Lastly, the pattern of research must now change. So far individual workers have been submitting schemes to ICMR for grants. Each study has been undertaken in isolation and many of them have not even been of urgent practical importance. This has naturally led to some frittering away of resources. It will be more rewarding if the Expert Group of the ICMR and the Research Sub-Committee of the Tuberculosis Association of India were to select a few of the several outstanding fundamental and operational problems on a priority basis. Urgency of the problem and expected dividends alone should determine priority. These selected problems should then be assigned to various institutions and workers in the country who are known to have the necessary wherewithal and aptitude. Such an approach will not only make research more purposeful but would also ultimately lead to maximum utilization of available resources which, unfortunately, are none too liberal.

CHANGES IN THE PATTERN AND BEHAVIOUR OF PULMONARY TUBERCULOSIS, 1955-65

GOVIND PRASAD

(From New Delhi Tuberculosis Centre)

There is a general impression amongst tuberculosis workers that type of cases which attend TB Clinics now a-days is considerably different from what it used to be a decade or two earlier. Difference has been noticed in the acuteness of illness. Patients attending the clinics now a day appear to be less toxic than before. Emaciated young men and women seen so often then are rare now. This impression of change in the acuteness of illness is not recent but has been developing gradually over the past few years.

With a view to confirm or controvert this impression, a study was undertaken in New Delhi Tuberculosis Centre in 1957 (Sikand, 1958). Extent, type, severity of disease and bacillary of sputum in the newly diagnosed cases of pulmonary tuberculosis who attended the Centre in the years 1945-46 and 1955 were compared and no difference was found in the two series in respect of nature and extent of disease. However, proportion of cases whose sputum was positive by direct smear examination in 1955 was significantly lower than 1945-46 series.

A large number of studies dealing with epidemiological indices such as changing trends in morbidity and mortality of tuberculosis have been and are being reported. On the other hand only a few workers have tried to study and report changing trends, if any, in the clinical pattern of disease. This lack of data is possibly due to several reasons. In the first place, clinical manifestations, especially symptoms, are difficult to quantify with any accuracy. Also, symptoms being subjective, patient's version of their nature, degree or duration is neither always correct nor consistent. Besides, in a large outpatient department it is doubtful if enough care is or can be taken to enquire about symptoms accurately in view of large work loads. History taking, more often than not, is perfunctory. In recent years this tendency has probably increased, because irrespective of symptoms or their severity, the specific anti-TB treatment is decided on other considerations such as treatment policy, cost and availability of drugs etc. and thus history recording becomes a casualty.

Midgley (1954) compared 430 cases of 1938 with 252 cases in 1952 of Devon (U.K.) and found that the proportion of early to advanced

cases had remained unaltered during the period. Marsh (1954) analysed the Camberwell Clinic cases in three groups, 1917-39, 1940-47 and 1948 onwards. No difference was noticed in cavitory cases in all the three series. Altmann (1963) compared the clinical picture of newly detected pulmonary tuberculosis in the years 1948-1960. Clinical picture of pulmonary tuberculosis was found to be unchanged in its nature over the past 10-12 years. However, slight fall in cavitory cases was noticed in 1960 series as compared to 1948 series. There was no change in the patients complaining of symptoms heralding pulmonary tuberculosis.

Lowe and Geddes (1953), on the other hand, reported a gradual decline in advanced cases of pulmonary tuberculosis attending the Birmingham Chest Clinic from 1935 to 1952. This decline in advanced cases was attributed to a concerted drive in case finding by Mass Radiography and Contact Examination. It was also found that there was a steady increase in the proportion of cases referred to the clinic as suspects from 1935 to 1947, but this proportion remained more or less constant thereafter from 1947 to 1952. Since suspects referred to a chest clinic are likely to be at an early stage of evolution of disease as compared to those who attend the clinic directly because of symptoms, this would tend to corroborate the findings of the study. Further, there was no difference in the proportion of cases found among contacts of patients diagnosed during the period 1935 to 1952.

In view of the conflicting evidence, it was thought worthwhile to analyse the data in respect of symptoms, extent and severity of disease and bacillarity of sputum in new patients who attended the New Delhi TB Centre in 1965 and compare it with 1955 patients. Comparison would thus be possible in respect of extent and severity of disease and bacillarity of sputum from 1945-1965. Since the earlier study from this institution (Sikand, 1958) did not compare symptoms and response to treatment, the comparison in respect of these is available only for 1955-1965.

Method

For the purposes of analysis a proforma was devised and all the available information

from patient's case sheets was entered accordingly.

Source of the cases attending the clinic was noted. Patients attended the clinic on their own initiative because of symptoms or were referred by general hospitals, dispensaries and private practitioners or were discovered during contact examination.

Information was collected about three main symptoms, viz. fever, cough and haemoptysis. Duration and degree of these symptoms were also taken into account. Coding for duration of symptoms was done as follows :

1. Less than 2 weeks.
2. Two weeks to 1 month.
3. One month to three months.
4. Three months to one year.
5. Over one year.

For degree of symptoms, the coding was done as follows :

1. Mild
2. Moderate
3. Severe.

Initial x-rays of all the patients included in the analysis were read by the author disregarding the earlier reading to avoid any bias that might have occurred in X-ray reading during 1955-65 due to a variety of readers. X-ray films were read in respect of type of disease, sides involved (unilateral or bilateral), number of zones of the lungs involved and cavitary status.

With regard to type, the disease was divided into three categories :

1. Pneumonic— disease presenting as consolidation of one or more lobes of the lung.
2. Fibrocaseous— infiltrative type of disease with or without cavitation and with or without associated atelectasis.
3. Miliary— bilateral miliary lesions distributed uniformly throughout both lungs.

It was also noted whether cavities were unilateral or bilateral, single or multiple and what was the size of the cavity. If more than one cavity was present, size of the largest cavity

was taken into account. The cavities were divided into three categories in respect of size:

	<i>12"x 15" film</i>	<i>75 mm film</i>
Small	Less than 2 cms. in diameter	Less than .5 cms
Medium	2 to 4 cms. in Diameter	.5 to 1cms
Large	More than 4 cm. in diameter	Over 1 cm

It is the routine of the clinic to provide sterile bottles to all patients for collection of sputum. All patients are asked to bring morning specimen of sputum for direct smear and culture examination for A.F.B. In 1955, if no bacilli were found on direct microscopy, the examination was repeated on one more day. Sputum was cultured for A.F.B. if direct microscopy showed no bacilli on both days. However, in 1965, in majority of the patients only one sputum sample was taken for direct microscopy and culture for A.F.B., was put up even if direct smear was positive. Sputum smear was stained by Ziehl-Neelsens technique using 0.5% methylene blue solution for counter staining. Sputum was taken as positive for A.F.B. if 10 or more bacilli were seen in about 5 minutes of microscopic examination. Lowenstein Jensen's medium was used in both the series for culture examination. Presence of 20 or more typical discrete colonies after 6 weeks was taken as positive for A.F.B. In case patients had no sputum, two laryngeal swabs were cultured. Sputum/laryngeal swab were cultured every three months in both the series. The sputum was taken as converted when two consecutive cultures were negative.

In 1955 pre-treatment drug sensitivity was not carried out routinely. On the contrary, in 1965 all positive cultures were put up for sensitivity. Since only selected cultures were put up for sensitivity in 1955, the pre-treatment drug sensitivity was not taken into account in final analysis.

In 1955, all the patients belonging to the domiciliary area of the clinic were eligible for admission irrespective of sputum status. Their names were put on the waiting list and after three to 6 months they used to get their turn for admission. However, criteria for admission in 1965 were made more rigid. Only cases with positive sputum were eligible for admission and after to two three months they used to get their turn for admission, and if during this period the sputum was found to be nega-

tive for A.F.B. they became ineligible for admission

Regularity with which patients took prescribed treatment in the first year and the second year treatment was also analysed. Regularity has been defined as 'drugs actually consumed as a percentage of the amount that should have been consumed in any period'.

Status of the patients, 12 months after stopping the treatment was also taken into account to find out relapse rate. Since majority of the patients in 1965 series completed their treatment not much longer than one year at the time of analysis, relapse rate only in the first year of follow up have been compared.

Material

AH newly diagnosed cases of pulmonary tuberculosis reporting for the first time at the New Delhi TB Centre in the years 1955 and 1965 and belonging to the domiciliary treatment area were included in the study.

Patients discovered during case finding surveys or as a by-product of epidemiological investigations have not been included in the study. This exclusion was necessary for two reasons. Firstly, such surveys are not undertaken by New Delhi Tuberculosis Centre as a routine, continuous programme, with the result that yield is subject to sharp variations from year to year. Secondly, since such cases are, in general, less advanced, and often asymptomatic, their addition to the group of symptomatic cases would have vitiated all findings. Patients coming from outside Delhi from neighbouring states have also been excluded from the study because such patients seldom report without considerable previous treatment and are usually far advanced due to lack of facilities for diagnosis and treatment in their home towns.

Total number of new patients diagnosed as pulmonary tuberculosis was 785 and 867 in 1955 and 1965 respectively. Ninety one of those in the 1955 series and 131 in the 1965 series had inactive disease at the time of diagnosis and have therefore been excluded from the analysis. Similarly, the record of 128 and 61 among 1955 and 1965 patients respectively was found incomplete and these have also been excluded, leaving 566 and 675 respectively for detailed analysis.

Findings

Data in respect of important characteristics

which have been compared in the two series have been set forth in the tables that follows. Table 1 shows the age and sex distribution of patients in the two series. In both series nearly 60% of the patients were males and more than half were in the age group 20 to 39 years. The only difference worth remarking is that the proportion of male patients in the age group 20 to 39 has increased somewhat since 1955. No epidemiological conclusions of any significance should however be drawn from this observation because the population from which the Centre draws its clientele has increased from 4 lakhs to 6 lakhs during the 10 years covered by this study and, as is well known, the main population increase in metropolitan cities is usually in the male population in the working age group. This alone can explain the increased proportion of cases in this age and sex group.

The sources from which cases were drawn are shown in Table 2. Voluntary attendance, contact examination and referrals from other health agencies accounted for 45.4%, 5.8% and 48.8% of the patients respectively in 1955 and 48.4%, 8.6% and 43.0% respectively in 1965. There are, thus, no important differences except that somewhat fewer cases than before are now being referred by other health agencies. A possible explanation is that with the growing knowledge about anti-TB treatment, general practitioners are treating more cases now at least in the initial period after diagnosis. This finding is corroborated by Table 3 which shows that the proportion of patients reporting with treatment longer than 15 days in the two series is more in 1965 as compared to 1955. Not only the referred cases but even those attending voluntarily show a much larger proportion of treated cases in the 1965 series.

Further analysis has been confined to previously untreated patients, those with less than 15 days' treatment having been included in that category. This has been done to avoid mixing up of two groups which may differ considerably from each other in respect of symptoms, extent of disease as well as subsequent behaviour.

Table 4 shows the initial symptomatology of 517 patients belonging to 1955 and 512 patients belonging to 1965 who gave a history of no or less than 15 days treatment. Whereas the frequency of cough and haemoptysis remained virtually unchanged (86.4% and 11.8% in 1955, 84.2% and 10.9% in 1965), significantly fewer patients in the 1965 series reported with fever (55.4% as against 75.5%; $X^2=45.2$ for 1 d.f., $P<0.001$).

GOVIND PRASAD

TABLE 1

Age and sex distribution of new patients attending the Centre in 1955 and 1965

		0 to 9 years	10 to 19 years	20 to 39 years	40 to 59 years	60 and over years	Total
Males	1955	5 1.5%	36 11.1%	180 55.6%	87 26.9%	16 4.9%	324 100.0%
	1965	3 0.7%	45 11.2%	255 63.4%	76 18.9%	23 5.7%	402 100.0%
Female	1955	4 1.6%	48 19.8%	156 64.5%	28 11.6%	6 2.5%	242 100.0%
	1965	4 1.5%	49 17.9%	184 67.4%	28 10.2%	8 2.9%	273 100.0%
Total	1955	9 1.6%	84 14.8%	336 59.4%	115 20.3%	22 3.9%	566 100.0%
	1965	7 1.0%	94 13.9%	439 65.0%	104 15.4%	31 4.6%	675 100.0%

TABLE 2 *Sources of new cases*

	Voluntary Attendance	Contact Examination	Referred by other health agencies	Total
1955	257 45.4%	33 5.8%	276 48.8%	566 100.0%
1965	327 48.4%	58 8.6%	290 43.0%	675 100.0%

TABLE 3

Proportion of patients reporting with treatment longer than 15 days

		1955		1965	
Source	Total patients	Patients with more than 15 days' treatment	Total patients	Patients with more than 15 days' treatment	
Voluntary Attendance	257	21 8.2%	327	97 29.7%	
Referred by other health agencies	276	27 9.8%	290	57 19.7%	

The fact that fewer patients (56.6% against 74.8%) reported with multiple symptoms is also explained by reduced febrility. The significance of this is discussed later in the paper. Tables 5 and 6 show the duration and

TABLE 4
Symptoms among untreated patients

	1955		1965	
	Number	Percent	Number	Percent
Fever	21	4.1%	24	4.8%
Cough	62	12.2%	143	28.3%
Haemoptysis	8	1.6%	5	0.9%
Fever and Cough	327	64.5%	236	46.7%
Fever and Haemoptysis	3	0.6%	4	0.8%
Cough and Haemoptysis	17	3.4%	30	5.9%
Fever, Cough and Haemoptysis	32	6.3%	16	3.2%
Others	21	4.1%	27	5.3%
None	16	3.1%	20	4.0%
Incomplete Records*	10		7	
Total Fever	383	75.5%	280	55.4%
Total Cough	438	86.4%	425	84.2%
Total Haemoptysis	60	11.8%	55	10.9%
Grand Total	517	100.0%	512	100.0%

*Excluded for calculation of percentages.

TABLE 5
Distribution of symptoms among untreated patients in the two series

		1*	2*	3*	4*	5*	Total patients with symptoms
Fever	1955	36 10.0%	146 40.7%	97 27.0%	51 14.2%	29 8.1%	359 100.0%
	1965	35 12.6%	81 29.1%	96 34.9%	5 20.2%	9 3.2%	277 100.0%
Cough	1955	41 9.9%	162 39.2%	116 28.1%	62 15.0%	32 7.7%	413 100.0%
	1965	44 10.6%	110 26.4%	152 36.4%	93 22.3%	18 4.3%	417 100.0%
Haemoptysis	1955	27 61.4%	9 10.5%	6 13.6%	2 4.5%	0 0.0%	44 100.0%
	1965	27 55.1%	13 26.5%	6 12.2%	2 4.1%	1 5.07%	49 100.0%

TABLE 6

Degree of symptoms among untreated patients in the two series

		1*	2*	3*	4*	5*	Total patients
Fever	1955	328 92.4%	17 4.8%	10	—	—	355 100.0%
	1965	224 81.5%	42 15.3%	2.8% 9 3.3%	—	—	275 100.0%
Cough	1955	300 73.3%	25 6- 1%	84 20.5%	—	—	409 100.0%
	1965	242 58.3%	32 7.7%	141 34.0%	—	—	415 100.0%
Haemoptysis	1955	21 42.8%	7 14.3%	21 42.8%	—	—	49
	1965	26 53.1%	22 44.9%	1 2.0%	—	—	100.0% 49 100.0%

*For definition, please see text.

degree of symptoms of untreated patients. Proportion of patients with fever is less in 1965; patients with fever of more than one month's duration are more in 1965 (54.8%) as against 1955 (41.2%). Similarly, patients with moderate to severe degree of fever are more in 1965 (18.6%) as compared to 1955 (7.6%). This anomaly could be due to the notorious inconsistency and unreliability and subjectivity of the patient's version of his symptoms.

