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No. 1

TUBERCULOSIS—A SERIOUS PROBLEM

Not very long ago, it was difficult, if not impossible, to prevent and cure tuberculosis. With the advent of antimicrobial drugs having specific bactericidal and bacteriostatic actions on the causative mycobacterium, such a grave outlook need not persist. The prognosis for those taking treatment regularly and adequately has improved tremendously and the fatality rate has gone down. A large majority of the patients need not enter hospitals. Not only domiciliary treatment is equally effective, but patients can work while under treatment. BCG vaccination of children has prevented the onset of the disease to some extent. Unfortunately, these silver linings on the cloud appear to have led to a feeling of complacency about the tuberculosis problem. We do not appear to pay the attention to tuberculosis which the problem calls for. We seem to be under the impression that of all the communicable diseases, only malaria, small pox and leprosy continue to be important health hazards and that tuberculosis is no longer a public health problem that it was. Facts and figures, however, show that such an impression is not in keeping with reality.

In spite of the dramatic efficacy of the antituberculous drugs, nearly 500,000 people still die of the disease every year in our country. The prevalence of active disease needing treatment is estimated to cover about eight million persons at any point of time. Two million of these are certainly in an infectious stage. Hardly 20 per cent of the children in the vulnerable age groups have been given even partial protection through BCG vaccination. Is there any other communicable disease whose record of mortality and morbidity is so dismal in our country? What then is the justification for complacency?

The national sample survey carried out in 1955-58 revealed that the prevalence of tuberculosis was almost as high in the villages as in the urban areas, but facilities for diagnosis and treatment were available then mostly in urban areas. Since it was not feasible to provide tuberculosis services from specialized institutions in the far-flung rural areas, the District Tuberculosis Programme was introduced in 1962 as the means to control the disease in the country. It aimed at integration of tuberculosis with the general health services whereby every health facility, particularly in the rural areas, was required to provide a diagnostic and treatment service under the guidance of the District Tuberculosis Officer. It has not been possible to implement this programme in all districts of the country so far. What is more disturbing is that even in the districts where the programme has been introduced, its working is far from satisfactory.

It is no secret that the number of fresh cases diagnosed at the peripheral health centres is woefully small and even all of the few who are diagnosed do not complete treatment. The services of the so-called peripheral health institutions do not reach the periphery and are limited only to the few villages near such institutions. In other words, acceptance of the concept of integration and its implementation have so far been more or less on paper only. The actual performance has been poor and short of expectations. Unless the performance is improved considerably and the plans and programmes are pursued with zeal and conviction in keeping with the seriousness and magnitude of the problem, it will not be possible to make even a dent on this colossal problem in the foreseeable future. Top priority, therefore, has to be given to tuberculosis control to strengthen the existing services and extend them to the whole of the country expeditiously.

Whether there has been any change in the prevalence of tuberculosis during the last eighteen years after the first national sample survey and if so the quantum and pattern of change is anybody's guess. The findings of small limited surveys being conducted in different parts of the country appear to be contradictory. This contradiction is, however, understandable since the conditions prevailing in the areas where these surveys are being conducted are not comparable. The Tuberculosis Association of India has been requesting the Government for the last few years to have a second national sample survey so that it may be possible to assess the current epidemiological situation. In fact, periodic surveys are essential in a country like ours as these alone can provide authentic data for assessment of the impact of policies and programmes and to plan and modify the strategy rationally and in a realistic manner. No doubt surveys are expensive but their usefulness is well worth the cost. To do is essential, while to know whether what has been done has or has not been effective, is more essential.

Tuberculosis Associations in general and the medical profession and tuberculosis workers in particular have a moral duty to bring home to all concerned, including the administrators, that there is no basis at all for complacency about the tuberculosis problem as this disease continues to be the most important infectious scourge that claims more lives than any other disease in our country. The points of emphasis may have changed but the problem continues unabated. We appeal to the Hon'ble Health Minister, to the Director-General of Health Services who is the Chairman of the Association and to the Planning Commission kindly to accord to tuberculosis control programme the place it deserves as India's PUBLIC HEALTH PROBLEM NUMBER ONE.

INCIDENCE OF TUBERCULOSIS AMONG NEWLY INFECTED POPULATION AND IN RELATION TO THE DURATION OF INFECTED STATUS

V.V. KRISHNA MURTHY, S.S. NAIR, G.D. GOTHI and A.K. CHAKRABORTY
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Introduction

In developed countries where the socio-economic conditions are good, the incidence of tuberculosis is reported¹ to be as low as 10 per 100,000 in the general population and 29 per 100,000 among natural reactors. Further, some workers^{2,3} from some of these countries have reported that about three-fourths of the new cases come from the reservoir of previously infected population. This may mean that about one fourth of the new cases originate from the newly infected.

In a developing country like India, the incidence of disease is reported⁴ to be as high as 132 per 100,000. In the same report though the incidence of disease in the tuberculin reactors was reported to be 291 per 100,000 the incidence of disease in the newly infected was not analysed in detail. Because of the unsatisfactory socio-economic conditions in India, chances of transmission of infection may be higher. In such a different epidemiological situation in India, it is also possible that the incidence of disease in the newly infected may be high. Moreover, in India detailed report on the incidence of disease among the newly infected population is rather scarce.

In this paper, it is intended to study the incidence of disease among the newly infected population by age and sex and in relation to the duration of infected status.

Material and Methods

Data collected for the five year study⁴ during 1961 to 1968 have been analysed. The survey was conducted in 119 randomly selected villages in the three taluks of Bangalore district and repeated three times at intervals of 1 1/2 years (II survey), 3 years (III survey) and 5 years (IV survey) from the initial survey employing same procedures as at I survey. At the I survey the entire population was registered on individual cards. All those registered were eligible for tuberculin test and all those five years and above for X-ray examination. At the time of tuberculin test both the shoulders were examined for the presence of previous BCG scar and the reactions to tuberculin test were read after 72-96 hours. The X-ray films were interpreted by two independent readers. Two

samples of sputum were collected from those whose films were interpreted as abnormal by any of the two readers or technically inadequate by both the readers. The sputa samples were examined by smear microscopy and culture examination for *Mycobacterium tuberculosis*.

The de jure population registered in the 4 surveys was on an average about 62,000. The coverage in the four surveys on an average was about 80 per cent for tuberculin test, 82 per cent for X-ray examination and 90 per cent for sputum examination.

Persons with X-ray abnormality but bacteriologically negative or with normal X-rays in all the preceding surveys, and who became culture positive with X-ray abnormality in the current survey were termed new cases. New cases who had shown a reaction of 10 mm and more for 1 TU RT 23 at I survey were considered as infected at I survey. New cases who were tuberculin negative at I survey and have shown an increase in reaction of 16 mms or more between two consecutive surveys were considered infected between those two surveys. New cases which did not show such an increase were considered as infected between the survey at which they were diagnosed and the preceding survey.

Between I and II surveys 70 new cases were diagnosed, 40 cases between II and III surveys and 62 cases between III and IV surveys. Tuberculin reactions at the previous surveys were not known for 3 cases each at II and III surveys and 6 cases at IV survey and these had to be excluded. Hence, 67, 37 and 56 new cases are considered for analysis.

In the five year study, the total number of newly infected in the population of age 5 years or more has been worked out to be 596, 372 and 346 between I and II, II and III and III and IV surveys respectively. For the methods adopted to estimate the total newly infected between two consecutive surveys the five year study⁴ may be referred.

Findings

Infected status of newly diagnosed cases

The new cases diagnosed at II, III and IV surveys are distributed according to the survey

TABLE I

Distribution of new cases diagnosed at the three repeat surveys according to the survey at/between which they were found infected

| Infected at /between survey (s) | New cases diagnosed at survey | | | |
|---------------------------------|-------------------------------|----------|----------|-----------|
| | II | III | IV | II-IV |
| I | 48 (72) | 28 (76) | 42 (75) | 118 (74) |
| I-II | 19 (28) | 2 (5) | 4(7) | 25 (16) |
| II-III | — | 7(19) | 2(4) | 9 (5) |
| III-IV | — | — | 8 (14) | 8 (5) |
| Total | 67 (100) | 37 (100) | 56 (100) | 160 (100) |

Figures in brackets indicate percentages.

at/between which they were observed to be infected. (Table 1).

Out of the 67 new cases diagnosed at II survey, 72 per cent (48) have come from the population infected at I survey (hereafter called previously infected) and 28 per cent (19) from the group of infected between I and II surveys. At III survey out of the 37 new cases, 76 per cent (28) have come from the group of previously infected and 19 per cent (7) from the newly infected between II and III surveys. The corresponding figures at IV survey are 75 per cent (42) and 14 per cent (8). Among the 160 new cases diagnosed during the three repeat surveys, 74 per cent (118) originated from those previously infected (at I survey or before) and 21 per cent (19+7+8) from the newly infected soon after infection i.e., within one and half to two years. The remaining 5 per cent (2+4+2) also came from those newly infected after I survey but one and a half years or more after getting infected.

Incidence of disease in newly infected

The incidence of disease among the newly infected is estimated to be 3.19, 1.88 and 2.31 at II, III and IV surveys respectively (Table 2). The differences in the estimated incidence rates of the three repeat surveys were not statistically significant.

The incidence of disease in the newly infected at the three repeat surveys was studied by sex (Table not presented). There was no significant difference in the incidence rates for the two sexes.

At II survey, the differences in the incidence rates for different age groups were not statistically significant. The incidence rates for different age groups at III and IV surveys were not compared because of the small number of cases in some of the age groups.

Comparison of incidence rates in newly infected and previously infected

The incidence rates at II survey for the newly infected between I and II surveys are compared with that for the previously infected in Table 3.

The overall incidence rates (all ages) for the newly infected was 7 times more than for the previously infected. A decrease (13, 10 and 3) in the ratio (NI/PI) of incidence rates was seen with the increase in age. The ratio of incidence rates for males was considerably more (12) than for females (4).

The incidence of disease among the newly infected in the three age groups were compared with the corresponding incidence rates reported for the general population.⁴ It was observed that the ratio of incidence rates was 44, 19 and 16 in the different age groups. The incidence of disease among the newly infected population was 16 times more than in the general population. The ratio of incidence rates was 21 for males and 12 for females (Tables not presented).