The nature and extent of disease and cavitation among the untreated patients in the two series is shown in Table 7. There has been no change in the type of disease, zones and sides involved. In both series, about 98% of the cases were fibrocaceous and about 1% miliary. About 60% in both years had bilateral disease and in nearly 20% four or more zones were involved. However, there were fewer cavitary cases in 1965 (48.0% as against 60.3% in 1955). Also fewer cases in 1965 (11.9% against 17.6%) reported with multiple cavities and the proportion of cases with "large" cavities was also lower (10.2% as against 19.7%). This taken along with the comments already made on Table 4 suggests that patients may probably be reporting for treatment earlier now. If this is so, it is not however reflected markedly in the initial bacillary status of the patients (Table 8). The proportion of bacillary cases has remained unchanged (75.8% in 1955, 76.5% in 1965)

and the relative contribution of those positive on direct microscopy has also shown little change i.e. 64.7% in 1955, 60.7% in 1965 ($X^2 = 1.70$ for 1 d.f., $P > 0.10$).

Nearly 10% of the patients in both series had some associated disease, pleurisy with effusion accounting for nearly 5% of them. The most common non-tuberculous complication was diabetes.

The varying periods for which patients continued treatment at the Centre is shown in Table 10. In both series nearly one fourth of the patients dropped out even before completion of 3 months. It can be seen that in both series more than half of the cases (53.2% in 1955 and 57.2% in 1965) took treatment upto 12 months. Thereafter more patients in 1965 continued treatment upto 18 months (45.3%) and 24 months (31.0%) as compared to 1955 (31.0% and 22.0%) respectively. This however is largely a reflection of the change in treatment policies. In the earlier years, 12 months anti-TB treatment was considered adequate whereas in later years the treatment policy had been changed to at least 2 years' treatment with antimicrobial drugs. More cases in 1955 (14.6%) took treatment over 36 months as compared to 1965 (10.2%) which reflects that more cases in 1955 failed to respond to treatment as a result of which they had to take treatment for longer period.

TABLE 7

Nature and extent of disease of patients in the two series

		1955		1965	
		Number	Percent	Number	Percent
Types of Disease	Pneumonic	—	0.0	1	0.2
	Fibrocaceous	510	98.6	506	98.8
	Miliary	7	1.4	5	1.0
Sides Involved	Unilateral	212	41.0	203	39.6
	Bilateral	305	59.0	309	60.4
Zones Involved	One	122	23.6	122	23.8
	Two	191	36.9	168	32.8
	Three	300	19.3	112	21.9
	Four or more	104	20.1	110	21.5
Cavitation : Sides Involved	Nil	205	39.7	266	52.0
	Unilateral	258	49.9	201	39.3
	Bilateral	54	10.4	45	8.8
Cavitation : Number	Nil	205	39.7	266	52.0
	Single	221	42.6	185	36.1
	Multiple	91	17.6	61	11.9
Cavitation : Size* of largest cavity	Nil	205	39.7	266	52.0
	Small	42	8.1	57	11.0
	Medium	168	32.5	137	26.8
	Large	102	19.7	52	10.2
Total		517	100.0	512	100.0

*For definitions, please see text.

TABLE 8

Initial bacillary status of patients with no or less than 15 days' treatment

	1955		1965	
	Number	Percent	Number	Percent
Sputum Direct Smear Positive	321	64.7	303	60.7
Sputum Direct Smear Negative Culture Positive	55	11.1	79	15.8
Sputum/Laryngeal Swab Culture Negative	120	24.2	117	23.4
Sputum examination not done or incomplete*	21	—	13	—
Total	517	100.0	512	100.0

*Excluded for calculation of percentages.

TABLE 9

Patients having diseases associated with pulmonary tuberculosis

	T.B. Adenitis	T.B. Abdomen	Osteoarticular T-B.	Pleurisy with effusion	T.B. other organs	Non-tubercular	None	Total patients
1955	3 0.5%	3 0.5%	5 0.9%	29 5.1%	3 0.5%	13 2.3%	510 90.1%	566 100%
1965	10 1.5%	5 0.7%	— 0.0%	34 5.0%	1 0.2%	6 0.9%	619 91.7%	675 100%

TABLE 10

Proportion of patients completing various periods of treatment

	Total Patients	Patients completing					
		3m	6m	12m	18m	24m	36m
1955	517 100.0%	362 72.0%	322 62.3%	275 53.2%	160 31.0%	113 22.0%	75 14.6%
1965	512 100.0%	387 75.6%	340 66.4%	293 57.2%	232 45.3%	159 31.0%	52 10.1%

TABLE II

Regularity in first year's treatment*

	Regularly Over 90%	Regularity 80%- 90%	Regularity less than 80%	Total Patients
1955	52 16.5%	145 46.0%	118 37.5%	315 100.0%
1965	177 53.1%	122 36.6%	34 10.2%	333 100.0%

* For definitions, please see text.

Table 11 shows the regularity in the first year's treatment among patients who completed at least 6 months. If 80% regularity is accepted as the minimum needed for effective results it can be seen that far more patients (89.7%) in 1965 were regular than in 1955 (62.5%). This is even more evident in the proportion of patients with more than 90% regularity (53.1% against 16.5%).

Table 12 which shows the extent of regularity in the second year of treatment has to be interpreted keeping in mind the change in

treatment policy whereby two years' antimicrobial treatment is now regarded as essential instead of one year's as in 1955. Thus the larger proportion of patients (83.5% in 1965 compared to 52.2% in 1955) continuing with a regularity over 80% does not have the same meaning as in Table 10 because in 1955 only treatment failure cases took treatment longer than 12 months.

Table 13 shows the rate of sputum conversion at different points of time. The percentages in the 3rd and 7th rows refer to the

TABLE 12

Regularity in second year's treatment*

	Regularity Over 90%	Regularity 80%—90%	Regularity less than 80%	Total Patients
1955	25	56	74	155
	16.1%	36.1%	47.8%	100.0%
1965	14	83	37	224
	46.4%	37.1%	16.5%	100.0%

* For definitions, please see text.

TABLE 13 *Rate of sputum**conversion in the two series of patients*

		Period				
		0—3 months	4-6 months	7—12 months	Over 12 months	
1955	Number treated during period	251	205	126	72	
	Number converted by end of period.	42	68	41	39	-
	Sputum conversion rate during period	16.7%	33.2%	32.5%	54.2%	-
	Cumulative sputum conversion rate till end of period	16.7%	44.3%	62.4%	82.8%	
1965	Number treated during period	296	144	85	48	
	Number converted by end of period	145	53	32	35	
	Sputum conversion rate during period	49.0%	36.8%	37.6%	72.9%	
	Cumulative sputum conversion rate till end of period	49.0%	67.8%	80.3%	94.7%	

conversion rates in successive periods among patients not converted during the previous period and continuing treatment. Cumulative percentages shown in the 4th and 8th rows have been calculated by the modified life table method on the assumption that unconverted patients not continuing treatment would have behaved in the same manner as those who continued treatment. A perusal of the figures suggests that right from the start, sputum conversion in the 1965 series is quicker and of

a higher order (49.0% as against 16.7% at 3 months, 67.8% as against 44.3% at 6 months and 80.3% as against 62.4% at 12 months). It has to be noted that the results reported are for all patients irrespective of regularity.

Table 14 gives the final disposal of patients according to the regularity of their treatment in the first year. Since patients had varying lengths of treatment, it is not possible to read much in this table except some broad character-

TABLE 14

Final disposal of patients in the two series related to regularity in first year's treatment

			Target point reached	Stopped against medical advice ; left area	Stopped against medical advice ; not left area	Died (T.B.)	Died (Non-T.B.)	Treatment continuing	Record Incomplete*	Total
	1955	Number of patients	133	29	14	18	2	0	1	197
Regularity over 80%		%	67.5%	14.7%	7.1%	9.1%	1.0%	0.0%	0.5%	100.0%
	1965	Number of Patients	173	80	15	9	0	12	0	289
		%	59.0%	27.7%	5.2%	3.1%	0.0%	4.2%	0.0%	100.0%
	1955	Number of patients	46	29	11	28	2	2	0	118
Regularity 80%		%	39.0%	24.6%	9.3%	23.7%	1.7%	1.7%	0.0%	100.0%
		Number of patients	6	20	3	3	0	3	0	35
		%	17.1%	57.1%	8.6%	8.6%	0.0%	8.6%	0.0%	100.0%

*Excluded for calculating percentages.

istics. Thus for instance it is worth noticing that whereas there were 9.1 % tuberculous deaths in the 1955 group, the corresponding figure for 1965 was only 3.1%. The higher rate of patients stopping treatment against advice (33.2% in 1965 as against 21.8%) in 1955 suggests that although the current treatment policy which advocates two years of antimicrobial treatment may be more effective than the previous one, the longer treatment spread over a longer period of absence of symptoms leads to more patients giving up treatment against medical advice.

In the 1965 group there were 124 patients who reached the target point of treatment and whose status at the end of one year's further follow up is known. Of these, as can be seen from Table 15, 4 relapsed within 12 months

TABLE 15

Relapses during first year following target point in the two series of patients

	Patients followed for 1 year completing treatment	Patients relapsing during 1 year after treatment was completed
1955	164	11 (6.2% per year)
1965	124	4 (3.2% per year)

(3.2% per year). In the 1955 series the corresponding figures were 11 relapses out of 164 (6.2% per year).

Discussion

A retrospective study like the present one relying on data collection from records maintained in the routine clinic work is bound to have many short-comings. In some respects it has been possible to reduce the influence of irrelevant factors which might ordinarily have vitiated a comparison of 1955 and 1965 patients. Thus, for example, the well known inter-reader differences in the interpretation of radioaraphic shadows would have made a comparison of the radiological extent of disease and cavitation among patients belonging to the two series meaningless ; this has been avoided by a single reader re-reading the initial films of all patients of 1955 and 1965 series. Because of their comparatively objective nature, bacteriological data did not need any such treatment. 'Patients' history of symptoms, inspire

of its subjectivity and, to some extent, unreliability, have been compared exactly as these were recorded. It is well known that in large out-patient departments with great pressure of work, symptom-taking is, to a large extent, perfunctory. Besides, the patients' own version of symptoms is also often inconsistent. Conclusions about these, therefore, have to be taken with a little caution.

In spite of all efforts, it was found impossible to obtain complete data about all the 1955 and 1965 patients belonging to the domiciliary treatment area of the Centre. Due to lapse of time and in some cases incomplete entries, a number of cases had to be excluded from the analysis and for some others, data in respect of certain characteristics was not available. The number of these patients was however too small to have affected any conclusions that might be drawn.

A study of the age and sex distribution of the patients in the two series reveals that the proportion of male patients in the age group 20 to 39 registered some increase. This is contrary to the epidemiological finding of increasing prevalence rates in higher age groups. It is however not proper to read anything significant in this finding from the epidemiological point of view. During the 10 years under review, the population of the area from which the Centre draws its patients increased from 4 lakhs to 6 lakhs and as in all metropolitan cities, this increase has been disproportionately high in the male population in the working age group. Thus the most likely reason for the increased numbers is the increase in the size of the denominator itself.

It is not surprising to find that many more patients than before are now attending the clinic with previous anti-TB treatment. This increase is confined not only to patients referred by other health agencies, notably general practitioners, but also to those attending voluntarily. Also, somewhat fewer cases than before are now being referred by general practitioners to the TB clinic. There is little doubt that this phenomenon is due to the growing knowledge and confidence among general practitioners about the anti-TB treatment. With free and unrestricted supply of anti-TB drugs at the TB clinics, one would have expected more patients reporting earlier for treatment directly at the TB clinics but apparently many of them still come after a spell of treatment elsewhere.

An analysis of initial symptoms of previously untreated cases brought forth an interesting

finding ; that fewer patients now report with fever than in previous years. The proportion complaining of cough or haemoptysis has remained virtually unchanged. Multiple symptoms are fewer and the reduction is due almost entirely to the reduced febrility. The reduction in symptoms found in current study is not however corroborated in a similar study carried out by Altman et al (1963).

The radiological extent of disease in the two series did not show any change over 10 years period, a finding which is similar to that of Midgley (1954) and Altman et al (1963). However there was a significant fall in the proportion of patients with cavitation. Thus as against 60.3% of the patients in 1955, 48.0% only in 1965 had any cavitation ($X^2=15.7$ for 1 d.f., $P<0.001$). The proportion of cases with multiple cavities too fell from 17.6% to 11.9%. Further, whereas 102 (32.7%) of the 312 cavitory cases in 1955 had "large" cavities, the corresponding figures for 1965 were 52 (21.1%) out of 246. Other reported studies have given varying findings on this subject. Marsh (1954) in a study extending from 1917 to 1950s found no difference in the proportion of cavitory cases but Altman et al (1963) comparing cases of 1948 and 1960 found a reduction in the proportion of cavitory cases as in the current study.

Two main differences were thus noticed in the pattern of disease; reduced febrility and lesser destructiveness of lesions. However, there was no difference in the extent of disease in 1955 and 1965. Since previously treated cases were excluded from the analysis, the reduction in symptoms can be explained either by increasing host resistance or by the fact that patients may possibly be reporting for diagnosis and treatment somewhat earlier than in previous years due to increased health consciousness. If the latter were true it would be reasonable to expect a corresponding change in the extent of disease also. Since this has not taken place the reduced febrility cannot probably be explained by increased health consciousness. This points to a possible increase in the host resistance.

In the earlier study (Sikand, 1958) which covered only patients with upto 4 zones involved, the proportion of 1 zone and 2 zones cases in 1945-46 was 23.4% and 32.4% respectively. If cases with 4 and 5 zones too had been included as in 1965 series, these percentages would have been lower (owing to increase in the denominator) than the corresponding percentages in 1965 series, suggesting that in the latter series the proportion of early cases

is more than in the 1945-46 series. Comparison of type of disease (whether fibrocaceous or pneumonic or miliary) has not shown any change since 1945-46. However the rate of bacillarity (as judged by the percentage of patients positive by direct smear examination) registered a fall, over 70% being positive in 1945-46 compared to about 61% in 1965. It has already been pointed out that the bulk of this fall had taken place from 1945 to 1955.

According to Rich (1951), development of symptoms depends upon extent and destructiveness of the lesion. Size of the lesion is, in itself, not the determining factor in the degree to which symptoms will occur. Extent and destructiveness of the lesion varies directly with number and virulence of bacilli and hypersensitivity and indirectly with native and acquired resistance of the host. All these factors are inter-related. Increased host resistance will limit the destructiveness and number of bacilli present in the lesion. This is supported by the finding that cavitory cases have significantly fallen in 1965 as compared to 1955 and also by the lowered rate of positive sputum by direct microscopy in 1965 as against 1945. It appears that some favourable change might have occurred in this direction, namely increased host resistance.

Since tuberculosis is a disease of slow evolution, the changes which are occurring in the pattern of disease are also slow. Bacillary positivity (as judged by percentage of patients positive by direct microscopy examination) registered a fall from 1945-46 to 1955, and further from 1955 to 1965. Destructiveness of the lesion (as judged by cavitory status) did not show any appreciable change from 1945 to 1955 but there has been a significant fall from 1955 to 1965. In short the first change to be noticed was in bacillarity of sputum, followed by change in toxæmia and destructiveness in the lesion. Probably in the next decade difference in the extent of disease may become more evident.

The length of treatment that patients undergo at the Centre has also increased considerably over the 10 years. Part of this is certainly due to increased and better facilities for treatment but in the main this is a reflection of the change in treatment policies. In the earlier years, 12 months' anti-TB treatment was considered adequate whereas in the later years, the treatment policy has been changed to at least 2 years' treatment with antimicrobial drugs. Also regularity with which patients attended the clinic has increased considerably, nearly 90% of those completing

over 6 months' treatment being regular to the extent of 80% or more during the first year compared to 62.5% in the previous series. This improvement has probably something to do with more liberal supply of free anti-TB drugs, supplementary foods and other amenities e.g. milk powder in later years. Since the majority of patients attending the Centre belong to the poorer classes, the provision of supplementary foods in particular is a great draw for enabling many more to be regular now than before.

The better treatment results obtained in 1965, as evidenced by the higher sputum conversion rates at each stage are obviously resultant of a somewhat better group of patients and more regular treatment. However a major factor has also been the change in the drug regimens prescribed to most patients in the two series. In 1955, due to comparative unavailability and high cost of drugs and also to some extent insufficient knowledge about the use of drugs, most patients were prescribed INH 200 mg daily and streptomycin 1 gram bi-weekly. In 1965 on the other hand, the standard practice was to initiate treatment with either INH 300 mg and streptomycin 1 gram daily or INH 300 mg and thiacetazone 150 mg or INH 300 mg and PAS 10 grams daily, all of which combinations are now proved to be therapeutically superior to the 1955 regimen. Improvement in results is specially highlighted in the sputum conversion rates during the first 3 months (49.0% as against 16.7%) and the lead is maintained at all stages.

Relapse rates too are lower in 1965 than in 1955, the rate in the first year having fallen from 6.2% to 3.2%. Studies have shown that maximum cases relapse during first year after the treatment is stopped (Sikand et al, 1959). It is reasonable to assume that this too is a result of better and more regular treatment.

Summary

An attempt has been made in the paper to study the changes in the pattern and behaviour of pulmonary tuberculosis in patients reporting at the New Delhi TB Centre during the period 1955 to 1965. Important changes were noticed in the symptomatology ; as against 75.5% in

1955 only 55.4% of the patients in 1965 reported with fever. This reduction in febrility was also reflected in the percentage of patients with multiple symptoms which fell from 64.5% in 1955 to 46.7% in 1965. Although no appreciable difference was noticed in the extent of disease, there was a fall both in the number of cavitory cases and in the number of patients with large cavities. Possible explanations of these changes are discussed and it is tentatively suggested that increasing host resistance rather than health consciousness of patients might have led to these differences.

A study of the results of treatment brought out the fact that sputum conversion in 1965 series was quicker than in the 1955 series. Also, more patients (89.8%) were regular in treatment than in the earlier series (62.5%). These are explained partly by more effective utilization of anti-TB drugs and partly by the longer duration of treatment (2 years in 1965 compared to 1 year in 1955). Relapse rates too were lower in the 1965 series.

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METHODOLOGY OF CONTROLLED CLINICAL TRIALS IN PULMONARY TUBERCULOSIS

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The aim of controlled clinical trials is the assessment of the value of therapeutic or prophylactic measures in human disease. In its simplest form it is designed to compare two groups to which patients are allocated randomly and treated similarly except that in one group they receive the treatment under investigation and in the other group they do not. This article discusses the methods used in the planning and execution of controlled clinical trials in the treatment of pulmonary tuberculosis. To illustrate these methods details of the trials, carried out at the Tuberculosis Chemotherapy Centre, Madras, will be mainly used as the author has been involved in these trials for ten years. References to trials in pulmonary tuberculosis carried out at other centres as well as to trials in other diseases will also be made.

Controlled clinical trials have been used on a wide scale only since the second World War and even now their importance is not appreciated by many physicians. Thus, Witts (1964) states, "The doctor's work in the past had often consisted in weighing a number of imponderables and coming to a decision. He was conscious of the variation between individuals and had felt it part of his skill to decide what would suit one and not the other. On this account practising clinicians have not always taken kindly to the statistical approach to medical problems in which patients are considered as units in a more or less homogeneous whole and their individual variations as an aspect of the normal distribution curve. It is doubtful if such rapid headway would have been made had it not been for the obvious contribution of statistical methods and planned trials to therapeutics. The accelerating pace of discovery entailed the constant trial of new remedies, whose value could not be left to be determined by the slow process of time and fashion as in the past.

"Few diseases offer such a simple problem as tuberculous meningitis, which was almost invariably fatal until the introduction of streptomycin. More often the problem is like that of the use of corticoids in ulcerative colities, where it could have been argued *a priori* that the anti-inflammatory action of the hormones might be either helpful or harmful and where the first trials gave equivocal results ; only a large-scale trial could decide

the balance of advantage and disadvantage. Again, any major advance in chemotherapy is followed by variations on the theme, and a succession of sulphanamides, anti-biotics or antithyroid drugs is produced. The difference between these variants is likely to be small but none the less important, particularly if it has to be weighed against differences in side reactions and cost. Reports of therapeutic trials have thus become one of the staple items in the medical journals and there can be few doctors now who do not have at any rate a nodding acquaintance with such concepts as controls and degrees of significance. Much of traditional therapeutics has been put to question and the new methods have been applied to the evaluation of the older drugs".

Controls

A control group is necessary because without proper controls it is often difficult, if not impossible, to determine whether a given treatment in any way influenced the observed progress of the patients on that treatment. The treatment can therefore get either credit or condemnation without justification. "Thus, with a somewhat ready assumption of cause and effect, and, equally a neglect of the laws of chance the literature becomes filled with conflicting cries and claims, assertions and counter-assertions. It is thus, for want of an adequately controlled test, that various forms of treatment have, in the past, become unjustifiably, even sometime harmfully, established in every day medical practice" (Hill 1962).

It is important that patients in the treated and control groups should be *concurrent*. It is dangerous to rely on past experience as a control because of the possibility of the variability of any disease, not only from individual to individual but also from time to time. Controls are, of course, unnecessary when the disease treated is normally 100% fatal.

In trials designed to study the effect of a drug on a symptom or in assessing its acute toxic effect each patient can be used as his own control, (In the criteria used are subjective and therefore such most cases trials should be "double-blind"). For example, this technique has been used to assess the painfulness of different sorts of streptomycin

(McLeod and Somner, 1952; Sandier and Grant 1956) and in assessing whether or not isoniazid produces weight-gain in normal subjects (Mudie, Home and Crofton 1954). Such trials gain in sensitivity by eliminating differences between patients but have only a limited application.

The use of controls is by no means new. In about 600 B.C. a control group was utilised to study the effects of diet on the well-being of some subjects of Nebuchadnezzar, King of Babylon (Book of Daniel, Chapter 1). In 1747 James Lind compared the effect of oranges and lemons in scurvy with other regimens then in vogue (Hill 1962). "Despite early attempts of this sort to utilise control groups in experiments, the term "control" in the sense of a check or test observation or experiment did not come into scientific parlance until relatively late in the nineteenth century". (Lasanga 1964). The earliest reported controlled trial in tuberculosis was a trial of sanocrysin undertaken by Anderson, McMohan and Pinner (1931). At present, many organisations are conducting controlled trials in tuberculosis, the most well known being the British Medical Research Council, United States Veterans Administration, the United States Public Health Service and the Tuberculosis Chemotherapy Centre, Madras.

Ethical considerations

A control group of patients in a trial brings the investigator face to face with a problem that is unique in the field of scientific experiment, namely, the ethical problem. When dealing with a trivial disease (like the common cold) or in a disease to which no known remedy exists, it is justifiable to have an untreated control group. In a disease where there is already an established treatment, it is necessary, for ethical reasons, to use this treatment as a control in order to investigate whether the new treatment offers any advantages. Thus, when streptomycin was first available in Great Britain, this drug plus bed rest was compared with bed rest alone as a control (Medical Research Council, 1948). About a decade later, in Madras, the effect of combined chemotherapy (isoniazid plus PAS) on patients in Sanatorium (as the control) was compared with the effect of the same chemotherapy on patients at home without the presumed advantages of sanatorium stay (Tuberculosis Chemotherapy Centre, 1959). In the former study a more complex form of treatment was investigated to see if it was therapeutically superior to the treatment in vogue at that time. In the latter study a less

complex form of treatment was investigated to see if it was as effective as the established form of treatment,

At the Madras Centre regimens of known efficacy have been used as controls in the therapeutic trials on newly-diagnosed patients (Tuberculosis Chemotherapy Centre, 1959, 1960, 1964 and 1966). However in the studies to determine the optimum duration of chemotherapy in patients with bacteriologically quiescent disease, it was considered quite ethical to use placebo-treated patients as controls (Velu et al 1964; Dawson et al 1966) as they were being investigated intensively and could be treated without delay if a patient relapsed. Moreover, 'reserve' drugs were available for the patients both in the therapeutic and the relapse studies. Indeed, it is essential for ethical reasons, to have a sufficient supply of such drugs when regimens less intensive than the established ones are being investigated.

It should be stressed that the environment has a bearing on the ethics of a trial. Thus a trial, considered to be ethically unjustified in a technically advanced country could be entirely justifiable, and even considered very desirable, in a developing country with limited technical and financial reserves (Tuberculosis Centre, 1965; Devadatta 1965). For example, a twice-weekly regimen of isoniazid plus streptomycin was compared with the standard daily regimen of isoniazid plus PAS at Madras (Tuberculosis Chemotherapy Centre, 1964); it is possible that an investigation of the twice-weekly regimen would have been considered unethical in a technically developed country like Great Britain with resources and facilities to administer daily triple drug chemotherapy which is

The object of trials

The object of any trial should be clear at the time of planning and should be precisely stated when the results of the trial are published. Thus, in the first study undertaken at this Centre, the object was to discover whether patients treated with isoniazid plus PAS under adverse environmental and dietetic conditions in their homes would respond as well as patients treated with the same chemotherapy at Sanatorium (Tuberculosis Chemotherapy Centre, 1959). The object of the second study was to discover the therapeutic efficacy of 3 different regimens of isoniazid alone when compared to the standard regimen of isoniazid plus PAS (Tuberculosis Chemotherapy Centre, 1960).

It is advisable to plan a trial with only one main object as more may only lead to imprecise answers from the trial. For example, it is not advisable to plan a trial to study the therapeutic efficacy of regimens as well as their acceptability to patients since procedures employed in the execution of such a trial will be at cross purposes. The same stricture, although to a lesser extent, applies to a trial whose main object is to obtain accurate information on therapeutic efficacy of regimens as well as their toxicity. This does not mean that a therapeutic trial will not yield any information about toxicity and acceptability but such information may be imprecise because in such a trial efforts will have to be made to combat toxicity and to chase the defaulting patients. If this is not done and if there is considerable defaulting of patients in the trial and a regimen is a therapeutic failure, it would be impossible to know whether the failure was due to the regimen in itself being therapeutically poor or whether it was due to the patients not taking the drugs due to toxicity or any other reason. At this Centre, the results of 5 therapeutic trials (Tuberculosis Chemotherapy Centre, 1959, 1960, 1964, 1966; Menon 1968) in newly diagnosed tuberculosis patients have been published so far. During the execution of these studies it was necessary to take measures, not usually possible in clinics in India to ensure that patients took their anti-tuberculosis drugs. This has led to the criticism that trials carried out at this Centre constitute "ivory tower" research by people who are apparently unaware of the objects of these trials.

Design of trials

The design or plan of a trial should be as simple as possible and normally there should be only one variable between the regimens being studied. This point can be illustrated by examining the design of the second trial carried out at this Centre. In this trial the following 4 regimens were investigated (Tuberculosis Chemotherapy Centre, 1960):

<i>Regimen</i>	<i>Daily dosage for a 100 lb. patient</i>
PH	Isoniazid 200 mg plus sodium PAS 10g. given together in 2 divided doses.
	Isoniazid alone 400 mg in 1 dose.
HI 2	Isoniazid alone 400 mg in 2 divided doses.
H	Isoniazid alone 200 mg in 2 divided doses.

It will be seen that there is only the variable between PH and H regimens, namely, PAS 10 g in 2 divided daily doses. Similarly, there is only 1 variable between H and HI-2 regimens, as also between the HI-2 and H-1 regimens. This type of design (with only one variable between regimens) enables us to study not only the merits of the regimens but also indicates why a regimen is a success or failure which in turn is of great help in planning the next trial. The results of the above-mentioned trial were as follows: bacteriologically favourable response was obtained in 91% of the PH, 73% of the HI, 58% of the HI-2 and 44% of the H patients. Thus it was concluded the addition of PAS 10 g in 2 daily doses would considerably enhance the efficacy of the H regimen but the *addition* of isoniazid alone 200 mg 2 daily dose (HI-2) would only slightly increase its efficacy. It also showed that isoniazid alone 400 mg in 1 dose (H-1) was definitely superior to isoniazid 400 mg in 2 daily divided doses (HI-2). This conclusion suggested a rational basis for the planning of the next therapeutic study undertaken at the Centre (Tuberculosis Chemotherapy Centre, 1964).

However, more than one variable can be studied in a trial provided the trial has been designed appropriately for this purpose. An example of this type of trial is one carried out recently in East Africa (East Africa/British Medical Research Council 1966) where 3 variables were studied (that is, a trial designed to answer 3 specific questions). In this study patients were allocated to either of 2 regimens of chemotherapy, also to treatment with either an initial period in hospital followed by out-patient treatment or out-patient treatment throughout and also to surprise home visits or no such visits. In a recent study at Madras Centre (Menon 1968;) patients were allocated to one of 4 regimens of chemotherapy containing streptomycin and also in each regimen to one of two dosages of streptomycin. Such designs are called factorial designs.

Patients to be admitted to trials

It is important to define clearly the criteria, especially diagnostic criteria, used to admit patients to a trial in order to get precise answers for the trial. This can be illustrated by considering some of the criteria used in the trials at this Centre. In these, only patients with bacteriologically confirmed pulmonary tuberculosis are admitted. This criterion ensures that only patients with active pulmonary tuberculosis are admitted but it necessarily also excludes patients with very early disease

—a price that has to be paid for precision. The patients admitted to the Madras trials should have had no previous chemotherapy or have had it for not more than 2 weeks, because it is known that previously treated patients respond differently (less favourably) to chemotherapy than those not so treated. The patients admitted were permanent residents of a defined area in Madras city and were judged to be co-operative; these criteria are necessary as the patients are followed intensively and for prolonged periods at the Centre. If patients are not so selected it is likely that a big proportion will drop out during the conduct of the trial and the interpretation of the results on the patients remaining in the trial becomes very difficult. It is better to have comparatively small number of patients (say 70 to 100) allocated to a regimen with none (or only a few) dropping out than to have large numbers (even 500 to 600) with a substantial proportion (say 25% to 50%) dropping out since it cannot be assumed that the patients dropping out would have responded in the same way to the regimen as those who did not drop out.

It is necessary to state precisely the conditions that make a patient ineligible for a trial besides those that do not fulfil the criteria for eligibility. For example, at this Centre, patients are ineligible if they are moribund, or have a non-pulmonary form of tuberculosis which might complicate the management of the patient or those who have concomitant chronic diseases like leprosy or diabetes.

"The groups (of patients) involved maybe made just as narrow or just as wide as one pleases. There is no limitation. The crucial point is that each group be clearly defined, and, as far as possible, be not open to such errors of inclusion, or exclusion, by different observers as must lead to incomparabilities. If the group is too narrow, then clearly the generality of the answer reached by means of it must be severely limited. If, on the other hand, the group is made too wide, there may be too many variables involved, all of which may influence the course of the disease. In deciding about the happy mean between these two extremes, the wise experimenter will first of all decide what it is he hopes to learn from his experiment. Precisions in the question is likely to lead to precision in seeking the answer". (Hill 1962).

The question regarding the number of patients to be admitted to a trial is usually asked of a statistician—a question to which he finds it almost impossible to give a simple answer. In a trial where the new regimen (or regimens)

is expected to be therapeutically superior to the control regimen, the answer to the following question would be of great value : "What would be regarded as the minimum benefit of the new treatment over the old (control) treatment of known efficacy, which would justify its widespread introduction ?" On the other hand, if the ccw regimen (or regimens) is not expected to be superior to the control regimen (being investigated because it is simpler and/or cheaper than the control regimen) than the question would be : "What would be the minimum therapeutic inferiority of the new treatment over the old (control) treatment, that would lead to rejection of the new treatment for widespread introduction ?" If a numerical answer to these types of questions is obtained, there is some hope of ensuring that the result, if it is attained (or exceeded) will be of statistical significance that is, unlikely to be due to chance. "The statistician, however, if he errs, must endeavour to do so on the side of larger numbers. A trial which does not give a decisive answer is often worse than no trial at all. Impressions of the value or otherwise of a new treatment will inevitably be formed from equivocal results, and an ethical situation may well be created in which any further comparative trial involving the treatment is quite impracticable. As far as possible, one must avoid the situation in which a poor treatment gains currency, or a good one is condemned, on insufficient evidence" (Sutherland 1958). Clark and Downie (1966) have published graphs which are of help in the determination of the number of patients to include in a trial.