Incidence rate according to duration of infected status

For the purpose of calculation of the duration

TABLE 2

Incidence of disease in newly infected

| Between surveys | Number newly infected (estimated) | New cases | Rate† |
|-----------------|-----------------------------------|-----------|-------|
| I— II | 596 | 19 | 3.19 |
| II— III | 372 | 7 | 1.88 |
| III— IV | 346 | 8 | 2.31 |

† Rate per 100

TABLE 3

Comparison of incidence of tuberculosis between I and II surveys among newly infected and the previously infected

| Infection status | Incidence rates (%) in different age and sex groups | | | | | |
|----------------------------------------------|-----------------------------------------------------|-------|------|-------|-------|---------|
| | 5—14 | 15—34 | 35 + | Total | Males | Females |
| Newly infected (NI) between I and II surveys | 3.85 | 3.92 | 1.90 | 3.19 | 5.06 | 1.95 |
| Previously infected (PI) i.e., at I survey | 0.29 | 0.38 | 0.55 | 0.45 | 0.43 | 0.48 |
| NI/PI | 13 | 10 | 3 | 7 | 12 | 4 |

of infected status of the newly infected persons, it was assumed that the infection took place in the middle of two consecutive surveys. This appears a fair assumption since the occurrence of infection is expected to be evenly distributed throughout the period between two consecutive surveys. To explain in brief, those who were found first time positive at II survey were presumed to have been infected in the middle of I and II surveys so that at II survey, they were infected on the average for 9 months, the interval between the I and II surveys being 18 months.

The incidence of new cases from the newly infected population at the three repeat surveys was observed at the end of different durations of infected status. From among 596 persons who were found to be infected between I and II surveys, 19 cases were diagnosed at the end of 9 months duration of infected status, 2 cases at the end of 27 months and 4 cases at the end of 51

months. Out of the 372 newly infected persons between II and III surveys 7 and 2 cases were found at the end of 9 and 33 months of infected status respectively. From 346 persons who were newly infected between III and IV surveys 8 new cases were diagnosed at the end of 12 months' duration of infected status.

The number of persons with various durations of infected status, (viz., 9, 12, 27, 33 and 51 months) number of cases diagnosed among them and the incidence rates are presented in Table 4. Because of the small number of cases diagnosed at the end of 27 and 33 months, these two durations were combined in Table 4. While computing the incidence rates at the end of different durations of infected status, actual number of persons at risk were considered as the denominator i.e., number of cases diagnosed at an earlier survey was excluded from the total number at risk.

TABLE 4

Incidence of disease in relation to the duration of infected status

| Duration of infected status (in months) | Number of persons | No. of cases diagnosed at the end of the period | Incidence rate (%) Col. (3) ÷ Col. (2) |
|-----------------------------------------|-------------------|-------------------------------------------------|-------------------------------------------|
| 1 | 2 | 3 | 4 |
| 9 | 968 | 26 | 2.7 |
| 12 | 346 | 8 | 2.3 |
| 27—33 | 942 | 4 | 0.4 |
| 51 | 575 | 4 | 0.7 |
| <12 | 1314 | 348 | 2.6 |
| >12 | 1517 | | 0.5 |

The chi-square (X^2) test was applied to find the association between the duration of infection and the incidence rates and also to test whether there was any trend in the rates. The significant chi-square value ($P < 0.001$) clearly demonstrated the association between the duration of infection and the incidence rates and further revealed that incidence rate is inversely proportional to the duration of infection. Also it was observed that the incidence among those who were infected since 12 months or less was about 5 times more than that among those who were infected for more than a year.

Discussion

Disease is an outcome of infection. In the process of the development of tuberculosis the interval between the two events is not precisely known, though it is believed to be considerable. Some parameters relating to the duration of infection and incidence of disease have been presented in this paper.

Out of the 42 new cases diagnosed from the newly infected during the five years, 34 cases (81 per cent), came from those who were within the first year of infection. This may indicate the fact that the incidence is more in the initial period after infection. This was further supported by the finding (Table 4) that the incidence of disease among those who were infected since a year or less was about 5 times more than those infected for more than 12 months. It was also observed that the incidence of disease steadily decreased with the increase in the duration of infection.

It was observed (Table 1) that at least 72 per cent of the new cases at any repeat survey came from the reservoir of previously infected

population which was similar to the observations made by some other workers^{2,3}. In spite of the vast differences in the epidemiological situations prevailing in the developed and the developing countries like India (see introduction), it is interesting to note that the relative contribution to the total new cases from the newly infected and the previously infected population remain the same.

It was observed in the main report⁴ that there was probably a natural decline in tuberculosis during the study period of five years in the area of the study and that the incidence of infection had significantly reduced from 1.63 per cent at II survey to 0.85 per cent at IV survey. But, it was observed in Table 2 that there was some decline in the incidence rates for the newly infected from II survey (3.19 per cent) to IV survey (2.31 per cent), but the difference in the incidence rates was not statistically significant. This means that while the incidence of new infection was declining, the incidence of disease among the newly infected did not change during the period of observation in the study area. However, if the trend observed in Table 2 was real, the natural decline of tuberculosis would be quite steep.

The incidence of disease among the newly infected was almost the same in the three age-groups i.e., 5-14, 15-34 and 35 years or more (Table 3). But the ratio of the incidence rates for the newly infected and the previously infected decreased from 13 for the age-group 5-14 to 3 for the age-group 35 years and above. In other words, the incidence of disease among the newly infected in the age-group 5-14 was thirteen times more than for the previously infected in the same age-group whereas in the age-group 35 years and above, the incidence among newly

infected was only thrice that among the previously infected. Hence, the policy of protection of the younger population from acquiring natural infection with mycobacterium tuberculosis by means of BCG vaccination is more appropriate.

In the present study, of the 160 total new cases diagnosed during the five years, 26 per cent (42 out of 160) of the cases were found to come from the newly infected which formed only about 3 per cent of the average test-read population of the three repeat surveys.

Out of the 160 new cases diagnosed during the three repeat surveys, 21 per cent (32) cases came from among those who were infected on the average for one year or less. This is almost in conformity with the hypothesis⁵ that one-fourth of all new active cases come from new infectious less than a year old.

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RELAPSES AMONG NATURALLY CURED CASES OF PULMONARY TUBERCULOSIS

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The reservoir of infectors in a community is subject to changes from time to time due to death, cure — natural as well as due to treatment - and addition of new cases due to incidence.* The inflow consists not only of cases** arising from the people already infected (“first timers”) but also of “cured” cases*** of tuberculosis who breakdown into positive sputum again at a later date (“Relapse”). In estimation of incidence rates it is customary to consider only the first timers, though some workers think it realistic to include the relapsed cases**** as well.¹ In any case for inflow of cases into the pool of infectors both the first timers as well as relapsed cases should be considered.

The five year longitudinal epidemiological study in South India conducted by the National Tuberculosis Institute (NTI), Bangalore has revealed that a considerable number of cases get cured naturally i.e., without proper anti-tuberculosis treatment.² In the absence of any nearby facilities in the survey area for diagnosis and treatment of tuberculosis, it was presumed that these cases got cured naturally. The pattern of drug resistance in repeat surveys also indicated the absence of organized treatment to any appreciable extent. The extent of natural cure and the subsequent fate of such cases in an infectious disease like tuberculosis, therefore, are important.

It has been contended that substantial self cure might mean a less serious public health problem owing to the relatively short period of sputum positive status of cases.³ This could indeed be so if a sizeable proportion of those who got self cured remained sputum negative for a length of time: there is no information as to what proportion of those naturally cured become

sputum positive subsequently. The material from the five year longitudinal epidemiological study in South India has therefore been analysed to study relapse rates among cases detected in an epidemiological survey who get cured naturally.

Briefly, the population of a random sample of 119 villages from three taluks of Bangalore district was surveyed four times from 1961 to 1968 employing exactly the same methods. The three subsequent surveys were conducted at intervals of one and half years, three years and five years from the initial survey. Persons aged five years and above were offered a 70 mm chest photofluorogram: X-rays read abnormal or technically inadequate by any of the two initial readers and those having physical inability to come for X-ray were eligible for sputum examination. Two specimens, one spot and the other overnight, were collected from each eligible person and examined by smear as well as culture. Smears unconfirmed by culture were disregarded. Cases diagnosed during the surveys could not be offered specific anti-tuberculosis chemotherapy nor was organized anti-tuberculosis treatment available to this population during the study period.

Study Population

In all 269 cases, 178 discovered among 61,663 persons at the first survey and 91 detected for the first time among 62,065 persons at the second survey were available for consideration of natural cure. Of the 178 cases, 48 became culture negative at the second survey and another 22 at the third survey. Of the 91 cases, 38 became culture negative at the third survey. Thus, 108 naturally cured cases of the first and second surveys constitute the material for this analysis (Table 1).

The initial bacteriological status of the 108 naturally cured cases is shown in Table 2: of these, 33 (30.6 %) were positive by smear and culture and 75 (69.4%) by culture alone. The difference in bacteriological status between cases derived from the first and second surveys attained statistical significance: it was apparently due to the fact that the first group contained prevalence while the latter group more of incidence cases. Their age and sex composition is shown in Table 3. Of the 70 cases derived from first survey, 12 were in the age-group 5-19 (17.1 %),

* Incidence case: Persons with chest X-ray abnormality but bacteriologically negative or with normal X-ray in all preceding surveys, who become tuberculosis cases at a subsequent survey.

**Cases: Persons with chest X-ray abnormality and sputum positive on culture or on culture and direct smear; the organisms grown on culture identified as *Mycobacterium tuberculosis*.

***Cured: Tuberculosis cases who become culture negative at a subsequent survey,

****Relapsed: Cured cases of tuberculosis detected as positive for *Mycobacterium tuberculosis* on any one culture of sputum at a subsequent survey (Definition used in this paper).