Division of patients into groups

Random allocation of suitable patients, to the treatment series, is fundamental to the success of a trial. This is usually done by means of random sampling numbers. It is also essential that the clinician *should not know in advance* which of the treatments under study a patient will receive if he is admitted to the trial. This can be achieved by incorporating, as at this Centre, the random sampling numbers in a series of numbered sealed envelopes before the commencement of the trial. The allocation is made from the next sealed envelope in the series. This method ensures that the treatment groups are not biased by the feelings and judgements of the clinician applied consciously or unconsciously. Moreover, by allowing chance to have full play in deciding what treatment a particular patient is to have, we *hope* to equalize the groups of patients in respect of {"actors of prognostic importance.

Any method which allows the clinician prior knowledge about what treatment the patient will receive, if admitted to the trial, may lead to serious bias in building up the various treatment groups. For example, "the treatment in which the clinician has the greater faith might tend to have assigned to it a preponderance of patients with mild diseases—if the clinician is anxious that the treatment should 'prove its worth'—or alternatively a preponderance of severally ill patients—just because of his greater confidence in it". (Sutherland, 1960). This danger can be illustrated by a trial of anticoagulant therapy carried out by Wright and his colleagues (quoted by Truelove, 1964). In this trial patients admitted on odd days received anticoagulants whereas those admitted on even days did not. When the intake was over it was found that there was 580 treatment patients and 442 control patients. There was thus a bias towards admitting patients to the anticoagulant group, and the findings must be viewed with reserve. If the patients had been admitted to treatment first and then allocated at random to the treatment or control group, the results would have been beyond criticism. This type of hazard is also inherent in trials where patients are allotted to groups alternately or according to hospital numbers or according to wards into which they are admitted.

When the groups have been randomly allocated it is essential to check their similarity in respect of factors of prognostic importance. Sometimes, by chance, a substantial dissimilarity between groups of such patients occurs; for example, in the first study carried out at this Centre, the female patients allocated to treatment at home were at a definite disadvantage in respect of extent of the disease and cavitation and bacterial content of sputum compared with female patients allocated to sanatorium treatment (Tuberculosis Chemotherapy Centre 1959). Thus, despite random allocation, the home and sanatorium series were not equivalent among female patients, in important factors at the start of treatment. This necessitated an adjustment of the results, by statistical standardisation, in order to obtain a valid comparison of the two groups. (Radhakrishna and Sutherland 1962).

In order to avoid substantial difference in important pretreatment factors between groups of patients, it is advisable to "stratify" patients in respect of these important factors into subgroups and to randomize each group separately. For example, in a study carried out at this Centre the patients were stratified into 3

subgroups on the basis of the presence and size of cavitation as seen in the pretreatment tomographic series (no cavitation, diameter of the largest cavity not exceeding 3 cm and diameter of largest cavity exceeding 3 cm) and allocated at random from 3 separate series of sealed envelopes, one for each of the above groups (Tuberculosis Chemotherapy Centre, 1964). In another study patients were stratified into 4 subgroups based on pretreatment bacterial content of the sputum and then allocated at random to the treatment series, (Tuberculosis Chemotherapy Centre, Madras 1966). This technique ensures that there are equivalent numbers of patients with the characteristic sub-groups in each treatment series.

Another technique is to pair patients with similar characteristics on admission to a trial and to allocate at random each patient to one of two treatment series. This has been done in a *small* trial at this Centre (Angel et al 1963), the patients being paired on the basis of radiographic appearance and bacterial content of sputum before allocation. The technique of pairing is, of course, an extreme example of stratification. It enhances the precision of assessment as the difference between the pairs is minimised. It is therefore possible to show a real difference between two regimens, if present, with a smaller number of patients. However, this technique because of its practical difficulties, has limited application especially in a disease like tuberculosis.

Treatment schedules and follow-up

The treatment schedules (or regimens) should be precisely laid down in the plan of study (usually referred to as the "protocol") and must be rigidly followed by the clinicians. (The treatment may be changed in a patient for ethical reasons, only under clearly defined circumstances). There should be no ambiguity about the nature of dosages of drug. For example, the term PAS is sometimes applied both to p-aminosalicylic acid and its salts despite the considerable differences this makes in the dosage, for 12 g of the acid are equivalent to 16 g of the sodium salt. Sometimes no information is given about the rhythm of administration of the drug, for example, whether it is given once, twice or thrice daily. Such ambiguities cause confusion in the literature.

It should also be stated in the protocol whether or not the dosage of the drug is dependent on the weight of the patient or any other factor. If it is to vary according to

weight of the patient, the intervals at which the patient is to be weighed should be stated in the protocol. For example, in a trial at this Centre (1964) comparing the efficacy of a regimen of isoniazid plus PAS with isoniazid plus streptomycin, the dosage of isoniazid and PAS depended on the weight of the patient but not that of streptomycin. The patients were weighed at monthly intervals and if a patient moved into a higher category, the dosages of isoniazid or PAS were increased appropriately but dosages were not reduced for loss in weight.

The provision, if any, for reduction of the dosage of a drug because of its toxicity in any patient, should be made in the protocol. For example, in a trial to study the efficacy of a regimen of streptomycin plus pyrazinamide at the Centre, there was a provision to reduce the dosage of streptomycin from 1 g (irrespective of the weight of the patient) to 15 mg/kg body weight in any patient who exhibited serious toxicity to the drug (Velu et al 1961b).

It is also important to specify the duration of treatment and follow-up. The period of follow-up should be long enough to detect patients who show late relapse of the disease. This is especially important in chronic diseases like tuberculosis and rheumatic diseases. One example arises with the use of A.C.T.H. and Cortisone in rheumatic fever; the therapeutic response was more rapid with hormones than with aspirin, but the differences disappeared during a period of follow-up without drugs (Medical Research Council and American Heart Association, 1954). In therapeutic trials at this Centre, patients with active pulmonary tuberculosis are allocated to a primary treatment for 1 year but are followed up for 4 more years (Dawson et al 1966).

Measurement of the results of a trial

The investigations to be carried out during treatment and their frequency should be clearly laid down in the protocol. At this Centre, the main investigations to assess the therapeutic efficacy of anti tuberculosis regimens are chest radiography, sputum examination by smear culture and drug sensitivity tests. It is important to avoid the temptation to make as many investigations as possible just because "they might turn out to be useful". Once the type of and frequency of investigations have been decided it is imperative to adhere to these as far practically possible for every departure from the design of the experiment lowers its efficiency to some extent and too many departures may wholly nullify it.

The results of the investigations should be entered, at the time, on carefully designed forms which require a minimum of writing. If the observations are numerical, this presents no problem. If not, it may be made possible for the clinician to specify certain alterations on the form by putting a distinctive mark in a particular box. These forms should not prevent the clinicians from making notes on the clinical progress of the patients; he should indeed be encouraged to do so, for if unexpected complications occur, the notes will be valuable.

It is fundamental that the type and intensity of investigations should be planned to be the same in all the groups of patients in a trial to ensure that no advantage or disadvantage occurs to a particular regimen merely because more or fewer examinations have been undertaken on those patients allocated to it.

The investigations should be as objective as possible in order to avoid bias. They should also, of course, be meaningful. The erythrocyte sedimentation rate, used to measure the progress of tuberculous patients, although objective is an unsatisfactory measurement of the activity of the disease (Tuberculosis Chemotherapy Centre 1959, 1960, Devadatta et al 1961a). Radiographic progress of patients assessed without bias (that is, by an independent assessor unaware of the treatment the patient is receiving) is used extensively in controlled trials in pulmonary tuberculosis but its value is limited since radiographic deterioration, for instance, an increase in the size of cavities, can occur in the presence of persistent bacteriologically quiescent disease (Devadatta et al, 1961a) and radiographic improvement is not necessarily associated with favourable bacteriological response (Devadatta et al 1961b). Of the methods used to follow the progress of patients with pulmonary tuberculosis, bacteriological assessments are the most valuable (American Trudeau Society 1959); if they (smear, culture or drug-sensitivity tests) are carried out by a technician, unaware of the treatment being given to the patient whose specimen he is examining, the assessments will also be unbiased. It has recently been shown that it is possible to draw accurate conclusions regarding the efficacies of anti-tuberculosis regimens from controlled trials, based only on smear examinations of sputum specimens (Devadatta et al 1966).

Removal of patients from the trial

Non-cooperation of the patients

The degree of irregularity that would necessitate the removal of a patient from the

trial has often to be decided arbitrarily. In the first 4 trials carried out at this Centre if the patient was found uncooperative and discontinued treatment for 6 weeks or more, he was either removed from the trial altogether or was left in the analysis only up to the time of discontinuation (Tuberculosis Chemotherapy Centre 1959, 1960, 1964 and 1966) although he may have subsequently continued to receive the allocated regimen for the rest of the stipulated period.

It is very important to keep this category of exclusion to a minimum as it is often difficult to assess the reason for a patient's non-cooperation. He may have symptoms of drug toxicity (like giddiness due to streptomycin) and become unco-operative without complaining; this is a 'black mark' against the treatment the patient is receiving and his exclusion will bias the results. Moreover, it cannot be assumed that the unco-operative patients would have responded in the same way to treatment, as the co-operative ones, had they continued to take the treatment for the full period.

Change of treatment by the clinician

Clinicians should be permitted to change the patient's allocated treatment for serious deterioration of the disease or for serious drug toxicity. It is desirable that the clinicians should agree in advance on the exact circumstances in which the treatment may be changed and an independent assessor, unaware of the treatment, should confirm that those circumstances apply, before treatment is changed. These safeguards for change of allocated treatment have been used at this Centre both for radiographic deterioration in therapeutic trials (Tuberculosis Chemotherapy Centre, 1960, 1966) and for development of peripheral neuropathy due to isoniazid in toxicity trials (Tuberculosis Chemotherapy Centre, 1963a, 1963b). Without these safeguards it would have been impossible to know whether changes of treatment in patients in any treatment group really represents a "black mark" against that treatment or merely lack of faith in the treatment on the part of the clinician.

The fullest details of all the deaths should be obtained together with post-mortem findings if available. It is important to decide, *at the time of death*, whether the patient died of the disease (representing a serious failure of treatment) or due to drug toxicity or to some cause unrelated to the disease or treatment.

Blind trials

Some authors make a distinction between a 'blind' trial and a 'double-blind' trial; the former being a trial where the patient is unaware of the treatment he is receiving and the latter being one in which both the patient and the clinician are thus unaware. In the present paper this distinction is not made for the sake of simplicity, and a 'blind' trial is referred to as one in which both the patient and the physician are unaware of the treatment which the patient is receiving. A blind trial is essential when the criteria for assessing the progress of patients is subjective because there is every possibility that the clinician may be biased in his assessments or he may over-compensate for a possible bias. This hazard can be overcome in a blind trial when the physician's errors can be expected to fall at random on the various treatment groups and the bias, if any, eliminated. At this Centre the two toxicity studies on isoniazid neuropathy (Tuberculosis Chemotherapy Centre 1963a, 1963b) were blind because there is a large subjective element in the diagnosis of the neuropathy.

On the other hand, the therapeutic trials at the Centre (Tuberculosis Chemotherapy Centre 1959, 1960, 1964, 1966) were not blind since it was possible to follow the progress of the patients with pulmonary tuberculosis without bias, by other means. Thus a trial should be blind only if essential and not "just to be on the safe side" or as a defence against some hypothetical critics. This is stressed because there are certain disadvantages to a blind trial which are not usually mentioned in the literature on controlled clinical trials. Authors usually hold up the blind trial as something to aim for and allow it to be non-blind only because of practical difficulties the blind study may entail (like administering dummy injections) or because, in a therapeutic study, the treatment may be guessed by the clinicians on the basis of the toxic symptoms encountered.

It is therefore necessary to discuss the disadvantages of blind trials. Firstly, if there is an accidental departure from the planned design for any patient, it will be more difficult to detect it in a blind study than in a non-blind study. For example, in a study at this Centre (Tuberculosis Chemotherapy Centre 1960) a patient, who was allocated to a regimen of isoniazid to be taken once daily but who took the drug, by mistake, in 2 daily doses, was excluded from the study. This departure was detected by a clinician who routinely questioned the patient about his

treatment which he would not have done if the study was blind. It is possible even for serious departures from the planned design to go undetected in a blind study. Secondly, a blind trial is more artificial than a non-blind trial because the; physicians in routine clinical practice always know what drugs they are prescribing to their patients. Thus the controlled trial should be as close to routine practice as possible, that is, it should be non-blind provided that bias can be avoided by other means. Thirdly, in certain circumstances the blind trial itself may lead to a greater bias than a non-blind trial. For example in a blind trial to determine the maximum tolerated dosage of a drug, the clinicians may get more nervous why they do not know the dosage of the drug the patient is receiving (by imagining that the patient is on a much higher dosage than what he is actually receiving) than if they had known the dosage. In such circumstances the maximum tolerated dosage obtained from a blind study will be lower (and biased) than in a non-blind study.

It follows also that a blind trial should not be more blind than necessary. For example, there is no need to keep the clinicians participating in a blind trial in ignorance of the treatments investigated and the design of the trial unless this knowledge enables them to know what treatment individual patients are receiving. It is possible that the design of the blind trial may be improved by involving the participating clinicians. On the other hand, if they are excluded from the planning of the trial they will feel that it is not their trial but something imposed on them; this feeling (expressed or unexpressed) will adversely affect the execution of the trial. Moreover, if the clinicians participating in a blind trial are ignorant of the treatments being investigated they may, in certain circumstances, be more nervous, as already explained, in the management of the patients which in turn may lead to biased conclusions.

In summary, it may be stated that it is essential that a trial be blind if the assessments are subjective. However, it must also be stressed that a trial need be blind if and only if essential and should not be more blind than necessary,

Sequential trials

The design of trials, as already described, involves the decision that a certain number of patients will be studied and the results then assessed. A sequential trial, on the other hand, terminates as soon as a statistically significant

difference is reached between the effects of two regimens (Armitage 1954). In such a trial the conclusions can be drawn with less effort and also with less risk to patients, should one treatment prove inferior to the other. However, this type of trial has only limited application because the interval between the start of treatment and the assessment of the results for each patient may be much longer than the average interval between the intake of successive patients; this disadvantage effectively precludes the use of sequential trials in the treatment of tuberculosis.

The results

Exclusion of patients from analyses

A patient may be excluded from the analyses of the results because of factors present before the admission of the patient into the trial or because of events occurring during the trial. Considering the former, every patient, who does not fulfil the criteria laid down for admission but who has been admitted to the trial inadvertently, should be considered as a *potential* exclusion. However, only such patients whose retention in the analyses would bias the results, need be excluded. For example, in studies at this Centre patients who had more than 2 weeks of previous antituberculosis chemotherapy and or subsequently found to have been excreting drug-resistant organism on admission to the trial are excluded because such patients are known to respond less favourably than the other; on the other hand, tuberculous patients with active leprosy (not eligible for admission because of difficulty of management but admitted inadvertently) are not excluded from the therapeutic trials because there is no reason to believe that their response to antituberculous drugs will be any different from tuberculous patients without leprosy.

Considering next exclusions due to events occurring during the trial, the three main reasons are non-cooperation of the patients, change of treatment by the clinicians and deaths. Patients who are uncooperative and have not taken their allocated treatment for longer than a certain period (usually arbitrary) may be excluded from the final analysis and kept in other analyses, if any, upto the time when the patient became uncooperative (Tuberculosis Chemotherapy Centre 1966). Treatment may be changed in any patient, during the course of a trial, due to serious deterioration of the disease. In a therapeutic trial, such a patient has to be included in all the analyses; if he is excluded (because treatment was changed) the results will obviously be

biased in favour of the regimen he is receiving. Treatment may also be changed for serious drug toxicity. In a therapeutic trial, such a patient should be excluded from the final analysis (since it is usually not possible to predict the therapeutic response had the patient continued to receive the regimen) but may be retained in the other analyses, if any, upto the time of change of treatment (Tuberculosis Chemotherapy Centre 1966). In a toxicity trial such a patient should, of course, be included in all the analyses (Tuberculosis Chemotherapy Centre 1963a; 1963b). A death due to the disease should be handled in the same way as a change of treatment due to deterioration of the disease and that due to other causes handled in the same way as a change of treatment due to causes unconnected with the disease (Tuberculosis Chemotherapy Centre, 1966).