TABLE 1

Culture positive cases detected during First and Second Surveys who became culture negative at Second/Third Surveys

| Survey | Cases detected for the first time | Sputum converted at subsequent surveys (natural cure) | | |
|--------|-----------------------------------|-------------------------------------------------------|-----------|-------|
| | | I Survey | II Survey | Total |
| I | 178 | 48 | 22 | 70 |
| II | 91 | — | 38 | 38 |
| Total | 269 | 48 | 60 | 108 |

TABLE 2

Initial Bacteriological Status of the 108 naturally cured cases

| Survey | Positive by smear and culture | Positive by culture alone | Total |
|--------|-------------------------------|---------------------------|--------------|
| I | 26 (37.1) | 44 (62.9) | 70 (100) |
| II | 7 (18.4) | 31 (81.6) | 38 (100) |
| Total | 33 (30.6) | 75 (69.4) | 108 (100) |

TABLE 3

Age-sex Distribution of the naturally cured cases by survey when first diagnosed

| Age group | Male | | Female | | Total | |
|-----------|--------------|--------------|-------------|-------------|--------------|--------------|
| | Survey | | Survey | | Survey | |
| | I | II | I | II | I | II |
| 5-19 | 9 (17.0) | 5 (20.8) | (17.6) | 2 (14.3) | 12 (17.1) | 7 (18.4) |
| 20-39 | 21 (39.6) | 5 (20.8) | 9 (53.0) | 7 (50.0) | 30 (42.9) | 12 (31.6) |
| 40+ | 23 (43.4) | 14 (58.4) | 5 (29.4) | 5 (35.7) | 28 (40.0) | 19 (50.0) |
| Total | 53 (100) | 24 (100) | 17 (100) | 14 (100) | 70 (100) | 38 (100) |

TABLE 4

Bacteriological status on follow up of naturally cured cases of pulmonary tuberculosis after varying period and computed relapse rates

| | Period of follow up | Cases followed | Dead | Remained Culture negative | Became Culture positive | Person years of observation | Relapse per 1000 P. Y. @ |
|----------------------------------------------------------------------------|---------------------|----------------|------|---------------------------|-------------------------|-----------------------------|--------------------------|
| Cases naturally cured at 11 survey & followed up for 3½ years after cure | Initial | | | | | | |
| | 1½ years | 42 | 2 | 35 | 5 | 61.5 | 81.3 |
| | Up to 3½ years | 47* | 3 | 32 | 12 | 137.25 | 87.4 |
| Cases naturally cured at III Survey and followed up for 2 years after cure | | 52** | 7 | 37 | 8 | 97.00 | 82.5 |
| Total | | 99 | 10 | 69 | 20 | 234.25 | 85.4 |

* Out of 48 cases, 47 could be followed up ** Out of 60 cases, 52 could be followed up @ One person observed for one year is taken as one person year (P.Y.)

30 in age group 20-39 (42.9%) and 28 in age group 40 and above (40%). Of the 38 cases diagnosed during second survey 7 (18.4%) were between 5-19 years, 12 (31.6%) between 20-39, and 19 (50%) were 40 years and above. There was no difference age-wise between the cases derived from first and second surveys.

Observation period

There was some degree of variability — in quality as well as period - - among the 108 naturally cured for the subsequent follow up. Some persons were not followed up at the intervening survey but examined at the last survey and some were followed up for 1½ years while others for 3½ years. To overcome the difficulty the results were computed by person years of observation: the person followed up for 1½ years has been taken as 1½ person years of observation (P.Y.); for persons not followed up at 1½ years but examined after 3½ years, the computed period was half of the actual i.e., 1.75 person years and for persons dead between two surveys have been taken as alive for half the entire follow up period.⁴

Thus, of the 48 cases becoming culture negative at the second survey (all eligible for follow up for 3½ years) 42 could be followed up for 1½ years till the third survey (61.5 P.Ys.) and 47 cases for varying period upto 3½ years till the fourth survey giving a total of 137.25 person years (Table 4). And, of the

60 culture negative cases at the third survey, 52 could be followed up till the fourth survey for 97 person years. Or, of the 108 cases only 99 were followed up for any length of time for a total of 234.25 person years of observation.

Results

Relapse Rates

Table 4 gives the bacteriological status of those alive at subsequent surveys of cases who had become culture negative at earlier surveys. Thus from the 48 cases naturally cured at the end of second survey, 42 were observed for 61.5 P.Ys. over the first, 1½ years during which 5 became culture positive giving relapse rate of 81.3 per 1000 P.Ys. From the same group, 47 cases were observed for 137.25 P. Ys. over 3½ years, during which 12 relapsed giving the relapse rate of 87.4 per 1000 P.Ys. Similarly, of the 60 naturally cured at the end of third survey, only 52 could be observed for 97 P.Ys. and the relapse rate was 82.5 per 1000 P.Ys. Since the rates computed in this way were not different, inspite of a difference in the initial bacteriological status of the two groups (Table 2), the average relapse rate based on 99 cases observed for 234.25 observation years works out to 85.4 per 1000 P.Ys.

Relapse by age and sex

There was no difference in relapse rates

TABLE 5

Relapse rates by age

| Age group | Total cases | Followed up for (in P. Y.) | No. Relapsed | Rate of Relapse per 1000 P.Y. |
|-----------|-------------|----------------------------|--------------|-------------------------------|
| 5—9 | 5 | 14.5 | 0 | — |
| 10-19 | 11 | 27.25 | 1 | 36.7 |
| 20-29 | 20 | 50.75 | 5 | 98.5 |
| 30—39 | 18 | 44.25 | 3 | 67.8 |
| 40+ | 45 | 97.5 | 11 | 112.8 |
| Total | 99 | 234.25 | 20 | 85.4 |
| 20+ | 83 | 192.5 | 19 | 98.7 |
| 5—19 | 16 | 41.75 | 1 | 23.9 |

between the two sexes (Table not presented). Only one case relapsed in 5-19 years age group and none in the age group 5-9 (Table 5). Relapse rates were higher in persons 20 years or more than those in 5-19 year age group. Relapses within different 10 years age groups among cured cases aged 20 years and above were however of the same order (85-113 per 1000 P.Y.).

Relapse by Bacteriological Status at the time of diagnosis

Table 6 shows that of the 99 naturally cured cases, 23 were positive by microscopy as well as culture. They were observed for 60.5 P.Ys. during which 6 cases relapsed giving the rate of 99.2/1000 P.Y. Of the remaining 76 cases observed for 173.75 P.Ys., 14 relapsed giving the relapse rate of 80.6 per 1000 P.Y. The difference was not statistically significant.

Relapse and drug resistance at the time of diagnosis

Only one of the 20 cases who had relapsed had INH resistant bacilli at the time of diagnosis: he relapsed with INH resistant bacilli. Of the remaining 79 cases who did not relapse, four had bacilli resistant to INH and one to all the drugs at the time of diagnosis.

Death

There were 10 deaths among the 99 naturally cured cases followed up for 234.25 P.Ys. Mortality, therefore, was 42.7 per 1000 P.Ys., i.e., exactly half of relapse rate among those who got naturally cured. The cause of death could not be established. Death among those who relapsed is not presented owing to small numbers.

Discussion

The definition of "cure" in the epidemiological survey in South India² was comparatively less exacting than is usually the case in clinical studies* in the sense that only two sputum specimens collected within 24 hours were examined instead of more specimens collected at 1-3 month intervals.³ This is understandable keeping in mind the operational characteristics peculiar to epidemiological surveys. Moreover, the "cure" was related to culture results only, without regard to radiological status. It is for this reason that the criterion of relapse in the present paper was reversion to the sputum positive status after 'cure' since these cases are transmitters of infection and are of immediate epidemiological consequence.

*Bacteriologically quiescent disease—All cultures (usually 7-9) negative at 10, 11 and 12 months of treatment⁵.

TABLE 6

Dead and relapsed cases by bacteriological status at diagnosis among the naturally cured after follow up and rate per 1000 person years

| | Bacteriological status at diagnosis | | | | | |
|-------------|-------------------------------------|--------------------------|-----------------------|----------------------------|------------------------|----------------------------|
| | Smear and culture positive | | Culture only positive | | Total Culture positive | |
| | No. | Per 1000 P. Ys. | No. | Per 1000 P. Ys. | No. | Per 1000 P. Ys. |
| Total Group | 23 | Observed for 60.5 P. Ys. | 76 | Observed for 173.75 P. Ys. | 99 | Observed for 232.25 P. Ys. |
| Relapsed | 6 | 99.2 | 14 | 80.6 | 20 | 85.4 |
| Dead | 2 | 33.1 | 8 | 46.0 | 10 | 42.7 |

That a significant proportion of cases (about 32%) got 'cured' with little specific treatment or mostly none at all raises many questions. It may be argued that this so called natural cure attained without treatment might not have any epidemiological significance on account of a very limited period of sputum negativity. But, it was seen from this analysis that out of the 108 cases naturally cured, the overall subsequent breakdown rate was about 82 per 1000 P.Ys., computed for varying periods of observation upto 3J years. The computed rate though not strictly comparable is not significantly different from the annual relapse** rate of 6.3 per cent during first year of follow up among adequately treated cases.⁵ However, in the cited chemotherapy trial the overall relapse rate during four years was 8.7 per cent with average annual relapse rate of about 2.2 per cent. This is in contrast to the relapse rates observed among the naturally cured in the present study, which were steady at three points of observation i.e., 1J years and 3½ years for one group of cases and 2 years for another group of cases. It is possible that relapses are more frequent among the naturally cured compared with the chemotherapeutically treated cases except the first year of observation after treatment but this material is not sufficient to comment with a degree of surety.

Superficially the 48 cured cases derived from first survey and 60 from second survey may not appear comparable because the latter group would naturally contain more of incidence

**Relapse-two or more positive cultures in any 6 months period.⁶

cases. This is further suggested by the difference in bacteriological status at the time of diagnosis (Table 2). However, it is seen that the 48 cured cases of the second survey were derived from 178 prevalence cases of the first survey and the 60 cured cases of the third survey were derived from 151 prevalence cases of the second survey, though 38 of the latter came from 91 incidence cases between first and second surveys and 22 from prevalence cases of first survey. Thus, there is really not much difference between the two groups apart from the fact that there are no significant age-sex differences either.

In an attempt to identify the most vulnerable group of people who were prone to relapse more after cure, it was seen that chances of relapse were more in age group 20 and above as compared to that seen in 0-19 years irrespective of sex. The initial sputum status of cases at the time of diagnosis i.e., whether they were only culture positive or positive on both culture and smear examination, was not found to be related to relapse. It seemed that once a sputum negative status was possible to obtain, subsequent fate did not depend upon the degree of sputum positivity at diagnosis.

In the population of about 60,000 in the present study, there were 178 culture positive cases at the first survey. Of these 48 were found cured in 1J years (about 27 per cent.) At relapse rate of 8 % per year, about 4 of them would be relapsing during the succeeding year. However, at the annual incidence rate of 0.13 per cent of population 5 years and above about 66 first timers (new cases) would be added to the existing pool of bacillary cases in a year's

time. Thus, as an input adding to the pool of bacillary cases in the community, the ratio of relapse cases to cases arising afresh from the general population in a year would roughly be in the order of 1:16 (4:66).

There were half as many deaths (42.7 per 1000 P.Y.) as there were relapses from among the naturally cured cases during the 3½ years of follow up: not all the deaths could ever be attributed to tuberculosis. If we consider that all those dead had died of tuberculosis this could be considered an unfavourable fate of the cured cases, over and above the unfavourable relapse: a total of 30 cases out of the 99 followed upto 3½ years (128.1 per 1000 P.Y.) had such a fate. Conceding that death in the immediate 4-5 years of follow up among the chemotherapeutically obtained cures would be few, it would appear that in this respect the phenomenon of natural cure suffers in comparison. This, however, may not adversely influence the epidemiological situation since death constitutes an outflow from the pool of infectors. The death rate among the naturally cured cases is, however, considerably less than the rate of 134 per 1000 per year over a period of 3 years among the cohort of the total 126 cases of the first survey in the same study.² Thus, it could be said that, on the whole the naturally cured status could be considered as an epidemiologically favourable situation, though much less so when compared to the chemotherapeutically achieved cure.

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LIVER FUNCTIONS DURING PYRAZINAMIDE THERAPY

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Hepato-toxicity to pyrazinamide therapy has been well-documented (Yeager & others 1954; McDermott and others 1954; Muschenheim and other 1955; Potter and Chang 1955; Allison 1956; Philips and Horton 1956; Desautels 1957; Morrissey and Rubin 1959; Mathews 1960; British Tuberculosis Association 1963; Kass 1965; East African and B.M.R.C. Trial 1971; Horsfall 1972). The serum levels of glutamate oxalacetate transaminase (SGOT) and glutamate pyruvate transaminase (SGPT) have been studied in patients receiving pyrazinamide to detect preclinical hepatic damage (Worblewski and La Due 1956; Allison 1959; Morrissey and Rubin 1959; Mathews 1960; Aquinas 1964; Kass 1965; Horsfall 1972). Almost all the workers have recorded a rise in the levels of these enzymes during pyrazinamide therapy. However, the criteria for the critical levels of these enzymes, at which the drug should be withdrawn, have been variously put forward (Morrissey and Rubin 1959; Somner and Brace 1962; British TB Association 1963; Menon 1968; Ramakrishnan and others 1968; Kent and Macfadyen 1969). Hepatotoxicity to pyrazinamide therapy as indicated by raised serum alkaline phosphatase has been encountered by Aquinas (1963) and British TB Association (1963).

The present study was conducted to find out if there was an association between the serum levels of pyrazinamide and the levels of these enzymes and whether on the basis of serum levels of these enzymes it would be possible to predict incipient hepato-toxicity.

Material and Methods

69 proved cases of pulmonary tuberculosis admitted to Kasturba TB Hospital, Lucknow, were studied for 6 months. These patients were divided randomly in 2 groups.

Group A :

38 patients; oral pyrazinamide 30 mgm/kg of body weight per day in a single dose -f streptomycin 1 Gm i.m. once a day for 3 months and INH 300 mgms/day by mouth (Daily regimen group).

Group B :

31 patients; oral pyrazinamide 60 mgm/kg of body weight in a single dose, streptomycin 1 Gm i.m, and INH 650 mg orally administered twice a week (biweekly regimen group).

On the initiation of the treatment and every month thereafter SGOT, SGPT/serum alkaline phosphatase and serum pyrazinamide concentration were estimated. The clinical examination of every patient was done regularly to observe the clinical toxicity of pyrazinamide.

Techniques Employed :

1. SGOT and SGPT levels were determined by Reitmans and Frankel method (1957).
2. Serum alkaline phosphatase was determined by King and Wotton's method (1964).
3. Serum pyrazinamide concentration was determined by Ellard's method (1969).

Observations :

The findings are set forth in the tables that follow.

TABLE I
Age and Sex distribution of cases

| Daily Regimen | | | | | | | | Biweekly Regimen | | | | | | | |
|---------------|-------|-------|-------|------------|-------|-------|-------|------------------|-------|-------|-------|------------|-------|-------|-------|
| Years | | Years | | Years | | Year | | Years | | Years | | Years | | Years | |
| 10—20 | 21—30 | 31—40 | 41—50 | 10—20 | 21—30 | 31—40 | 41—50 | 10—20 | 21—30 | 31—40 | 41—50 | 10—20 | 21—30 | 31—40 | 41—50 |
| M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| 2 | 1 | 6 | 5 | 13 | 6 | 3 | 2 | 3 | 1 | 6 | 2 | 9 | 7 | 2 | 1 |
| Males 24 | | | | Females 14 | | | | Males 20 | | | | Females 11 | | | |

TABLE II
Incidence of clinical toxicity during pyrazinamide therapy

| Clinical Toxicity | Daily Regimen (38) | | Biweekly Regimen (31) | |
|-------------------|--------------------|-----|-----------------------|-----|
| | No. | % | No. | % |
| Nausea, Vomiting | 1 | 2.8 | nil | nil |
| Clinical Jaundice | 1 | 2.8 | nil | nil |

TABLE II
Monthly changes in serum concentration of pyrazinamide (Daily Regimen)

| Serum pyrazinamide concentration | MONTHS | | | | | |
|--------------------------------------------------|--------|-------|-------|-------|-------|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Mean serum concentration of pyrazinamide (ug/ml) | 52 | 58 | 62 | 57 | 59 | 60 |
| Range of serum concentration | 46—58 | 52—65 | 52—72 | 51—64 | 52—64 | 54—66 |

TABLE IV

Monthly changes in serum concentration of pyrazinamide (Biweekly Regimen)

| Serum pyrazinamide concentration | MONTHS | | | | | |
|--------------------------------------------------|--------|-------|-------|-------|-------|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Mean serum concentration of pyrazinamide (ug/ml) | 80 | 83 | 87 | 90 | 87 | 87 |
| Range of serum concentration | 78—82 | 79—88 | 80—94 | 81—99 | 81—93 | 84—89 |

TABLE V
Monthly changes in serum enzyme levels (Daily Regimen)

| SI. No | Serum Enzyme levels No. | 1 | 3 | 4 | 5 | 6 | 7 |
|--------|-------------------------------------------|------|-------|-------|-------|-------|-------|
| | Range of SOOT | 8—12 | 10—22 | 11—39 | 12—24 | 13—25 | 14—24 |
| 3. | Mean SGPT (IU) | 9 | 13 | 20 | 18 | 18 | 18 |
| 4. | Range of SOFT | 5—13 | 7—19 | 13—27 | 12—24 | 12—24 | 13—23 |
| 5. | Mean serum alkaline phosphatase (KA Unit) | 7 | 8 | 17 | 13 | 12 | 12 |
| 6. | Range of serum alkaline phosphatase | 5—9 | 6—10 | 10—24 | 10—16 | 8—16 | 9—15 |

TABLE VI

Monthly changes in serum enzyme levels (Biweekly Regimen)

| Sl No | Serum Enzyme Levels | MONTHS | | | | | |
|-------|-------------------------------------------|--------|------|-------|-------|-------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 7 |
| 1. | Mean SGOT (IU) | 13 | 15 | 17 | 19 | 17 | 13 |
| 2. | Range of SGOT | 8—18 | 8—22 | 10—28 | 10—28 | 10—24 | 12—24 |
| 3. | Mean SGPT (IU) | 8 | 10 | 13 | 17 | 13 | 13 |
| 4. | Range of SGPT | 7—15 | 7—22 | 11—24 | 10—24 | 10—22 | 12—16 |
| 5. | Mean serum alkaline phosphatase (KA Unit) | 5 | 9 | 14 | 15 | 14 | 13 |
| 6. | Range of alkaline phosphatase | 4—6 | 7—11 | 9—19 | 9—21 | 8—20 | 12—14 |

TABLE VII

Incidence of abnormal serum enzyme level

| Serum Enzymes | Normal Values. | Daily Regimen Group (38 cases) | Biweekly Regimen Group (31 cases) |
|-------------------------------|----------------|--------------------------------|-----------------------------------|
| 1. SGOT | 4—17IU | 7(18.5%) | 3(9.7%) |
| 2. SGPT | 3—15IU | 4(10.5%) | 2(6.4%) |
| 3. Serum alkaline Phosphatase | 3—13 KA Unit | 2(5.2%) | 1(3.2%) |

Discussion

In the present study, mean peak serum pyrazinamide level, in daily regimen in the 1st month was 52 ug/ml, which gradually reached its maximum in the 3rd month i.e., 62 ug/ml (Table 111). In the biweekly regimen group the mean peak serum concentration in the first month was 80 ug/ml which attained its maximum of 90 ug/ml in the fourth month of treatment (Table IV).

Likewise gradual rise in the level of SGOT and SGPT was also noted simultaneously in both the groups. The SGOT level reached its maximum average value in the 3rd month in patients on daily regimen i.e. 25 IU (Table V). In the biweekly regimen group, the highest average value of SGOT was noted in the 4th month i.e. 19 IU (Table VI). The overall incidence of raised

SGOT was greater (18.5 per cent) in the daily regimen group than in the biweekly regimen group (9.7 per cent). The same was found to be true with SGPT values. The incidence of raised SGPT was found to be greater (10.5 per cent) in the daily regimen group compared to the biweekly regimen group (6.4 per cent) (Table VII). The rise in the level of these enzymes paralleled the rise in the level of serum pyrazinamide.

Despite the raised values of these enzymes, clinical jaundice was apparent in only one case in daily regimen group (Table II) in the 3rd month of treatment (Serum enzyme values at the time of appearance of clinical jaundice: SGOT 30 IU SGPT 24, IU serum alkaline phosphatase 17 KA Unit). The jaundice was not seen in any of the patients in the other group. Similar incidence of jaundice during pyrazinamide therapy has been

reported by many other workers. (Yeager *et al.*, 1952, 4.6 per cent; Phillips *et al.*, 1954, 3.4 per cent; Schwartz *et al.*, 1954, 1.8 per cent; Muschenheim *et al.*, 1955, 3.2 per cent; Allison 1956, 1.4 per cent; U.S. Public Health Report, 1959, 2.3 per cent; Matthews 1960, 2.3 per cent; Kass 1965, 4.1 per cent; East African and B.M.R.C. trial 1971, 3 per cent; and Horsfall 1972, 2.8 per cent). In fact some of the workers have not encountered even a single case of clinical jaundice in their series (Krasner 1957; Salkin 1957; Velu *et al.* 1961; Somner *et al.* 1962; Aquinas 1963; Research Committee of British TB Association 1963; Menon 1968 and Ramakrishnan *et al.* 1968).

This raises an important question: what level of rise in the values of SCOT and SGPT should be considered significant as to necessitate the cessation of pyrazinamide therapy? Unfortunately we have not been able to find an answer from our study. The highest level of SGOT recorded in our cases was 39 IU in the daily regimen group and 28 IU in biweekly regimen group (Table V and VI). Likewise the highest levels of SGPT were 27 IU and 24 IU respectively. Despite these high levels none of these patients developed clinical jaundice. In fact despite continuation of pyrazinamide therapy, the serum levels of these enzymes declined somewhat in the subsequent months. Our observations would, therefore, reveal that it may be safe to continue the administration of pyrazinamide despite the SGOT level of 29 IU and SGPT levels of 27 IU. These observations are in accordance with those recorded by Somner and Brace (1962) and Kass (1965). It may be pertinent to point out that Morrissey and Rubin (1959) observed that when "significant" enzyme elevation occurs (usually above 40 units), the drug should be discontinued.