Analysis and presentation of results

There should be a separate card, for each patient, on to which all salient information from the record forms are transferred. The transfer is best done as soon as the form has been completed by the clinician, as this provides a check on the completeness of the form. In order to include as much information on one-card as possible, complex data, if any, may be represented by code numbers of letters.

"In considering the relative merits of hand analysis and mechanical sorting of the data, it is my view that hand sorting of analysis cards is usually preferable, unless the trial includes large numbers of patients and relatively small amount of clinical information in each. In these circumstances, machine sorting is clearly advantageous. But with complex material important association can often be noticed by close scrutiny of the data displayed on the hand analysis card, which would have been missed if the information had been translated into a series of holes". (Sutherland 1960).

In reporting the results of a clinical trial it is necessary to describe the whole plan and conduct of the study so that the reader may see precisely what was done. It is also necessary to show whether or not the randomly allocated groups were in fact equal at the start of the

Analyses of the results should be carried out keeping the object of the trial in view. If the results show definite superiority of one treatment over another, each step of the trial should be reviewed to see whether there could be any difference between the series, other than

the difference in treatment, which could account for the results obtained. The results of the analyses are tabulated, described clearly, statistically appraised and conclusions as precise as possible, drawn. Finally it is usual to discuss the overall implications of the results and suggest leads for further investigations.

Statistical significance

In papers reporting the results of controlled clinical trials, the terms "statistically" and "not statistically significant" are frequently used. Statistical significance is merely a mathematical function which implies that an observed difference between two treatments is to a greater or less degree unlikely to be due to chance ; that the difference is in fact a "real" one. The lower the value of "P" the more likely is this the case. This, however gives no indication about the degree of difference between the two treatments. The smaller the *real* difference the greater will be the number of patients required in each treatment group to show a statistically significant result. On the other hand, if the difference between the treatments is said to be not statistically significant, it merely means that a real difference, if any, has not been proved by the trial.

These are the limitations of the tests of statistical significance but it is often seen that clinicians (especially those less experienced in in controlled trials) seem to place undue reliance on these tests. Also, clinicians are sometimes tempted to use these tests in a biased way. If statistically non-significant difference occurs in favour of their beliefs regarding the relative efficacies of the regimens studied they sometime ask the statistician : "How many more patients can we admit to make *this* difference statistically significant ?" They do not, of course, realise that if a real difference does not exist, that, with more patients the difference may diminish, disappear or reverse itself. On the other hand, such a question is not asked if the observed statistically non-significant difference does not favour their belief.

Deterioration of drugs

The danger of deterioration of drugs is not usually stressed in the literature on controlled clinical trials. This danger should be especially guarded against in trials in tuberculosis as treatment with drugs is for a prolonged period. For example, para aminosalicylic acid tends to deteriorate to metaminophenol (Weinstein 1965) In a trial at this Centre ampoules containing solution of isoniazid, used to determine the rate of isoniazid inactivation in patients, was

found to be 15% less than that stated on the labels (Tuberculosis Chemotherapy Centre 1963a). In another controlled trial capsules and tablets of cycloserine were found to have deteriorated considerably (Stott and Rao 1968). It is, thus, very important to assay periodically the drugs in use in a trial.

Physician or scientist

The controlled clinical trial is a planned experiment. The clinician is part of a team of physicians, laboratory workers and statisticians that plans, executes, analyses and reports the results of an experiment. Difficulties often arise because, whereas laboratory workers and statisticians are trained in the methodology of scientific investigations, the physician is usually not. In fact, the difficulty is even more fundamental in that there is an antithesis between the medical and scientific approach. To make this point clear an extensive quotation is given below from Pickering's Harvian Lecture delivered at the Royal College of Physicians of London in 1964.

"The scientific methods represent disciplined curiosity . . . he (the: scientific worker) is obsessed by his ignorance and by his desire to know. Once he knows, or thinks he knows, then he ceases to contribute to that branch of knowledge and it is time to seek a new field or leave the stage . . . It is quite different for the physician. His patient expects him to know, indeed, if the patient finds out that his physician does not know, he is quite likely to leave him for one who does, or rather for one who says he does. From the time of Galen to our own, therefore, medicine has always presented a facade of systematised knowledge, or alleged knowledge, for like religion medicine does not tolerate ignorance. . . . One of the lessons learned by anyone who has seriously attempted scientific work is its immense demands on time and energy. One gets possessed by the problem. It drives all else out of mind and frequently wakes one from sleep. . . . This monopoly of time and attention which scientific work exercises, and indeed demands, is difficult to combine with the practice of medicine. . . . That the physician places himself first and foremost at the service of the sick—and may it ever be so—is the chief reason why scientific work is so difficult for him".

Thus a well qualified physician with a lot of experience in any particular disease is not necessarily suited to form part of a team carrying out a controlled clinical trial even in that disease. A clinician with a scientific out-

look is best suited to form a part of this team. But, how does he play his role seeing that it is difficult, if not impossible, to combine the physician's approach and the scientist's approach at a point in time? He should, in the opinion of the author of the present report, primarily play the role of the physician when considering the ethical aspects of the trial but in the scientific planning of the trial, in its execution and in the analysis and interpretation of the results, he should primarily play the role of a scientist. During the execution of the trial as a scientist he should be concerned with individual patient not as a mere individual but as an individual who is part of a group in a scientific investigation.

Conclusion

This article has discussed the details of the methods employed in a controlled clinical trial which is in fact a planned scientific experiment. It should be emphasised that the essence of a successful trial lies in painstaking attention to every detail; a badly planned or executed trial, because it may give misleading answers, is worse than no trial at all. On the other hand, a well planned trial meticulously executed can yield clear-cut information on any treatment in a remarkably short space of time. For example, accurate information was obtained on the efficacy of isoniazid in active pulmonary tuberculosis in little over than 18 months whereas prior to that over a period of 15 years, conflicting and unestablished opinions were being expressed concerning the value of gold therapy in this disease (Fox 1954).

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EPIDEMIOLOGY OF HAEMOPTYSIS

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The Hippocratic aphorism, "the spitting of pus follows the spitting of blood, consumption follows the spitting of this and death follows consumption", portrays the significance attached to haemoptysis in ancient medicine (Pursel et al, 1961). The expectoration of blood has for centuries been regarded as pathognomonic of tuberculosis. Many non-tuberculous patients were sent to tuberculosis sanatoria merely because of this symptom. Weintzen and Ajorslev (1936) noted that only 582 of 869 patients admitted in sanatoria because of haemoptysis were actually suffering from tuberculosis. Even to-day some physicians consider haemoptysis, invariably, as tuberculous in origin, despite the constantly expanding catalogue of diseases known to be associated with it.

As many as 110 causes of haemoptysis, many of them rare and bizarre, have been reported in literature (American Thoracic Society, 1966). The most frequent of these are tuberculosis, neoplasm, respiratory tract infections and cardiovascular diseases.

The purpose of this paper is to determine the frequency and severity of this symptom in the average run of patients seeking relief at a TB clinic, and to determine its association with common chest diseases. An attempt has been made to evaluate statistically the clinical significance of haemoptysis.

Material

This is a retrospective study based on all new patients who attended the New Delhi TB Centre in 1966 with a history of haemoptysis. These patients have been divided into the following two broad groups :—

Group A : Where haemoptysis was the presenting symptom i.e. patient was either actually having haemoptysis at the time of first attendance at the Centre or had it within the preceding one week.

Group B : Where haemoptysis was not the presenting symptom, but it had occurred sometime earlier during the course of illness and the attendance at the Centre was

due to some other pressing symptom/symptoms.

From the point of view of severity of haemoptysis the cases were graded as follows :-

First degree : Streaking or tinged sputum
Second degree : Frank but less than 4 oz.
Third degree : Frank and profuse (more than 4 oz.)

There were in all 7,143 new patients, 4,232 males and 2,911 females, who attended this Centre in 1966. Out of these, 776 i.e. 10.9% gave a history of having had haemoptysis some time or other.

Analysis

Age and sex distribution of haemoptysis cases in both the groups (group A and group B) is shown in Table 1. It would be seen that whereas male patients with haemoptysis constituted 13.2% of the total male patients (561 out of 4,232), females constituted only 7.4% of the total (215 out of 2,911). Majority of the patients in both sexes and in both groups were in the age-group 15 to 34 years. There was no appreciable difference in the age and sex distribution of patients in group A and group B.

Severity of haemoptysis, except for 4 cases where this information was not available, is shown in Table 2. Groups A and B differ somewhat in respect of severity of haemoptysis and the differences are statistically significant ($X^2 = 8.52$ for 2 d.f. $P < 0.02$). The important contributory factor appears to be the somewhat larger proportion of third degree haemoptysis in group A.

Table 3 shows the final diagnosis of the 776 haemoptysis cases separately in groups A and B. Tuberculosis is by far the commonest cause in both the groups and accounts for more than half the patients. Respiratory tract infections including chronic bronchitis, bronchiectasis etc. accounted for 12.8% of the cases and 27.8% had to be labelled as cases of 'undetermined aetiology'. In these latter, the plain skiagram of the chest did not show any abnormality and the sputum was negative by direct smear and culture. Special examinations

TABLE 1

Age and sex distribution of haemoptysis cases in the two main groups

		0-4	5-14	15-24	25-34	35-44	45-54	55 years	
	M	1	8	86	89	49	23	7	263
Group A	F	—	8	28	33	11	8	9	97
	T	1	16	114	122	60	31	16	360
Group B	M	—	4	83	102	51	31	27	298
	F	—	10	26	35	25	15	7	118
	T	0	14	109	137	76	46	34	416
Total	M	1 (0.2%)	12 (2.1%)	169 (30.1%)	191 (34.0%)	100 (17.8%)	54 (9.6%)	34 (6.1%)	561 (100.0%)
	F	0 (0.0%)	18 (8.4%)	54 (25.1%)	68 (31.6%)	36 (16.7%)	23 (10.7%)	16 (7.4%)	215 (100.0%)
	T	1 (0.1%)	30 (3.9%)	223 (28.7%)	259 (33.4%)	136 (17.5%)	77 (9.9%)	50 (6.4%)	776 (100.0%)

TABLE 2

Distribution of haemoptysis cases according to the degree of haemoptysis in the two main groups

	Degree of Haemoptysis				Total
	1	2	3	Not recorded	
Group A	176 (49.3%)	153 (42.8%)	28 (7.9%)	3	360 (100.0%)
Group B	193 (46.7%)	207 (49.7%)	15 (3.6%)	1	416 (100.0%)
Total	369 (47.9%)	360 (46.5%)	43 (5.6%)	4	776 (100.0%)

like bronchoscopy, bronchography, special radiological examinations etc. were not carried out, though some of these cases were kept under observation for a few months following haemoptysis. The proportion of various diseases in groups A and B is nearly the same and the differences are not statistically significant ($X^2=2.58$ for 3 d. f., $0.30 < P < 0.50$).

The proportion of cases of different diseases with varying degrees of haemoptysis is shown in Table 4. Data have been given separately for males and females since the degree of haemoptysis, as well as the proportion of different diseases in different degrees of haemoptysis does not appear to be the same for males and females. Thus, for instance, far more males than females had haemoptysis of

EPIDEMIOLOGY OF HAEMOPTYSIS

TABLES

Diagnosis of haemoptysis cases in the two main groups

	Group A	Group B	Total
Tuberculosis	201 (55.9%)	231 (55.5%)	432 (55.7%)
Respiratory tract infection	40 (11.1%)	59 (14.2%)	99 (13.0%)
Neoplasm	2 (0.5%)	3 (0.7%)	5 (0.6%)
Cardio-vascular disease	2 (0.5%)	3 (0.7%)	5 (0.6%)
Miscellaneous	8 (2.2%)	11 (2.6%)	19 (2.4%)
Undetermined aetiology	107 (29.7%)	109 (26.4%)	216 (27.8%)
Total	360 (100.0%)	416 (100.0%)	776 (100.0%)

the first degree. The difference is statistically significant ($X^2=229.6$ for 2 d.f., $P<0.001$). What is more interesting, even with the same degree of haemoptysis, the proportion of various disease categories is not the same for males and females. For instance, whereas 51.1% of the males with haemoptysis of first degree were diagnosed to have pulmonary tuberculosis, the corresponding figures for females was only 27.8%. Similarly, of the male cases having haemoptysis of the second or third degrees, 73.7% were suffering from pulmonary tuberculosis, the corresponding figure for females being 44.3%. These differences too are statistically significant ($X^2=45.61$ for 4 d.f., $P<0.001$). It can also be seen from the same table that cases of 'undetermined aetiology' were proportionately more in first degree haemoptysis which might suggest that in many of these undiagnosed cases, haemoptysis might have been more or less insignificant. Inexplicably, many more females than males (36.7% as against 24.4%) fall in the 'undetermined aetiology' category, even though males had a much higher proportion of first degree haemoptysis cases. All the 5 cases of neoplasm were among males.

Table 5 shows the age distribution of haemoptysis patterns in various aetiological

groups. Excepting persons below 14 years of age, tuberculosis as a cause of haemoptysis was more or less equally common in other age groups. All cases of neoplasm were over 45 years and cases of 'undetermined aetiology' got progressively fewer with higher age. It could be that many of these were not cases of haemoptysis at all.

The 394 cases of haemoptysis who were diagnosed as tuberculous have been further studied in relation to the extent and type of disease. Table 6 shows the distribution as to extent of disease of the 394 'haemoptysis' patients having pulmonary tuberculosis as also of 2,970 'non-haemoptysis' patients in the same year. The differences are statistically significant ($X^2=9.86$ for 2 d.f., $P<0.01$). Close scrutiny shows that the difference lies in the relative proportion of moderately advanced and far advanced disease, patients with minimal disease being of the same order in both groups.

Table 7 shows that the proportion of cavitory and non-cavitory cases is almost similar in patients with the three degrees of haemoptysis ($X^2=0.11$ for 2 d.f., $P>0.90$). This table also shows that the extent of disease was not significantly different in

TABLE 4

Diagnosis related to degree of haemoptysis

	Diagnosis	Degree of Haemoptysis							
		1		2		3		Total	
		No.	%	No.	%	No.	%	No.	%
Male Patients	Pulmonary Tuberculosis	168	51.1	140	74.1	28	71.8	336	60.3
	Non-TB chest diseases	57	17.3	22	11.6	6	15.4	85	15.3
	Undetermined aetiology	104	31.6	27	14.3	5	12.8	136	24.4
Female Patients	Total	329	100.0	189	100.0	39	100.0	557	100.0
	Pulmonary Tuberculosis	11	27.5	81	47.4	1	25.0	93	43.2
	Non-TB chest diseases	4	10.0	36	21.0	3	75.0	43	20.0
	Undetermined aetiology	25	62.5	54	31.6	—	—	79	36.7
	Total	40	100.0	171	100.0	4	100.0	215	100.0
	Grand Total	369	—	360	—	43	—	772	

patients with varying degrees of haemoptysis ($X^2=5.82$ for 4 d.f., $0.30 < P < 0.50$).

It may also be pointed out that out of 394 haemoptysis patients found tuberculous, bacillary status of 348 cases was known; out of these, 67.8% were sputum positive and the remaining 32.2% were sputum negative. The percentage of bacillary cases, again, is more or less the same as amongst patients who had not had haemoptysis (66.3%).

Discussion

Haemoptysis is an alarming symptom and therefore seldom remains unnoticed or neglected. Nor is it so infrequent. Though usually not an initial symptom in the real sense of the word, yet it is the most dramatic of all symp-

toms and has been considered as an important diagnostic and prognostic sign since ages. An attempt has been made for fresh appraisal of the significance of haemoptysis in chest diseases.