The situation with regard to serum alkaline phosphatase levels was equally confusing. In this hospital we keep 12KA units as upper limit of normal. However, the average levels recorded by our patients in the 3rd and the 4th month were 17 KA Unit and 13 KA unit respectively in the daily regimen group (Table V), and 14 KA Unit and 15 KA unit respectively in the biweekly regimen group (Table VI). In the latter group the average values for the 5th and 6th months continued to be above the normal limits i.e. 14 KA unit and 13 KA unit. None of our patients, who had attained highest serum levels of serum alkaline phosphatase, suffered from clinical jaundice despite continuation of pyrazinamide therapy. In fact, as with the transaminase studies, the level of this enzyme also declined during the subsequent months despite administration of the drug. It might, therefore,

be justifiably concluded that even as high a level of serum alkaline phosphatase as 24 KA Unit should not necessitate the withdrawal of pyrazinamide if overt evidence of clinical jaundice does not manifest. These observations are in accordance with those recorded by Aquinas (1963) and British TB Association (1963).

Summary and Conclusion

69 proved cases of pulmonary tuberculosis were studied for 6 months. They were getting pyrazinamide 30 mg/kg of body weight in the daily and biweekly regimen groups, respectively. On initiation of the therapy and after every one month serum pyrazinamide concentrations, SGPT, SGOT and serum alkaline phosphatase of all the patients of both groups were estimated.

It was concluded that rise in the levels of SGPT, SGOT and serum alkaline phosphatase, during therapeutic administration of pyrazinamide did not imply impending hepatic damage (during an observation period of 6 months). The rise in the level of these enzymes paralleled the rise in the level of serum pyrazinamide.

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SERUM LEVELS OF PYRAZINAMIDE AND PYRAZINOIC ACID FOLLOWING LONG TERM ADMINISTRATION OF PYRAZINAMIDE ORALLY

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Serum concentrations of pyrazinamide following a therapeutic dose of the drug have been studied for a period of 24 hours by various workers (Cassia 1957; Simane *et al.*, 1964; Subbamal *et al.*, 1969). However serial serum levels of pyrazinamide and pyrazinoic acid following the administration of the drug for a period of 24 to 48 hours have been recorded only by Ellard (1969).

Pyrazinamide is a known "second line" anti-tuberculosis drug. In the management of drug resistant cases this drug needs to be administered in combination with other anti-tuberculosis drugs for a period of at least 2 years. A review of the literature revealed that the serial serum levels of this drug during a span of a few weeks or a few months of its administration have not been studied so far.

This study was undertaken to record the serum levels of pyrazinamide during a span of 6 months of its administration.

Material and Methods

To determine the serum pyrazinamide concentrations in normal subjects, 18 volunteers were selected from the residents working in G.M. & Associated Hospitals, Lucknow. These volunteers received drug in following dosage:-

The Control Group :

For Measurement of serum pyrazinamide levels:

Group A —6 subjects : oral pyrazinamide 30 mgm/kg of body weight in a single dose.

Group B —6 subjects : oral pyrazinamide 60 mgm/kg of body weight in a single dose.

For measurement of serum pyrazinamide & serum pyrazinoic acid levels :

Group C —6 subjects (derived from group A & B) (i) 3 subjects received the same

dose of pyrazinamide as in group A. (ii) 3 subjects received the same dose of pyrazinamide as in group B.

The Study Group

87 proved cases of pulmonary tuberculosis admitted to Kasturba T.B. Hospital Lucknow, were studied for 6 months. These patients were divided randomly in the following groups,

For measurement of serial serum pyrazinamide levels for 6 months :

Group A —38 patients: oral pyrazinamide 30 mgms/kg body weight per day in a single dose + streptomycin 1 Gm i.m. once a day for 3 months and INH 300 mgms/day by mouth (daily regimen group).

Group B —31 patients : oral pyrazinamide 60 mgms/kg of body weight in a single dose, streptomycin 1 Gm i.m. and INH 650 mgms orally administered twice a week (biweekly regimen group).

For measurement of serum pyrazinamide & pyrazinoic acid levels :

Group C —10 patients : drugs in the same dosage as in group "A" administered only once.

Group D —8 patients : drugs in the same dosage as in group "B" administered only once.

Technique Employed :

Serum pyrazinamide concentrations and serum pyrazinoic acid levels were determined by Ellard's method (1969).

Results

I findings in normal subjects are shown in Tables I-III and among patients in Tables IV-VI.

TABLE I
Serum concentrations of pyrazinamide, levels in group A (30 mg/kg of body weight) of normal subjects in

| Sl. No. | 1st HR. | 2nd HR. | 3rd HR. | 4th HR. | 5th HR. | 24th HR. | 25th HR. | 26th HR. | 27th HR. |
|---------|---------|---------|---------|---------|---------|----------|----------|----------|----------|
| 1. | 30 | 66 | 48 | 39 | 28 | 4 | 36 | 60 | 47 |
| 2. | 34 | 54 | 49 | 38 | 26 | 5 | 38 | 56 | 46 |
| 3. | 38 | 52 | 45 | 35 | 25 | 4 | 39 | 54 | 46 |
| 4. | 33 | 50 | 42 | 31 | 22 | 4.6 | 37 | 54 | 42 |
| 5. | 35 | 51 | 44 | 35 | 24 | 3.9 | 38 | 55 | 43 |
| 6. | 32 | 49 | 42 | 33 | 23 | 5 | 36 | 53 | 41 |

TABLE II
Serum concentration of pyrazinamide, levels in Group B (60 mg/kg- of body weight) of normal subjects in $\mu\text{g/ml}$.

| Sl. No. | 1st HR. | 2nd HR. | 3rd HR. | 4th HR. | 6th HR. | 24th HR. | 25th HR. | 26th HR. | 27th HR. |
|---------|---------|---------|---------|---------|---------|----------|----------|----------|----------|
| 1. | 52 | 85 | 72 | 58 | 44 | 7.5 | 58 | 85 | 70 |
| 2. | 58 | 89 | 76 | 60 | 44 | 8.5 | 61 | 90 | 74 |
| 3. | 56 | 88 | 74 | 57 | 40 | 8 | 58 | 90 | 72 |
| 4. | 59 | 92 | 77 | 62 | 45 | 9 | 60 | 92 | 75 |
| 5. | 54 | 86 | 73 | 55 | 43 | 7 | 56 | 88 | 69 |
| 6. | 61 | 94 | 78 | 64 | 46 | 9.2 | 63 | 93 | 72 |

TABLE III
Serum concentration of pyrazinamide and pyrazinoic acid, in Group C of normal subjects, in

| Sl. P | 2nd Hour | | 3rd Hour No. | | 4th Hour P | | 5th Hour | | 6th Hour | | 24th Hour | |
|----------------------|----------|-----|--------------|-----|------------|--------------------|----------|-----|----------|-----|-----------|-----|
| | PA | P | PA | | PA | | P | PA | P | PA | P | PA |
| 30 mg/kg body weight | | | | | | | | | | | | |
| 1. | 53 | .8 | 42 | 1.4 | 34 | 1.7 | 28 | 3.0 | 25 | 5 | 4.2 | 1.2 |
| 2. | 52 | .8 | 41 | 1.3 | 35 | 1.8 | 30 | 3.0 | 25 | 5 | 3.8 | 1.0 |
| 3. | 56 | .9 | 44 | 1.3 | 32 | 1.6 | 28 | 3.1 | 28 | 5.6 | 4.0 | 1.2 |
| 60 mg/kg body weight | | | | | | | | | | | | |
| 1. | 85 | 1.3 | 72 | 2.3 | 60 | 4.3 | 59 | 6.3 | 44 | 9.5 | 8 | 2.2 |
| 2. | 91 | 1.4 | 75 | 2.6 | 60 | 4.4 | 54 | 6.2 | 45 | 9.9 | 8.6 | 2.5 |
| 3. | 85 | 1.2 | 74 | 2.3 | 59 | 4.2 | 56 | 6.2 | 41 | 9.2 | 7.9 | 2.0 |
| P—Pyrazinamide | | | | | | PA—Pyrazinoic Acid | | | | | | |

TABLE IV

Number of cases (Groups A&B of the patients) followed for 6 months

| Daily Regimen Group | | Biweekly Regimen Group | |
|---------------------|---------|------------------------|---------|
| Males | Females | Males | Females |
| 24 | 14 | 20 | 11 |
| Total 38 | | Total 31 | |

TABLE V

Serum levels of pyrazinamide following administration of the drug for a period of 6 months

| | Months (Daily Regimen Group) | | | | | |
|----------------------------------------------------------------|---------------------------------|-------|-------|-------|-------|-------|
| | 1st | 2nd | 3rd | 4th | 5th | 6th |
| 1. Mean serum concentration of pyrazinamide $\mu\text{g/ml}$. | 52 | 58 | 60 | 57 | 59 | 60 |
| 2. Range of serum concentration | 46—88 | 52—65 | 52—72 | 51—64 | 52—64 | 54—66 |
| | Months (Biweekly Regimen Group) | | | | | |
| | 1st | 2nd | 3rd | 4th | 5th | 6th |
| 1. Mean serum concentration of pyrazinamide $\mu\text{g/ml}$. | 80 | 83 | 87 | 90 | 87 | 87 |
| 2. Range of serum concentration | 78—82 | 79—88 | 80—94 | 81—99 | 81—93 | 84—89 |

TABLE VI

Serum pyrazinamide level in relation to body weight

| Age in years | Daily regimen $\mu\text{g/ml}$ | Biweekly regimen $\mu\text{g/ml}$. |
|--------------|--------------------------------|-------------------------------------|
| 10—20 | 46—50 | 78—82 |
| 21—30 | 52—57 | 80—88 |
| 31—40 | 58—70 | 81—92 |
| 41—50 | 58—72 | 82—99 |

TABLE VII
Serum pyrazinamide level in relation to body weight

| Body weight in Kgs. | Daily regimen group $\mu\text{g/ml}$. | Biweekly regimen group $\mu\text{g/ml}$. |
|---------------------|----------------------------------------|-------------------------------------------|
| 44—46 | 54—72 | 78—82 |
| 47—49 | 52—66 | 80—88 |
| 50—52 | 50—59 | 81—92 |
| 53—55 | 46 | 82—99 |

TABLE VIII

Showing serum pyrazinamide and pyrazinoic acid concentrations —at different hours in patients (C&D Groups') in $\mu\text{g}\%$

| SI. No. | 2 Hours | | 3 Hours | | 4 Hours P | | 5 Hours | | 6 Hours | | 24 Hours | |
|------------------|---------|-----|---------|------|-----------|-----|---------|-----|---------|-----|----------|-----|
| | P | PZA | P | PZA | PZA | P | PZA | P | PZA | P | PZA | |
| Daily Regimen 38 | | | | | | | | | | | | |
| 1. | 53 | .8 | 42 | 1 .4 | 1 .9 | 34 | | 3.2 | 28 | 5.4 | 4.8 | 1.6 |
| 2. | 56 | .9 | 40 | 1 .3 | 32 | 1.6 | 28 | 3.1 | 24 | 5.2 | 4.0 | 1.2 |
| 3. | 58 | .9 | 42 | 1 .5 | 30 | 1.5 | 27 | 3.0 | 22 | 5.0 | 3.9 | 1.1 |
| 4. | 56 | .9 | 50 | 1 .8 | 34 | 1.6 | 30 | 3.2 | 25 | 5.6 | 4.7 | 1.6 |
| 5. | 57 | .8 | 42 | 1 .3 | 33 | 1.6 | 28 | 3.1 | 23 | 5.0 | 4.0 | 1.2 |
| 6. | 53 | .9 | 41 | 1 .2 | 31 | 1.5 | 27 | 3.0 | 22 | 5.6 | 3.8 | 1.1 |
| 7. | 58 | .9 | 42 | 1 .3 | 32 | 1.7 | 26 | 3.0 | 22 | 5.7 | 3.8 | 1.3 |
| 8. | 59 | .9 | 42 | 1 .4 | 34 | 1.8 | 30 | 3.0 | 22 | 5.3 | 4.2 | 1.4 |
| 9. | 52 | .8 | 44 | 1 .3 | 31 | 1.6 | 27 | 3.0 | 24 | 5.4 | 3.9 | 1.3 |
| 10. | 56 | .9 | 42 | 1 .4 | 36 | 1.8 | 28 | 3.1 | 24 | 5.5 | 3.8 | 1.2 |
| Biweekly Regimen | | | | | | | | | | | | |
| 1. | 89 | 1.4 | 73 | 2 .3 | 64 | 4.6 | 55 | 6.2 | 46 | 9.9 | 9.0 | 3.0 |
| 2. | 87 | 1.3 | 72 | 2 .6 | 62 | 4.3 | 54 | 6.1 | 41 | 9.5 | 8.1 | 2.9 |
| 3. | 86 | 1.3 | 72 | 2 .3 | 66 | 4.7 | 59 | 6.3 | 47 | 9.6 | 9.0 | 2.9 |
| 4. | 84 | 1.3 | 73 | 2 .8 | 62 | 4.2 | 54 | 6.2 | 40 | 9.4 | 8.9 | 3.1 |
| 5. | 88 | 1.4 | 73 | 2 .7 | 65 | 4.5 | 58 | 6.1 | 43 | 9.5 | 8.9 | 3.0 |
| 6. | 83 | 1.3 | 72 | 2 .8 | 63 | 4.3 | 56 | 6.2 | 41 | 9.6 | 8.2 | 2.8 |
| 7. | 88 | 1.4 | 74 | 2 .9 | 64 | 4.6 | 53 | 6.0 | 40 | 9.7 | 8.0 | 2.9 |
| 8. | 84 | 1.3 | 75 | 2 .7 | 65 | 4.4 | 53 | 5.9 | 41 | 9.2 | 7.9 | 2.6 |
| 9. | 88 | 1.4 | 76 | 2 .9 | 64 | 4.5 | 52 | 6.1 | 40 | 9.5 | 8.0 | 2.8 |

P — PYRAZINAMIDE.

PZA — PYRAZINOIC ACID.

TABLE IX

Ratios of serum pyrazinamide/pyrazinoic acid at different hours

| Sl. No. | 2 Hours | 3 Hours | 4 Hours | 5 Hours | 6 Hours | 24 Hours. |
|------------------|---------|---------|---------|---------|---------|-----------|
| DAILY REGIMEN | | | | | | |
| 1. | 1/66 | 1/30 | 1/20 | 1/10 | 1/5 | 1/3 |
| 2. | 1/65 | 1/30 | 1/20 | 1/9 | 1/4 | 1/3 |
| 3. | 1/66 | 1/29 | 1/20 | 1/9 | 1/4 | 1/3 |
| 4. | 1/66 | 1/30 | 1/21 | 1/9 | 1/4 | 1/3 |
| 5. | 1/64 | 1/28 | 1/20 | 1/9 | 1/4 | 1/3 |
| 6. | 1/65 | 1/30 | 1/20 | 1/9 | 1/10 | 1/3 |
| 7. | 1/66 | 1/30 | 1/19 | 1/9 | 1/4 | 1/3 |
| 8. | 1/66 | 1/30 | 1/19 | 1/9 | 1/4 | 1/3 |
| 9. | 1/66 | 1/30 | 1/19 | 1/9 | 1/5 | 1/3 |
| 10. | 1/65 | 1/30 | 1/20 | 1/9 | 1/4 | 1/3 |
| BIWEEKLY REGIMEN | | | | | | |
| 1. | 1/64 | 1/31 | 1/14 | 1/9 | 1/4 | 1/3 |
| 2. | 1/66 | 1/29 | 1/14 | 1/9 | 1/4 | 1/3 |
| 3. | 1/66 | 1/30 | 1/14 | 1/9 | 1/4 | 1/3 |
| 4. | 1/65 | 1/29 | 1/15 | 1/9 | 1/4 | 1/3 |
| 5. | 1/64 | 1/30 | 1/14 | 1/9 | 1/4 | 1/3 |
| 6. | 1/64 | 1/29 | 1/15 | 1/9 | 1/4 | 1/3 |
| 7. | 1/64 | 1/29 | 1/15 | 1/9 | 1/4 | 1/3 |
| 8. | 1/65 | 1/31 | 1/14 | 1/9 | 1/4 | 1/3 |
| 9. | 1/64 | 1/30 | 1/14 | 1/8 | 1/4 | 1/3 |

Discussion

In the present study, the peak serum pyrazinamide concentrations were detected at 2nd hour after oral administration of the drug. The same has been observed by Cassia (1957); Simane *et al* (1964) and Ellard (1969).

Serum pyrazinamide concentrations were

proportional to the size of the dose. Thus the concentration of serum pyrazinamide after the administration of 60 mg/kg of body weight was nearly double of that noted after the administration of 30 mg/kg of body weight of pyrazinamide. These findings were in accordance with those obtained by Ellard (1969) and Subbammal *et al* (1969). When the same dose of pyrazinamide was repeated after 24 hours of the

first dose, pattern of rise in the serum drug level was similar to that recorded after the initial dose. This time however serum drug levels at 1st, 2nd and 3rd hour were somewhat higher (vide tables 1 and 2). This could be due to the cumulative effect of the residual drug level in the serum (after the initial dose) added to that obtained after the second dose of pyrazinamide. Subsequently the drug levels declined in the same pattern as that noted after the initial dose (Ellard 1969).

Serial serum pyrazinamide concentrations were estimated among patients during a span of 6 months of its administration at monthly intervals. Mean peak serum pyrazinamide concentration, in the daily regimen, in the first month, was 52 μ g/ml which gradually reached its maximum in the 3rd month i.e. 62 μ g/ml (Table III). In the biweekly regimen group the mean peak serum concentration in the first month was 80 μ g/ml which reached its maximum of 90 μ g/ml in the 4th month of the treatment.

The gradual rise in the serum concentrations in the daily regimen group reaching maximum in the 3rd month could be due to the fact that total quantum of the drug administered every month in the daily regimen group was higher (42.5 G/month) than the biweekly regimen group (24 G/month). The drug appeared to accumulate in the serum (vide supra).

Higher serum pyrazinamide concentration were observed in adults and older age group of patients (between 30-50 years) than the adolescent and younger patients (Table 6). It might be due to the reduced capacity of drug metabolism and excretion in the higher age group (Goodman and Gillman 1966).

Body weight was also found to be related to serum pyrazinamide concentrations. There was an inverse relationship between the serum drug level and the body weight (Table 7).

Serum pyrazinoic acid, a metabolite of pyrazinamide was estimated in 6 volunteers and in 19 cases of pulmonary tuberculosis (Tables 3 and 8). The peak serum pyrazinoic acid concentrations were noted at the 6th hour after the administration of the drug (Ellard 1969). This indicates that pyrazinamide takes time to get metabolised into pyrazinoic acid (Allen *et al.*, 1953).

Not unlike the relationship between the oral dose of pyrazinamide ingested and the serum pyrazinamide concentration, the serum pyrazinoic acid levels also showed similar proportionate attainment of serum concentrations. Compared to 30 mg/kg body weight, 60 mg/kg body weight

pyrazinamide administration produced almost double serum concentration of pyrazinoic acid.

The ratios between serum pyrazinoic acid and pyrazinamide at their respective peak hours were constant both in the volunteers and the patients (Table 9) at 2nd, 3rd, 5th, 6th and at 24 hours. However, at the 4th hour, the pyrazinamide/pyrazinoic acid ratios in the daily and the biweekly regimen were 1/19.8 and 1/14.3 respectively. On the basis of fourth hour ratio we suspected that there might be two groups of patients i.e. slow and rapid inactivators of pyrazinamide. However, subsequent studies conducted in this department have failed to confirm this observation (Gupta *et al.*, unpublished data).

Summary & Conclusion

18 volunteers and 87 proved cases of pulmonary tuberculosis were studied. The patients were getting pyrazinamide 30 mg/kg of body weight and 60 mg/kg of body weight in daily and biweekly regimen groups respectively.

Serum concentration of pyrazinamide following the above mentioned dose of the drug have been studied for a period of 24 hours among volunteers. Serial serum drug concentrations were studied on initiation of treatment and at monthly interval in patients for 6 months.

Serum pyrazinoic acid concentrations were simultaneously estimated in 6 volunteers and 18 patients.