Out of a total of 7,143 new patients who attended this Centre in 1966 with symptoms, 776 or about 10% gave a history of haemoptysis. This percentage varies considerably in the reported studies, since to a certain extent it would depend upon the material on which a particular study is based. The frequency of haemoptysis on the whole is low in series based on a clinic service (Chaves et al 1951, 7% ; Pursel et al 1961, 11% ; Johnson et al 1960, 15%) whereas the series based on hospital/surgical units report a much higher percentage (Abbott 1948, 38% ; Moersch 1952,

TABLE 5

Diagnosis of haemoptysis cases in relation to age of the patients

	Age (Years)					
	0- 14	15-24	25-34	35-44	45 and above	Total
Tuberculosis	9 (29.0)	131 (58.2%)	141 (54.4%)	84 (62.2%)	67 (53.2%)	432 (55.7%)
Respiratory tract infections	3 (9.7%)	21 (9.3%)	26 (10.0%)	17 (12.6)	32 (25.4%)	99 (12.8%)
Neoplasm	—	—	—	—	5 (4.0%)	5 (0.6%)
Cardiovascular diseases	1 (3.2%)	1 (0.4%)	2 (0.8%)	1 (0.7%)	—	5 (0.6%)
Undetermined aetiology	17 (54.8%)	69 (30.7%)	82 (31.7%)	30 (22.2%)	18 (14.3%)	216 (72.8)
	1 (3.2%)	3 (1.3%)	8 (3-1%)	3 (2.2%)	4 (3.2%)	19 (2.4%)
Total	31 (100.0%)	225 (100.0%)	259 (100.0%)	135 (100.0%)	126 (100.0%)	776 (100.0%)

TABLE 6

Extent of tuberculous disease in patients with and without haemoptysis

	Haemoptysis	No Haemoptysis
Minimal	108 (27.5%)	855 (28.8%)
Moderately advanced	151 (38.3%)	914 (30.8%)
Far advanced	135 (34.2%)	1201 (40.4%)
Total	394 (100.0%)	2970 (100.0%)

30%). Since the patients in a hospital or a surgical unit are usually selected patients, the higher percentage of patients with a history of haemoptysis is understandable.

Haemoptysis was found to be more frequent

in males than in females. Out of 4,232 males, 561 (13.2%) had haemoptysis whereas amongst 2,911 females, only 215 (7.4%) had haemoptysis. This is statistically significant ($P < .001$). Apart from haemoptysis being more frequent in males, the same situation could result if females neglect haemoptysis more than males and do not attend the clinic for investigations. Whether the former is true, can be verified only by a community survey to determine the prevalence of haemoptysis in general population. In the absence of that, the following observations are pertinent:—

1. Table 1 has shown that the proportion of patients in whom haemoptysis was the presentirig symptom was almost the same in males and females. If females were inclined to neglect haemoptysis more than males, the percentage would not have been similar.

2. A total of 2,290 males and 1,074 females were diagnosed as tuberculous out of 7,143 new patients. Of the male tuberculous, history of haemoptysis was present in 14% as against 8% in tuberculous females.

There is, thus, some indirect evidence to

TABLE 7

Extent & cavity status of tuberculous patients in relation to degree of haemoptysis

	Degree of Haemoptysis			Total
	1	2	3	
Cavitary	86 (53.1%)	116 (55.0%)	14 (51.8%)	216 (54.8%)
Non Cavitary	70 (44.9%)	95 (45.0%)	13 (48.2%)	178 (45.2%)
Minimal	41 (26.3%)	62 (29.4%)	5 (18.5%)	108 (27.5%)
Moderately advanced	54 (34.6%)	82 (38.9%)	15 (55.6%)	151 (38.3%)
Far advanced	61 (39.1%)	67 (31.8%)	7 (25.9%)	135 (34.2%)
Total	156 (100.0%)	211 (100.0%)	27 (100.0%)	394 (100.0%)

show that haemoptysis is more common in males than in females. The same conclusion could be drawn from the studies reported by Rao (1943), Chaves (1951), Moersch (1952), Pursel et al (1961) and Kotaiah (1967).

Although tuberculosis is more common in males than in females yet the frequency of haemoptysis in various age groups is practically the same in males and females. There is very little haemoptysis below the age of 14 (also reported by Rao, 1940) and nearly 79% in both sexes were in the age group 15: to 34 years.

The proportion of third degree haemoptysis in group A is naturally more but what is surprising is that nearly one-third of the third degree haemoptysis cases did not attend the clinic till some other symptoms appeared. It appears that quite often the speed of action (to seek diagnosis and relief) appears to depend more upon the individual's psychological pattern than the degree of haemoptysis.

It must however be remembered that classification of haemoptysis into first, second and third degree is based entirely on the patients' own description. This is highly subjective and could be inaccurate specially in group B cases where the passage of time since

haemoptysis may have affected the patient's recollection regarding the degree of haemoptysis. Because of this possible lacuna, one should resist the temptation of attaching undue importance to the degree of haemoptysis.

Tuberculosis was found to be the most frequent cause of haemoptysis in this material. Out of the 776 patients with haemoptysis, 432 or a little more than half were found tuberculous. The frequency of tuberculosis amongst haemoptysis patients, on the whole, is low in studies from western countries where prevalence of tuberculosis is also known to be very low. Johnson et al (1960) found only 5% of the new patients attending a clinic in 1956 with history of haemoptysis to be tuberculous. Abbott (1948) and Pursel et al (1961) in series based on surgical units found 22% and 13% respectively of haemoptysis patients to be tuberculous. Mital et al (1966) found 71% of their haemoptysis patients to be tuberculous. It is quite likely that the difference between Mital's series and ours is because in the former, many patients are referred to that unit for surgical treatment after the diagnosis has been arrived at.

Out of 3,364 tuberculous cases, nearly 12% gave a history of haemoptysis. Trenchard

(1945) after a mass radiography survey found that 6% of the 650 male patients found tuberculous had a history of haemoptysis. Heller (1946) and Pursel et al (1961) found haemoptysis in 15% and 19% respectively amongst tuberculous patients in their series. This percentage however has been reported to be much higher (36.5%) by Abbott (1948) and 36.6% by Anders (quoted by Fishberg, 1932). Frank and profuse haemoptysis was present only in less than 1% of tuberculous patients in our series. Haemoptysis of first and second degrees was almost equally distributed in the remaining tuberculous patients.

The large number of cases of haemoptysis where diagnosis could not be established in this study needs some comment. It has already been stated that they were all x-ray negative and sputum negative. Other investigations like bronchography, bronchoscopy etc. were not feasible in view of the work-load involved. Many of these cases could have been due to bleeding from the nose, gums and throat; or what was considered as haemoptysis may have been haemetemesis; or they could be early cases of bronchiectasis or chronic bronchitis where the skiagram was within normal limits.

The reported relative frequency of this group of 'undetermined aetiology' varies considerably with the material in various studies. Abbott (1948) and Mital et al (1966) placed only 4% and 10% cases respectively in this category amongst hospital patients, whereas Johnson et al (1960) and Chaves (1951) found 21% and 50% in this category amongst clinic patients.

The question arises, whether prolonged follow up (which could not be rigidly enforced in this series) could have helped to arrive at a diagnosis in some of these. Poole and Stradling (1964) found that a repeat X-ray in haemoptysis cases of 'undetermined aetiology' initially, helped to establish the diagnosis in as low a percentage as 0.35, and therefore concluded that his second "precautionary" skiagram is not warranted in those cases of haemoptysis whose initial x-ray is negative, specially when considered in relation to the work-load involved. Johnson et al (1960) could establish a diagnosis in 3 cases of 'undetermined aetiology' after a follow up of over 200 such persons for 2 years. The repeat x-ray in some of the patients in our material, who attended for a follow up, was negative. Prolonged follow up, thus, of such persons is neither rewarding nor perhaps a psychologically sound procedure.

This study has also shown that the degree of haemoptysis amongst tuberculous patients has no relationship to the extent and type of disease. This has also been the experience of Chaves (1951), Pursel et al (1961) and Mital et al (1966) among others. The extent of disease amongst those tuberculous patients with haemoptysis and those without haemoptysis is significantly different. Whereas the percentage of minimal cases in those with haemoptysis and without is comparable, the far advanced cases are found more frequently among those without haemoptysis than with haemoptysis. This is, more or less as it should be. Haemoptysis, if it occurs, is less likely to be neglected than other common symptoms of tuberculosis, especially cough. Haemoptysis, thus, will impel a patient to seek relief where other symptoms usually already present, did not and may not for some time more.

Apart from this contribution towards urgent action for diagnosis, no prognostic significance can be attached to haemoptysis. It can occur in early cases and may not occur even in very advanced cases.

Summary

Seven hundred and seventy six new patients who attended the Centre during 1966 with history of haemoptysis, sometime or other prior to attending this Centre have been analysed. They constituted nearly 10% of the total new patients. Haemoptysis was the presenting symptom only in half of the patients. While no marked variations with age were seen, haemoptysis appears to be more frequent in males than in females.

Pulmonary tuberculosis was found to be the most frequent (55.7%) etiological factor. Next in order was a loose group of respiratory tract infections including pneumonitis, chronic bronchitis, bronchiectasis etc. Malignancy accounted for only 5 out of 776 cases.

The degree of haemoptysis seems to have no relationship to the extent, severity and bacillarity of lesions in pulmonary tuberculosis.

The cause of haemoptysis could not be established in nearly one fourth of the cases. They were all X-ray and sputum negative.

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TUBERCULOSIS OF STOMACH

(A case report)

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(From J. L. N. Medical College, Ajmer.)

Primary tuberculosis of the stomach is a relatively uncommon disease, although there have been many reviews of the subject from time to time in the past (Broders 1917, Good 1931, Clagget and Walters 1938, Binders et al 1945 and Gaineset al 1952).

Being rare, it was considered worthwhile to report a case of tuberculosis of stomach which came under our observation.

Case Report

P.O., 32 yr. H.F. (Reg. No. 15746) was admitted in J.L.N. Hospital, Ajmer, on 24.9.69, with the complaints of pain over epigastric region for the last 4 months and fever off and on for the last 10 days. Epigastric pain used to increase after taking meals. There was no history of any vomiting or haemetemesis.

Family history revealed that her father died of tuberculosis of lungs four years back.

On physical examination she was found to be poorly built and nourished. Cervical glands were palpable on both the sides of neck, which looked clinically to be tubercular in nature.

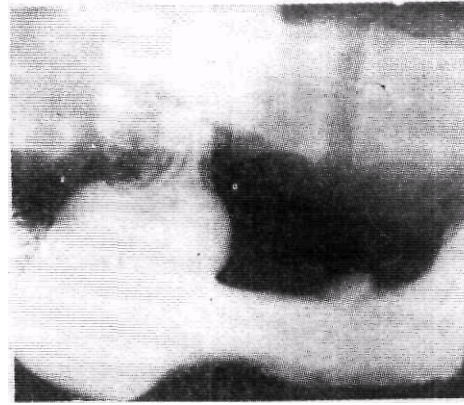
On abdominal examination, deep tenderness was present in the epigastric region, but no lump was palpable. Liver was just palpable below the costal margin.

Investigations done were—Hb 7 gm%, TLC 6400/Cumn with P 70%, L28% M 2%. ESR was 30 mm for 1st hour. Urine and stool examinations were normal. Examination of sputum for A.F.B. was negative.

A fractional test meal revealed a slight high acid curve. Screening of chest was normal.

Barium meal examination showed evidence of an ulcer along the lesser carvature of stomach at its junction of proximal 1/3 with distal 2/3rd.

Pre-operative treatment : She was given two units of blood pre-operatively to improve anemia.



Barium meal of the stomach showing **an ulcer along** the lesser curvature.

On 16.10.69, an upper right paramedian incision was made and abdomen opened. Mesenteric glands were significantly enlarged. There was an ulcer, oval in shape, about 1/2" in diameter—along the lesser carvature at its junction of proximal 1/3rd with distal 2/3rd. A Bilroth type-I partial gastrectomy was done. A mesenteric lymph node was also removed for biopsy.

On 21.10.69, she had burst abdomen, which was resutured. After that she had an uneventful recovery with the help of anti-tubercular drugs.

Histopathological (No. 3993/17.10.69) examination of the ulcer revealed the lesion to be tubercular ulcer of the stomach. Biopsy of the mesenteric gland too showed evidence of tuberculosis.

Discussion

The incidence of disease varies from 0.36—2.3% in patients with pulmonary tuberculosis, although the cases have been reported without any clinical Koch's lesion elsewhere in the body. (Chatterjee and Dutt 1955, Jain and Agarwal 1965 and Sharma 1967).

Pathologically Broders (1917) have described six types of lesion :—

- (i) Tubercular ulcer of stomach, which may be single or multiple, larger or small.
- (ii) Miliary tuberculosis of stomach,
- (iii) Hyperplastic or infiltrative type.
- (iv) Solitary tuberculoma.
- (v) Tuberculosis pyloric stenosis.
- (vi) Tubercular lymphangitis of the stomach.

Clinically the disease is usually seen in young adults. Usual symptoms are like those of peptic ulcer i.e. epigastric pain and vomiting, rarely pyrexia of unknown origin (Amesur 1962), haemetemesis, melaena etc. Sometimes a lump may be palpable (Walters et al 1936).

Pre-operating diagnosis is rather difficult. However, systemic manifestations of tuberculosis elsewhere in a young subject with a gastric trouble should arouse suspicion about the nature of the disease. In our case, associated cervical lymph-adenopathy was suggestive of the nature of the lesion.

Routine investigations are not always diagnostic, because it is difficult to exclude peptic ulcer or even malignancy radiologically. However sometime gastroscopy may prove helpful in diagnosing the tuberculous nature of the lesion by the presence of following features :— (Chatterjee and Dutt 1955).

1. Undermined edge of the ulcer.
2. Irregular outline of the ulcer with numerous fistulous tracts and
3. Presence of superficial tubercles in the neighbourhood of the main lesion.

A therapeutic test suggested by Gaines et al (1952) may be helpful in detecting the diagnosis. A retrogression in the size of the lesion demonstrated by radiologically or gastroscopy after a course of antitubercular treatment is suggestive of lesion to be tubercular in nature.

But in clinical practice, the diagnosis is usually suspected at the operation table when abdomen is explored for epigastric pain and later on confirmed by the histopathological study of the resected lesion.

Prognosis : Prognosis is excellent after the surgical resection of the stomach, followed by anti-tubercular drugs.

Summary

A case of tuberculosis ulcer at the stomach is reported. The literature has been reviewed briefly.

ACKNOWLEDGEMENT

Thanks are due to Dr. M.N. Kathju, Principal, Jawahar Lal Nehru Medical College, Ajmer for his permission to publish the case report.

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REPORT OF A CASE WITH TUBERCULOSIS IN ONE LUNG AND PERIPHERAL BRONCHIAL CYSTS IN THE OTHER

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M.D., 22, Hindu male, a school teacher, was admitted on January 2, 1968 with complaints of cough with expectoration, recurrent hemoptyses and pain in left side of chest. He was alright until five months before admission when he started complaining of cough productive of yellow, fetid sputum. He had three episodes of rather massive hemoptysis. In the past he had kept rather indifferent health and had recurring attacks of "pneumonia" on the right side during childhood. Family history was essentially unrevealing.

Examination on admission revealed an average built young man, slightly anemic. There was grade 3 clubbing and his breath had a fetid odour. There were signs of a cavity in the left suprascapular and sub clavicular regions and He was expectorating six oz. of yellow sputum per day.

Montoux test with ITU of RT 23PPD was positive (induration 15 mm.). Sputum was repeatedly positive for A.F.B. on smear. Culture of the sputum grew *Niesseria catarrhalis* and *Klebseila Puumoniae*; the organisms were sensitive to tetracyclines, streptomycin and chloramphenicol. There was moderate polymorphonuclear leucocytosis. Haemoglobin was 10.5 gm%.

A radiograph of the chest on admission (fig. 1) showed widely diffuse ring shadows the wall of which were of hairline thickness in the upper and middle zones of the right lung; trachea was markedly shifted to the right side. **Left** lung showed patchy shadowing with a 4 cm. cavity in the subclavicular region.

He was treated with streptomycin, PAS and isoniazid. Sputum became negative for A.F.B. after two months treatment. An X-ray chest done showed marked radiological improvement of the left lung but the picture on the right side was stationary. There was also relief in chest symptoms except for the amount of expectoration which was still three oz. per day.

At this stage chloramphenicol 0.25 gm q.i.d. was added to the treatment and postural drainage given. After a fortnight chloramphenicol was replaced by tetracycline. After a month of treatment with broad-spectrum antibiotics the daily amount of sputum was reduced to half an oz.