The following conclusion have been drawn:

1. The peak serum pyrazinamide concentration was noted in 2nd hour in both regimen groups. Serum drug levels of pyrazinamide were proportional to the dose size.
2. A measurable quantity of drug was noted even after 24 hours. The drug tends to get accumulated in the serum.
3. The mean peak serum pyrazinamide concentration was noted in the 3rd month in the daily regimen group. On the other hand in the biweekly regimen group it was noted in the 4th month.
4. The serum drug concentration showed an inverse relationship with the body weight of the patient. The serum pyrazinamide concentration was higher in the older age group of patients.
5. The peak serum pyrazinoic acid concentra-

tions both in volunteers and the patients were noted in 6th hour in both the regimen groups. The serum concentrations of pyrazinoic acid were proportional to the dose of pyrazinamide.

6. The ratios between serum pyrazinoic acid and pyrazinamide at their respective peak hours were constant both in the volunteers and the patients, except at the 4th hour.

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CASE REPORTS

MEDIASTINAL EMPHYSEMA AS A COMPLICATION OF ARTIFICIAL PNEUMOPERITONEUM

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Mediastinal emphysema or extravasation of air into the mediastinum as a complication of Artificial Pneumoperitoneum therapy is very rare. The first case was reported by Jehn and Nissen (1927). Breathnach (1955) reviewed the literature on this subject beginning from the first reported case and got only 46 cases including three of his own. A few more cases have been reported by others e.g. Bruel *et al*, 1955; Thompson Wells, 1956; Razden *et al*, 1972. We observed mediastinal emphysema as a complication of artificial pneumoperitoneum in only four cases among 9,562 air injections.

Clinical Features

The main complaints were pain in front of neck with swelling on either sides or over the suprasternal notch, dysphagia, dyspnoea and fever. The onset of symptoms varied from half-an-hour to four hours after the injection of air. The patients on examination seemed to be in moderate discomfort. There were palpable emphysema over the neck. Crunching sounds synchronous with systole were heard over the precordium (Hamman's Sign). The symptoms began to decrease after a few hours and practically disappeared within three days. There was no cyanosis in any case and none was extremely ill. None had pneumothorax. Mediastinal emphysema developed between second and tenth air injections. It occurred following refills and none developed it after primary induction.

It is astonishing to note that all the four cases reported below developed the complication in quick succession within a very short span of two months, like the cases of Razdan *et al* (1972).

Case Reports :

Case 1 : K.D., a man aged 40 years, medium built, was admitted on 29 June 1972. Before admission he had anti-tuberculosis drugs for four months. His chest film showed bilateral disease. Tubercle bacilli were found in his sputum. He was allergic to PAS and Streptomycin. He had first artificial pneumoperitoneum on 21 October 1972. On 4th January 1973 he had sixth air injection with 1000 ml of air; the final pressure recording was 4- 14 mm H₂O. During the later part of air injection he felt slight pain in front of the neck with fullness, pain on coughing, slight dysphagia and mild change of voice.

Palpable crepitus was present in front of the neck. On auscultation, Hamman's sign was noted very clearly. Skiagram of chest (Fig. 1) showed air column between the heart and the diaphragm. The right cardiophrenic angle and the right border of the heart shadow were demarcated by air. There was gross subcutaneous emphysema in the soft tissues of both sides of the neck. The lateral X-ray showed air behind the sternum. There was very little air under the diaphragm.

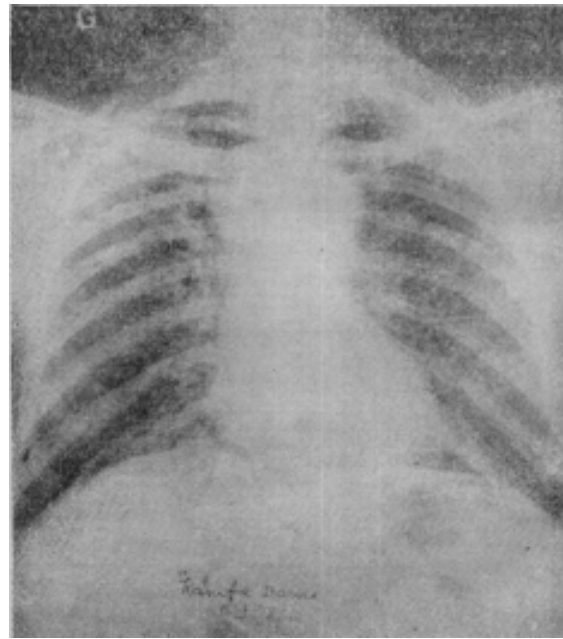


Fig. 1.

Case 2 : M.L.D., a man aged 27 years, thin built, was admitted on 20 September 1972. He was suffering from pulmonary tuberculosis since 1964 and had many short courses of treatment with anti-TB drugs. X-ray chest of September 1972 showed extensive bilateral opacities with many translucent areas. Tubercle bacilli were recovered from his sputum.

On 27 November 1972 he had first artificial pneumoperitoneum, with 500 ml of air. There was no special complaint. On December 4, 1972, he was given second air injection with 1000 ml. The pressure recording on that date after pneumoperitoneum was + 3 mm H₂O. Two hours after the air injection he got pain over right

side of the neck with swelling and crepitus on pressure. There was no subcutaneous emphysema around the needle prick. An X-ray chest taken on the next day showed moderate elevation of diaphragm by air underneath, air under the soft tissues of both sides of neck and left border of trachea was outlined by air (Fig. 2). The patient improved gradually without special treatment. After 48 hours he had no complaints and emphysema over the neck was not palpable.

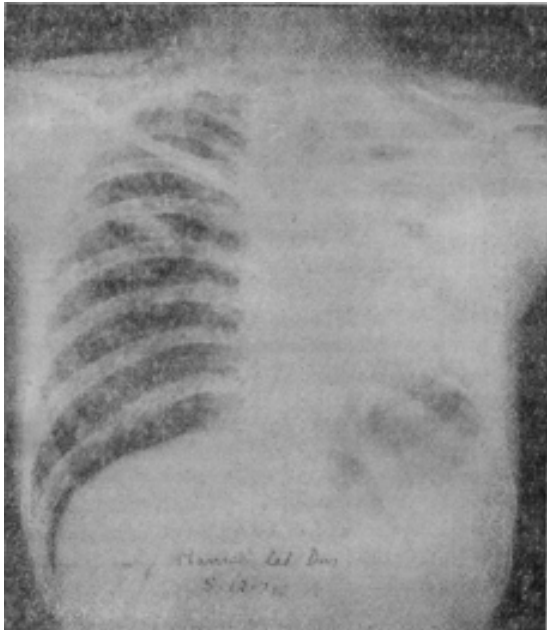


Fig. 2.

No complaints were noted after subsequent small refills.

Case 3 : R.P.M., a man of 35 years was admitted on 11 October 1972 with ten months' irregular treatment with anti-T.B. drugs. A chest film showed bilateral tuberculosis with cavities. Tubercle bacilli were found on direct examination of sputum.

On 24 October 1972 he had first artificial pneumoperitoneum with 500 ml followed by three refills of 1000 ml on each occasion without any complaints. Fourth refill was given on 1st December 1972 with 1000 ml of air, through left lumbar region. The final pressure recordings of the five air injections were +4, +8, +4, +6, +8 mm H₂O. After four hours of last air injection he felt pain over both sides of neck with mild dysphagia, dyspnoea and difficulty in speaking. There was palpable crepitus over both supraclavicular regions. The features persisted for

twelve hours, then slowly disappeared within two days. No radiograph was taken immediately. On 5 December 1972 one chest radiograph was taken which showed moderate amount of air under diaphragm. There was no air inside mediastinum nor in the soft tissues of the neck. Subsequent small refills did not give rise to any complaints.

Case 4 : B.M., a short man, moderate built, was admitted on 23rd August 1972 with a history of pulmonary tuberculosis of six years duration. On admission a chest radiograph showed extensive bilateral disease and tubercle bacilli were isolated from his sputum.

On 29th August 1972 he had first pneumoperitoneum with 500 ml of air (final pressure recording was +15 mm H₂O) without any complaint. On 2 December 1972 he had tenth artificial peritoneum through left lumbar region with 1000 ml of air with final pressure of + 8mm H₂O. Immediately after pneumoperitoneum he noted swelling of left flank of abdomen and left side of scrotum. After one hour he developed pain in front of neck and dysphagia. There was small palpable crepitus over the suprasternal notch and mild fever. No radiograph was taken. After three days, symptoms of mediastinal emphysema disappeared. The swelling of flank and scrotum took another few days to disappear.

Mechanism of Production

The route by which the air enters the mediastinum from the peritoneal cavity is not fully understood. Experimentally, a reverse route, i.e. from the mediastinum to the peritoneum, was demonstrated. Jehn and Nissen (1927) and Joannides and Tsoulos (1930) injected air under pressure into mediastinum in animals. The air descended along oesophagus downwards through the diaphragm into the abdomen; it collected retroperitoneally around the perirenal tissues forming bulla which ruptured into the peritoneal cavity causing pneumoperitoneum. Macklin (1939) likewise demonstrated the passage of air from mediastinum into the peritoneal cavity through retroperitoneal space. That ascent of air from peritoneum to the mediastinum along large structures may occur in the reverse order of the animal experiments, is postulated by Small and Fremont (1951), Hamman (1939), Stein (1951), Simmonds (1946) and Banyai and Jurgens (1939). Breathnach (1955) is of the opinion that the air escapes through the oesophageal opening an the diaphragm where the peritoneum is least protected and postulated that fibrous healing of the perforated area is possible which is evidenced by non-recurrence of mediastinal emphysema after subsequent pneumoperitoneum refills.

Types of mediastinal emphysema

Depending on the pressure of air inside the mediastinum, two varieties of mediastinal emphysema are described: benign and malignant (Banyai, 1954). In benign type the air is not under tension as a large amount of air escapes the mediastinum, producing subcutaneous emphysema over the neck. Few serious pictures are met with in this type and treatment is mostly symptomatic. In malignant type the air is under tension as large quantity of air is trapped inside the mediastinum following its escape from the peritoneum. The malignant type causes serious clinical features of mediastinal compression such as pain (simulating coronary thrombosis), dyspnoea, cyanosis, engorged veins with impairment of venous return to the heart. Blood vessels, particularly the veins, are more easily compressed than trachea or bronchi. The entrapped mediastinal air is drained by incising over the suprasternal notch. The removal of air from the peritoneum does not make much difference.

The present reports were of benign type in which the air escaped from the peritoneum to mediastinum and then to the soft tissues of the neck. The symptoms were not very serious and settled down without special treatment.

Summary

Four cases of mediastinal emphysema following artificial pneumoperitoneum are described and the mechanism of production is briefly reviewed. All of them were of benign type. No special treatment was needed for this complication.