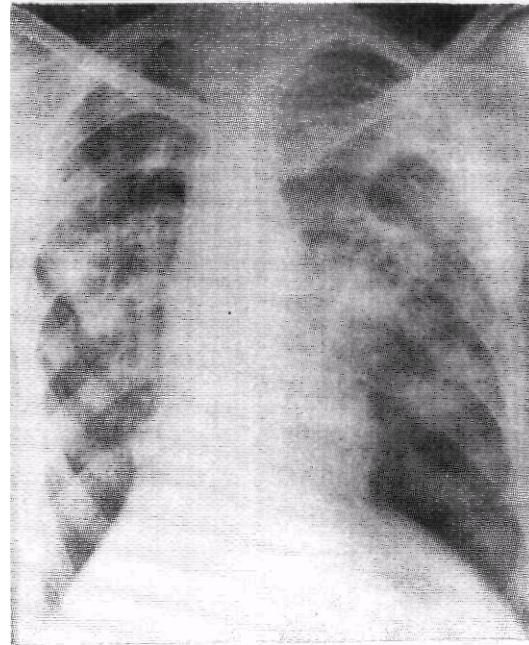


Fig. 1

Skiagram chest showing ring shadows with hairline-thickness walls in the right lung. Left lung shows patchy shadowing with a cavity in the subclavicular region.

A bronchogram was done now. It showed (fig. 2) cystic dilatations of bronchi on the right side; the radio-opaque material readily flowed into the cysts. The left lung showed distorted bronchial pattern only.

Summary

The diagnosis of infected peripheral bronchial cysts was suggested by profuse fetid expectoration, clubbing, the rather suggestive picture on the radiograph and the response to treatment to broad-spectrum antibiotics. The diagnosis was confirmed on the typical findings on the bronchogram.

Pulmonary tuberculous was diagnosed on the radiographic findings and the bacteriologically positive sputum and was confirmed by response to antitubercular drugs.

The bronchial cystic disease can simulate tuberculosis or actually become superimposed

with acid fast infections (Andrews et al, 1959). In the present case there was no evidence of

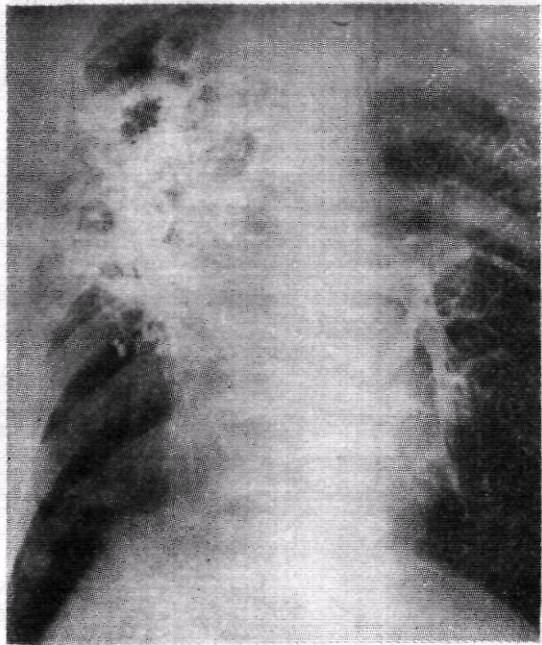


Fig. 2

Bronchogram of the same case. Cystic dilatations of the bronchi corresponding to the ring shadows on the straight X-ray.

cystic disease on the side where tuberculosis disease was present. So there was obviously no etiological relationship.

Residual annular shadows after chemotherapy of tuberculosis can be mistaken for cystic disease. But the differentiation is easy on bronchography; the contrast material flows easily into the cysts through several large bronchial communications but it is difficult to fill the post chemotherapeutic spaces (Andrews et al, 1967).

The presence of pulmonary tuberculosis in one lung and peripheral bronchial cystic disease in the other is rare and interesting occurrence. We did not find a comparable case in the literature.

Comment

A case is reported with pulmonary tuberculosis in one lung and peripheral bronchial cysts in the other. This is an interesting and rare combination.

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BOOK REVIEWS

BY

S. P. PAMRA

MODERN DRUG TREATMENT IN TUBERCULOSIS by J. D. Ross and N.W. HORNE, Fourth Edition 1969. Published by Health Horizon Limited for Chest & Heart Association, London. Price 17s. 6d.

The authors have condensed in 112 pages a wealth of information about chemotherapy of tuberculosis. This concise, yet comprehensive book is intensely practical; theoretical aspects and mere academic discussions have been avoided. Its simple language and easy style makes it invaluable for postgraduate and under-graduate medical students and for general practitioners who want to treat tuberculosis correctly and effectively. The utility of the book is further enhanced by the inclusion of short chapters on management of extra pulmonary tuberculosis, role of corticosteroids and preventive measures such as contact examination, case-finding, BCG vaccination etc.

THE INNERVATION OF THE LUNG by EDWIN F. HIRSCH and GEORGE C. KAISER. Published by Charles C. Thomas, Springfield Illinois- U.S.A. Pp. 105. Price \$11.50.

The authors have adopted an anatomic approach to study the structure, location and distribution of sensory and motor pathways and receptors in the lungs of man, dog, cat, frog, birds, rodents, reptiles etc. Comparatively little known data about innervation of the lungs have been presented. The authors have also studied the phenomenon of wallerian degeneration of nervous tissue beyond the level of neurotomy and other pulmonary tissue changes experimentally in reimplanted dogs' lungs. Since repair of nerves is impossible on reimplantation, role of nervous tissues in respiratory functions of the lungs and restoration of innervation in reimplanted lung tissue has also been studied.

In these days of transplantation surgery, the transplantation of lung is bound to come sooner or later and to that effect, this small but highly informative book will not only be

valuable for anatomists but surgeons also.

Excellent reproduction of histological section photographs is a special feature of the book.

FUNDAMENTAL AND POSSIBILITIES IN ANTI-TUBERCULOSIS VACCINATION by Richard Prigge and Gunther Heymann. University of Toronto Press.

The book under review is an English translation by H.C. Elliott of the original work in German. The authors have condensed a wealth of information within its 100 pages. The main theme of the book is immunization against Tuberculosis with B.C.G. in all its perspectives. The more or less controversial basic problems have been critically dealt with. The nature of allergy and immunity and their relationship, relationship between acquired immunity and natural resistance and humoral antibodies have also been covered. A chapter on immuno-chemistry of the bacillus and antigenicity of its various constituents has been included.

Evidence in favour of and against the 'fixed' virulence of B.C.G., its harmlessness and efficacy, is critically presented. The authors, while pointing out the difficulties in organising a rigorous, scientific, controlled trial to prove conclusively the efficacy of B.C.G., consider a definite verdict on value of B.C.G. to be premature. However vaccination in situations where the exposure hazard is high is not opposed. The role of vaccination with Vole bacillus, killed bacilli and with metabolic products of bacilli is also included. The authors agree with what Bruno Lange wrote nearly four decades ago "Regarding anti-tuberculosis vaccination we have not gone far beyond experiments which are not very encouraging and there is scant hope of achieving results in this way even in future".

On the whole it is an excellent and thought-provoking treatise on the subject of fundamentals and possibilities of vaccination with an exhaustive bibliography.

"ASTHMA : A GUIDE FOR PATIENTS" by K. Michael Hume, MD, published by the Chest and Heart Association, Tavistock House North, Tavistock Square, London, WC Pp 104 Price 16 s.

This small book presents in simple, almost non-technical language, all that is known and worth knowing about common yet not fully understood condition of Asthma. All aspects of this complex problem likely to interest a layman, viz., its causation, management and prevention are adequately covered. Illustrative cases help to make the text more interesting

and educative. The important role of 'Trigger' mechanism in precipitating an attack is duly stressed and would help a sufferer to identify and avoid it in his own case, if possible.

Although the book is written primarily for laymen, it would be useful for medical students and general practitioners as well. The printing and general get up of the book are very pleasing. The British Chest and Heart Association is to be highly complimented for bringing out this useful volume which, in an easy reading, provides necessary information to Asthma sufferers, their families, and general public.

Ind. J. Tub., Vol. XVII, No, 3

NEWS AND NOTES

NATIONAL CONFERENCE ON TB AND CHEST DISEASES

The twenty-sixth National Conference on TB and Chest Diseases will be held in Bangalore from 2nd to 5th January, 1971. Dr. K. Somayya of Hyderabad will preside over the Conference and Mysore State TB Association will play the host.

The main subjects selected for the conference are : "Progress ' and evaluation of national tuberculosis control programme", "Chemotherapy", "Role of steroids in tuberculosis", "Emphema", "Social aspects of tuberculosis". Details of the Conference may be had from the Tuberculosis Association of India, 3 Red Cross Road, New Delhi.

TB SEAL CAMPAIGN

The twenty-first TB Seal Sale Campaign will commence as in previous years on October 2,—Mahatma Gandhi's birthday. The campaign closes on 26th January,—the Republic Day. The selected Seal for 1970-71 is captioned "Deer in Motion".

HEALTH VISITORS' COURSE

The 1970 TB Health Visitors' Course commenced in New Delhi TB Centre on 1st July, 1970. The duration of the course is for 9 months of which 5 months will be in the New Delhi TB Centre. 2 week in Lala Ram Sarup TB Hospital, Mehrauli, 2 weeks for examination and 3 months internship which will last from 1st January to 31st March, 1971.

DR. N.K. MENON HONOURED

Dr. N. K. Menon, Adviser-in-Tuberculosis, Government of India and a member of the Standing Technical Committee of the Tuberculosis Association of India, has been elected to the fellowship of Royal College of Physicians of Edinburgh.

CPEST AND HEART ASSOCIATION FELLOWSHIP, LONDON—1970

The Chest and Heart Association, London, have offered a Fellowship to the value of £500 to enable a young Doctor from India to study in the United Kingdom during the year. The period of study is for 3 months and the selected candidate will begin his training in mid-September this year. This is the eighth Fellowship offered by the Chest and Heart

Association to the Tuberculosis Association of India.

DONATION OF BOOKS

The Chest and Heart Association, London, have donated to this Association 50 copies each of their publications: (1) Protection of Nurse against tuberculosis, (2) Tuberculosis Prevention and Control, (3) Pneumococcosis (4) Health and TB Conference, Nigeria and (5) 6 copies of Modern drug treatment in tuberculosis.

TEXT BOOK ON TUBERCULOSIS

The Text-book on Tuberculosis which the Association has compiled under the General Editorship of Dr. K.N. Rao is expected to be out from the press by the end of this year. The 1000 pages Text Book includes chapters on epidemiology of the tuberculosis, methods of diagnosis, differential diagnosis and tuberculosis of different organs like bones, joints and genito-urinary tract etc. The book also covers details on radiology, BCG and TB control in rural and urban areas. The book which will approximately cost between Rs. 45/- to Rs. 50/- can be had from Messrs Kothari Book Depot, Acharya Dhonde Marg, Parel, Bombay-12 and its branches in Ahmedabad, Poona, Indore, Madras and Hyderabad.

ANH-TB SHIBIR CAMP : MAHARASHTRA

The Maharashtra State Anti-TB Association organised its 8th anti-TB shibir at Alibag, Nagao and Revdanda in March, 1970. The earlier camps were organised at Bombay, Tare, Chinchani, Mangaon, Mahad and Ashta in Maharashtra State. These camps are being organised under the direction of Dr. M.D. Deshmukh, Honorary Secretary, Maharashtra State Anti-TB Association.

The preliminary arrangements for the Camp were made by Shri Y.D. Deshmukh, Honorary Secretary, Kolaba District Anti-TB Association. The GramPanchayat of Revdanda had agreed to hold the main camp there with the team visiting Nagao on their way to Revdanda from Alibag to give preventive inoculations to school children. As neither Revdanda nor Nagao had facilities of screening of chest the arrangements were that the symptomatics could attend the civil hospital at Alibag, sputum and urine examination for diabetes were also to be conducted there. At the main camp at Revdanda children from

primary school were to be surveyed for BCG, oral polio, triple vaccine along with the usual propaganda meeting at the end of the camp.

An advance party of doctors, BCG technicians and public health nurses were sent to Alibag. Dr. M.M. Wagle, the pediatrician opened his nutritional clinic for small groups of women. Dr. Mrs. M. Lalita Rao, President of the Bombay branch of Indian Medical Association joined the group at Revdanda to examine and look into gynaecological complaints. About 40 symptomatics were examined here and 6 of these were brought to Alibag for screening of chest. The total number of persons examined and screened during the camp were 350 and 143 respectively. The number of BCG, oral polio and triple vaccinations given amounted to 1729, 190 and 180 respectively. The camp concluded with a public meeting presided over by the Deputy Collector.

The main party consisted of Dr. M.D. Deshmukh, Dr. S.A. Shah, Dr. J.C. Kothari, Dr. Mohanty, Dr. Thippanna, Dr. Vyas, Miss Putane, Dr. (Miss) Virani and Mr. Kale. Shri N S. Phansalkar, Sales Executive of Chemo-Pharma and 2 medical representatives carrying anti-TB drugs and general tonics also accompanied the party.

CAMP, KHED

The 10th anti-TB Shibir (TB Camp) at Khed in Poona District held on 15th June, 1970 marked the beginning of a effort made by the Maharashtra State Anti-TB Association towards initiative to be taken by district branches for organising Shibir in their areas. This was an important step in the view of the fact that the activities of the State branch alone could not adequately serve all the 26 districts in the Maharashtra State. Dr. V.M. Bahulkar and Dr. H.V. Bahulkar of the Poona district branch played a leading part in the planning and conduction of this Shibir.

TB WORKERS CONFERENCE : DELHI

The Care and After-Care Committee (TB) of Delhi held the 7th Delhi TB Workers' Con-

ference in association with the Delhi TB Association on 15th March, 1970. The Conference which was inaugurated by Dr. A.N. Jha, Lt.-Governor, Delhi was attended by a large number of TB workers and specialists.

INDIAN ACADEMY OF MEDICAL SCIENCES

The Indian Academy of Medical Sciences has been conducting post graduate examinations in different disciplines of medical sciences on an All India basis with a view to admit candidates to the Membership of the academy. The examinations are held twice a year in January and July. The next examination will be held in January 1971. Details about the examinations and application forms can be obtained from the Executive Director, Indian Academy of Medical Sciences, C-II/2, Medical Institute Campus, Ansari Nagar, New Delhi-16 on payment of Rs. 3.

TUBERCULOSIS AND PNEUMOLOGY CONFERENCE ; PRAGUE

A conference on Tuberculosis and Pneumology will be held in Prague from October 5-9th, 1970 under the auspices of the Czechoslovak - phthisiological Society. The main topics of the conference include Tuberculosis, lung cancer, pneumopathies. There will also be an international symposium on recent experimental and clinical experiences with Rifampicin. Detailed information and preliminary application forms may be obtained from the Congress Office (Medical Society), Sokolska 31, Prague-2).

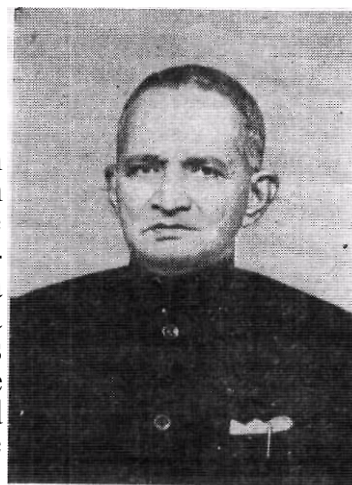
TUBFRIM

The Tuberculosis Association of India is collecting used Indian postal stamps for sending them to TUBFRIM in Nesven in Norway. This organisation has promised to sell used stamps and remit the proceeds to the Association. The stamps should not be peeled off from the envelopes or wrapping paper but cut around the stamps leaving a slight margin so that the perforation remains intact. The Association will be grateful to all those who can send used stamps.

DR. M. UMESHA RAO

We regret to announce that Dr. M. Umesha Rao, past Chairman of the Standing Technical Committee and President of the 25th National

Born in 1901 in a respectable Saraswath family Dr. Umesha Rao had his early education in Mangalore. In 1926 he passed out from the Madras Medical College and later he had his post-graduate course in Tuberculosis in the All India Institute of Hygiene and Public Health, Calcutta and in K.P.T. Sanatorium, Mysore. He took his T.D.D. in Wales in 1938. He acquired considerable experience at Cheshire Joint Sanatorium and Brompton Hospital, London and also at the Papworth Colony, England.



Dr. Umesha Rao held various appointments as Medical Officer in rural and semi-rural areas. He was honorary physician in Medical and TB wards and head of the TB department in the Government headquarters hospital, Mangalore. He was lecturer in TB in Kasturba Medical College, Mangalore. After retirement in 1961 he continued as consultant in the Government headquarters hospital, Mangalore. He was elected Honorary Secretary and later President of the Indian Medical Association, South Kanara branch. He was Honorary Secretary of the St. John's Ambulance Association in South Kanara. He received an award for his distinguished services as President of the Federation of Welfare Agencies, Mangalore. He was President of the Mangalore Citizens' Association and Vice-President of the Governing Body of the Saraswath Education Society.

Dr. Umesha Rao was responsible for the organisation of the South Kanara District TB Association. His benevolent and humane disposition, devotion, vision and drive found fulfilment in this voluntary field. He was a good organiser and silent worker. He rendered yeoman service to the TB Association as Honorary Secretary of the South Kanara District Association. He was a member of the Standing Technical Committee of the Tuberculosis Association of India from 1964 to 1970 and member of the Central Committee. For the past two years he was Vice-President of the Mysore State Tuberculosis Association. The Tuberculosis Association of India elected him, in 1969, as Chairman of its Technical Committee and as President of the 25th National Conference on Tuberculosis and Chest Diseases.

In the death of **Dr. Umesha Rao** the Tuberculosis Association of India has lost a senior **worker**.

The Indian Journal of Tuberculosis

ABSTRACTS

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Pulmonary Edema of high altitude I, II & III

R. Viswanathian et al Amer. Rev. Resp. Dis. ; 1969, 100, 327-349

Experimental studies have shown that there is a species difference in the development of pulmonary oedema of high altitude (POHA) and that within the same species of animals, susceptibility to POHA is variable. That POHA occurs only in a few of the patients who go to higher altitudes suggests that there are certain constitutional factors underlying the development of this condition. Most of the cases occurred at heights above 3,600 metres. In 75% of the patients, the disease occurred on re-entry to high altitudes, after spending home leave in the plains for 30 to 60 days. Persons who were susceptible had shorter chests, smaller lung volumes, increased pulmonary arterial pressure and higher pulse rate. Hypoxic breathing lowered the oxygen saturation of the arterial blood to a greater extent in susceptible persons than in normal subjects. They were hyper-reactors to hypoxic stress. Their pulmonary arterial pressure rose significantly more than in normal subjects. The rise in pulse rate was also greater. On the other hand, they were hypo-reactors to the cold pressor test.

The basic mechanism underlying the development of POHA is an abnormal reaction of certain parts of the pulmonary vasculature to low PO₂ at high altitudes in susceptible individuals. Whereas susceptibility may be determined genetically, it becomes manifest in the form of greater pulmonary vascular resistance at the precapillary level, presumably as a result of an increased amount of circular muscle fibers in the arterioles of certain areas within the lungs.

The abnormal reaction consisting of severe contraction of muscular arterioles might result in wider opening of perpendicular non-muscular arterioles and consequent loading of capillaries supplied by them, and the resulting rise in capillary hydrostatic pressure might lead to exudation of fluid into alveoli. Alternatively, constriction to the point of occlusion of the

terminal branches causes capillary blood stasis, that, with concomitant regional hypoxia, leads to increased permeability and seepage of fluid into the interstitial spaces and alveoli. It is possible that both mechanisms operate in certain cases,

>*

S.P.P.

The pulmonary tuberculosis lesion in North India : A study in medico-legal autopsies

N.C. Nayak, B.D. Sabharwal, D. Bhatena, G.S. Mital and V. Ramalingaswami. Amer. Rev. Resp. Dis. ; 1970, 101, 1.

An anatomic study of tuberculous lesions of the lungs was carried out in 1,680 medico-legal autopsies in Delhi. All age groups, with the exception of children younger than 10 years and both sexes were adequately represented in the series. Active pulmonary tuberculous lesions were found in 17.0% of the cases. Of these, approximately one half were fibro-caseous lesions and the remainder, small or large nodules. The small nodules showed low grade smouldering activity and simultaneous attempt at healing.

Histological demonstration of acid fast bacilli was easier and more frequent in fibro-caseous lesions than in the nodular. In fibro-caseous and large nodular lesions, the bacilli were identified as frequently in tissue sections as by micro-biological techniques. There was no co-relation between the anatomic characteristics of the lesion and the virulence of the bacilli isolated from them. It is suggested that host factors are important in determining the nature of the lesion and its subsequent evolution.

Only one strain of atypical myco-bacterium was isolated. The large nodule from which this strain was obtained differed in no respect from other similar lesions in the series. No case of histoplasmosis was seen.

S.P.P.

A comparison of regimens of Ethionamide, Pyrazinamide and Cycloserine in re-treatment of patients with pulmonary tuberculosis

Bull. Inf. Un. Tuberc. ; 1969, 42, 7.

A controlled trial was carried out from 28 centres in 14 countries to study various combinations of Ethionamide (ETH), Pyrazinamide (PZA) and Cycloserine (CS) with or without INH in patients who had previously been treated and had cultures resistant to INH.

The main treatment groups were ETH, PZA and CS for 12 months ; ETH, PZA and CS for 16 weeks followed by either ETH and PZA or ETH and CS for 36 weeks ; ETH and PZA for 12 months ; ETH and CS for 12 months. Half the patients in each of these groups received INH and the other half did not receive INH. Patients were allocated to the above ten treatment groups at random.

The doses of the drugs were ETH 0.5 grams twice a day ; PZA 1 gram twice a day; CS 0.25 grams three times a day and INH 300 mg once daily.

One hundred and forty out of the 393 patients allotted to the treatment groups had to be excluded. Of the remaining 253, 220 had cultures sensitive to ETH, PZA and CS and in 33 the pre treatment culture was resistant to one or more of these drugs. Of the 220 with sensitive cultures, only 102 (46%) completed 52 weeks treatment. In 27% the regimen was changed because of toxicity or intolerance and 23% did not co-operate fully in the trial.

The results of treatment with various combinations of ETH, PZA and CS were not improved by adding INH to the regimen. The results with ETH and PZA were significantly less good than those with either ETH and CS or all three drugs. Although the bacteriological results with three drug regimen were slightly better than with two drug regimens but the intolerance was also more. Thus taking into account toxicity and intolerance along with bacteriological results, the results in ETH/PZA regimen were almost similar to ETH/CS and three drug regimens. After 16 weeks of three drug regimen, stopping either PZA or CS did not reduce the chances of the patient's disease becoming bacteriologically quiescent.

In 46 out of 220 patients (21%) treatment had to be changed for toxicity or intolerance. Liver damage was the cause in 4%, gastrointestinal symptoms in 6% and mental changes due to CS in 10%. The mental change com-

monly occurred early, during the first 16 weeks in 14 patients,

S.P.P.

Death following massive ingestion of Isoniazid

Steven Arthur Friedman, Amer. Rev. Resp. Dis. : 1969, 100, 859.

A case is reported where, death followed ingestion of 30 g. of INH by an 18 year old male. Even though some of the ingested INH was vomitted out soon after ingestion, frequent convulsions, persistent sinus tachycardia, metabolic acidosis and severe coma followed. Fever and leucocytosis also occurred. Treatment with gastric lavage, anticonvulsants, endotracheal incubation and ventilation, intravenous fluids, 600 mg. of pyridoxine intramuscularly, and peritoneal dialysis controlled the convulsions and acidosis to some extent but death occurred 44 hours after ingestion of INH while the person was still in coma.

S.SP.

Isoniazid prophylaxis in Alaskan Boarding Schools

George W. Comstock, Laurel M. ffarnines & Antonic Ph. Amer. Rev. Resp. Dis. ; 1969,100, 773.

A comparison of the effectiveness of two regimens of INH in preventive tuberculosis was started in 1958 in 4 schools in Alaska. The standard regimen of 5 mg. INH per kg. per day was compared with the test regimen of 1.25 mg. per kg. per day. Both were given for a period of 6 months. In the following 10 years, active tuberculosis developed among 1.9% of the students who took the standard dose as against 5.7% of those who were given the test dose.

In another study, placebo was also included. It was found that the dose of 1.25 mg. was no more effective than the placebo. Although 6 months' administration of INH may not be optimal, the reduction in tuberculosis attributable to this regimen is similar to that achieved by a full year of INH in most other trials.

SS.P.

Late results of pulmonary surgery

Osamu Miyashita. Reports on Medical Research Problems of the Japan Anti-TB Association.

Impairment of pulmonary function after surgery developed with the lapse of time after

ABSTRACTS

the operation. Out of the 71 cases who were studied in detail, only 2 were found to have developed cor pulmonale, an unexpectedly low incidence. The rate of relapse after a follow up of 2, 5, 10 and 15 years was 1.1%, 3%, 2% and 3% respectively.

In resection cases, the tuberculous death rate was 2.3%, out of which the operative mortality was 1.6%. With 1% non-tuberculous deaths, the total loss because of death was 3.3%. In the case of thoracoplasty total deaths were 9.3%, out of which non-tuberculous deaths were 3.6% and operative mortality was 1.9%.

The difficulties of a long-term follow up are discussed and the authors are of the opinion that a close co-operation between the physicians and surgeons is necessary, both to avoid surgery being unduly delayed and also for satisfactory follow up.

S.S.P.

Study on the anti-tuberculous activity of Tuberactin, a new Antibiotic

M. Toyohara Reports on Medical Research Problems of the Japan Anti-TB Association.

A new antibiotic 'Tuberactin' has been isolated and purified from the culture filtrate of *Streptomyces griseovorticillatus* var *tuberacticus*. The chemical formula of the antibiotic is not yet decided but it is a basic peptide and is easily soluble in water. Its anti tuberculous activity has been studied both *in vitro* and *in vivo* and found to be somewhat better than viomycin but less than streptomycin. The drug, however, is less toxic than viomycin. Cross resistance between tuberactin and viomycin has also been demonstrated. Studies on the drug are continuing.

S.S.P.

Tuberculosis studies in Muscogee County, Georgia

George W. Comstock & Ruth G. Webster. Amer. Rev. Resp. Dis. ; 1969, 100, 839.

In 1947, a controlled trial of BCG vaccination was under taken by the US Public Health Service among 11,262 school children in Muscogee County. Twenty years after the start of the trial, 47 cases of definite tuberculosis had been identified among the study population. The average annual case rate per 100,000 was 156 among low reactors, and even

more in high reactors. Non reactors had an average annual case rate of only 16. Vaccinees had a slightly higher rate than the control group. Difference was not significant.

The findings indicate that the risk of acquiring tuberculosis disease has been very low in Muscogee County for the past 20 years, and the need for protection that vaccination can give was correspondingly low. What was true for Muscogee County 20 years ago must be even more true for virtually all part of U.S. today.

S.S.P.

Cooperative international study in the demographic & geographic distribution of low, medium and high grade tuberculin sensitivity

M.A. Bleiker Bull. Int. Un. Tuberc. 1969, 42 65.

75,000 children in 21 countries were tested with human and avian PPD. The technique, syringes, needles, tuberculin and recording cards etc. were uniform. The percentage of children previously vaccinated with BCG varied from regimen to regimen. No BCG vaccination was found in Spain and Southern Algeria ; low percentage of vaccinees in Great Britain, Netherlands, Portugal, Jerusalem and Surinam ; and a high percentage in Yugoslavia, Czechoslovakia, Poland and West France.

The percentage of reactors to 2 TU of PPD RT XXIII in children without previous BCG vaccination was lowest in Netherlands, Vancouver and Great Britain (1.3, 1.4 and 1.5 respectively). It was higher in Belgium (2.8 and 4.1) still higher in France (9.4 and 11.7) and Spain (10.0 and 14.4). In Portugal the index was 5.0 and 6.1. In Surinam, Algeria and Poland it was highest.

Non-specific tuberculin sensitivity was found in the Netherlands, France and Spain (alicanta). Absence of non-specific sensitivity was found in Yugoslavia and Czechoslovakia.

S.S.P.

Causes of death in patients with Bronchiectasis

Nikolaus F.J. Konietzko, Robert W. Canon & Elite P. Leroy. Amer. Rev. Resp. Dis. ; 1969, 100, 852.

During the period 1956 to 1968, 62 patients of bronchiectasis were followed up. Twenty

six of them died but the cause of death was known only for 18. In one half of these patients it was unrelated to bronchiectasis. Broncho-pulmonary infections have declined sharply as a cause of death, whereas cor pulmonale and other cardio-vascular diseases have risen in importance. The average age at death (55.7 years) continues to increase compared with that in earlier studies, reflecting the nature of the population of patients with bronchiectasis and improvements in medical therapy.

S.S.P.

Atypical pulmonary patients of congestive failure in chronic lung disease

WE F. Hublitz, & Jerome H. Shapiro. Radiology; 1969, 93, 995.

The basic pattern of gross intra-alveolar pulmonary oedema, consisting of large, homogeneous, confluent, amorphous, ill-defined, symmetrical, perihilar opacities is well known. Several variations of this classical pattern may however be present. Co-existence of left-sided heart failure and pulmonary oedema in chronic lung disease is common. The pathological entities interact in such a way as to produce atypical radiological patterns of failure. Four patterns, in decreasing order of frequency are : (a) regional, (b) interstitial, (c) reticular and (d) miliary-nodular. These failure patterns should be recognised and differentiated from the changes seen in chronic obstructive lung disease.

S.S.P.

The multiple presentations of bronchial adenomas

Peter E. Giustra and Gorge Stassa, Radiology 1969, 93, 1013.

Ninety nine cases of radiologically proved bronchial adenoma have been reviewed regarding their radiological presentation. Fifteen of these were found at autopsy or thoracotomy for unassociated diseases. The remaining 84 cases were classified as having no positive radiological findings or occurring as pulmonary infiltrates or a focal zone of atelectasis or a peripheral nodule or a hilar mass alone or in combination with peripheral nodule or atelectasis.

No radiological pattern has been found to be diagnostic. A hilar mass alone or in

combination with a parenchymal lesion was the most common presentation. Pleural effusion or a negative chest x-ray was a rare finding, Metastases in bones do occur and bronchial adenomas are often indistinguishable radiologically from bronchogenic carcinoma.

S.S.P.

A comparison of pulmonary function in bronchial asthma and chronic obstructive bronchitis :

K.N.V. Palmer, M.L. Diament: Thorax (1970), 25, 101.

The dynamic and static lung volumes, arterial blood gas tensions and single breath carbon monoxide transfer factor have been compared in 72 asthmatic and 45 bronchitic patients with airway obstruction of comparable severity to determine which measurement might be used to discriminate between the two diseases. The forced vital capacity, total lung capacity, arterial carbon dioxide tension and transfer factor were useful in this respect.

Thus in patients with airway obstruction, the finding of low % predicted FVC (< 70) and low % predicted DLCO (Z50) with a relatively normal $\frac{1}{2}$ predicted TLC and raised Pa Co₂ is strongly suggestive of chronic obstructive bronchitis, whereas the finding of a relatively normal % predicted FVC and a high % predicted TLC (7115) with a nearly normal DLCO and a normal or low Pa Co₂ is most compatible with diagnosis of bronchial asthma.

H.B.D.

The management of spontaneous pneumothorax.

LTC Michacal G Seremetis. Chest, Vol, 57, No. 1, Jan, 70.

In 155 patients with spontaneous pneumothorax, the recurrence rate was 41 percent. It was 49 percent for patients with bed rest, 40 percent for those treated first with bed rest and later with tube thoracotomy and 38 percent for the group treated with tube drainage. There was no recurrence after open thoracotomy and pleuropesis. Hospitalization was considerably shorter after tube thoracotomy which is preferred as treatment of choice for initial management.

H.B.D.