ACKNOWLEDGEMENT

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SPONTANEOUS PNEUMOTHORAX DURING CORTICOSTEROID THERAPY

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In the recent past corticosteroids have secured a definite place in the management of tuberculosis. Spontaneous pneumothorax complicating pulmonary tuberculosis has been observed to occur more frequently in cases receiving corticosteroid therapy (Armstrong *et al.*, 1960; Segra *et al.*, 1962; Imri 1962; Goldman 1962; and Khanna 1969).

We are reporting five cases with this complication arising under therapy with corticosteroids under full cover of antituberculosis drugs.

Case No. 1 :

A.T.J., a student nurse, aged 18 years, female was admitted on 6.10.73 with complaints of cough with expectoration and fever for 15 days. She had not taken any antituberculosis treatment prior to admission.

Total leucocyte count was 12400 per cumm. with polymorphs 84 per cent, lymphocytes 14 per cent and eosinophils 2 per cent. E.S.R. was 65 mm for the first hour (Wintrobe). Sputum was positive for A.F.B. by direct smear method.

Skiagram chest (Fig. 1) showed homogenous opacity in right upper and part of middle zone with cavitation in the upper zone.

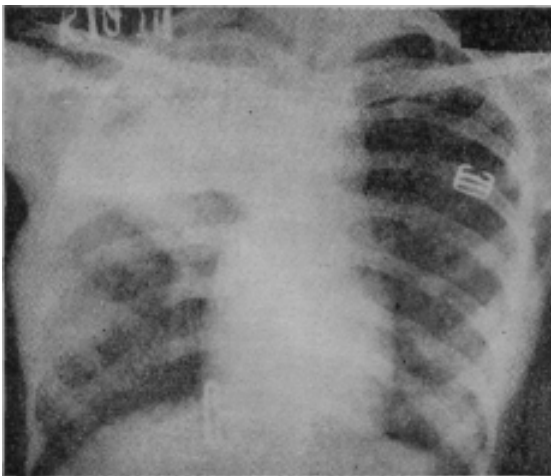


Fig. 1.

Skiagram chest P.A. View showing homogenous opacity in right upper and part of middle zone with cavitation in upper zone

She was given streptomycin, isoniazid and PAS & penicillin therapy in usual dosage along with prednisolone 30mgs. per day in divided dosage. During 3rd week of her treatment a right sided pneumothorax was suspected on routine examination and confirmed on radiograph (Fig. 2). Prednisolone at this stage was withdrawn in tapering dosage. Complete expansion of lung was achieved by closed aspiration alongwith the same antituberculosis drugs.

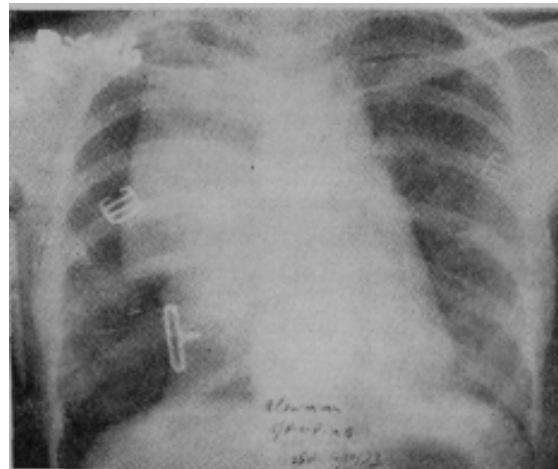


Fig. 2.

Skiagram chest P.A. View showing pneumothorax on right side

Case No. 2 :

J.P., aged 18 years, was admitted in July 1974 with cough, expectoration, high fever and headache for one month.

Examination revealed a young man of thin built with signs of meningeal irritation. Radiograph chest showed miliary disease in both lung fields.

The C.S.F. was clear, under raised tension and formed a cobweb on standing. Biochemical analysis revealed proteins 60 mgs per cent, sugar 35 mgs per cent and chloride 680 mgs per cent.

He was administered streptomycin, INH and ethionamide in usual dosage alongwith prednisolone 40 mgs. per day. After 2 weeks he

complained of acute pain on right side of the chest and became dyspnoic. Clinical and radiological examination revealed a right sided pneumothorax. Prednisolone was withdrawn in tapering dosage. Intercostal intubation alongwith antituberculosis drugs helped in re-expansion of lung.

Case No. 3 :

A., aged 42 years, male was admitted on 17.8.74 with the complaints of cough with expectoration, dyspnoea, and mild grade fever for one year. He was taking streptomycin, INH and PAS, alongwith prednisolone 20 mgs per day for three weeks prior to hospitalization.

Admission X-ray chest showed bilateral far advanced cavitary disease. Sputum was positive for A.F.B. E.S.R. was raised.

He was administered streptomycin, INH and PAS in full dosage. Prednisolone was withdrawn in tapering dosage. On 25.8.74 he complained of acute pain on left side of chest and became dyspnoic. Clinical and radiological examination revealed left sided pneumothorax. Intercostal intubation was done and slow suction instituted but inspite of all possible efforts patient expired on 28.8.74.

Case No. 4 :

O.P., aged 30 years, male was admitted with the complaints of cough with expectoration and fever for 2 months. He had not received any antituberculosis treatment.

Total leucocyte count was 11200 per cu mm with polymorphs 70 per cent, lymphocytes 28 per cent, and eosinophils 2 per cent. E.S.R. was 40 mm for the 1st hour (Wintrobe). Sputum was positive for A.F.B. by direct smear examination.

Skiagram chest (Fig. 3) showed heterogenous opacities with cavitation in right upper zone.

He was given three primary antituberculosis drugs in standard dosage alongwith prednisolone 20 mgs daily. During the 4th week of treatment he complained of chest pain on right side and became dyspnoic. Physical examination and skiagram chest (Fig. 4) revealed a hydropneumothorax on the right side.

Prednisolone was withdrawn and antitubercular drugs continued. Repeated closed aspiration helped the lung to re-expand.

Case No. 5 :

A.G., student of medicine, was diagnosed

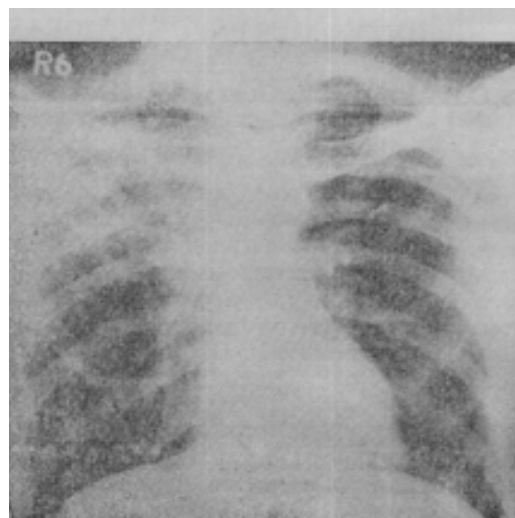


Fig. 3.

Skiagram chest P.A. View showing heterogenous opacities with cavitation in right upper zone

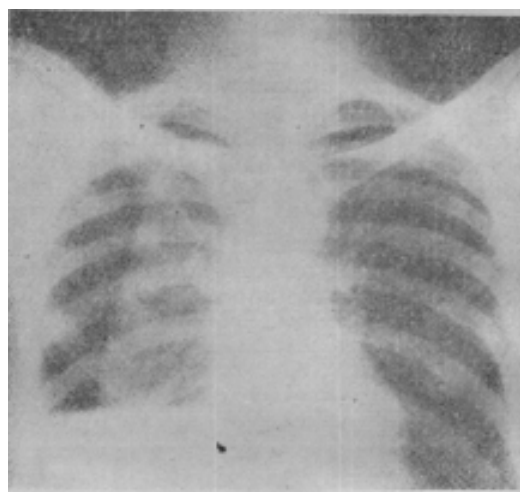


Fig. 4.

Skiagram chest P.A. View showing hydropneumothorax on right side

as a case of minimal pleural effusion on 3.7.74. He was given antituberculosis treatment (3 primary drugs). Toxemia was persistent so corticosteroids were added 30 mgm per day. After 2 weeks he developed a small pneumothorax which was aspirated and the lung expanded fully. Corticosteroids were withdrawn. The student is on antituberculosis treatment and is doing well.

Discussion

In these five cases who were getting corti-

steroids with antituberculosis drugs, spontaneous pneumothorax occurred in three and hydropneumothorax in 2 cases. In none of the cases previous history of pneumothorax was obtained. All were getting adequate antituberculosis treatment under supervision. Pneumothorax in all the cases appeared within 4 weeks of commencement of therapy.

Corticosteroids have a tendency to suppress the normal fibrotic reaction around the tuberculous lesion and thus interfere with the natural mechanism of healing of tubercular granuloma, thereby facilitating the perforation. Subpleural foci under these circumstances may end up in spontaneous pneumothorax (Goldman 1962).

Pneumothorax is most likely to occur during the initial period of treatment, when the steroids, exert their effect but the caseous lesion has not yet been inactivated by chemotherapy (Goldman 1962). In our cases pneumothorax has occurred within the 4th week of treatment.

Corticosteroid may mask the symptoms of pneumothorax (Imri 1962). In one of our cases patient had no complaints inspite of developing a pneumothorax which was detected on routine check up.

Hydropneumothorax occurring during corticosteroid therapy is still uncommon. Only 4 cases have been recorded so far (Brocard *et al*, 1956, McLean *et al*, 1960, Simmonds 1962, Khanna 1969).

In hydropneumothorax it appears that the effusion is likely to follow infection of pleural cavity by tubercle bacilli either due to rupture

of a tubercular cavity or a subpleural caseous focus teaming with bacilli (Khanna 1969).

In our opinion, corticosteroid should only be used in pulmonary tuberculosis where there are specific indications for its use like acute toxæmia due to tuberculosis and haematogenous tuberculosis and not merely to obtain a rapid clinical improvement.

Summary

Five cases of pulmonary tuberculosis are described, three developing spontaneous pneumothorax and the two hydropneumothorax due to corticosteroids supplemented to the antituberculosis drug therapy.

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TOXIC EPIDERMAL NECROLYSIS DUE TO ISONIAZID

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Toxic epidermal necrolysis is a rare occurrence characterised by sudden development of constitutional symptoms with vesiculobullous eruptions involving the face, hands, feet, with extensive peeling of the skin, ulceration of buccal mucosa, ocular lesions and genital involvement. Sometimes bronchopneumonia also develops. It is rare with antitubercular drugs and only few cases have been reported with PAS, Streptomycin and Thiacetazone, (Pagel 1964; Goodman & Oilman, 1964; Agnihotri & Rastogi, 1972; Handa *et al.*, 1974). Toxic epidermal necrolysis due to INH is, as far as known, not reported so far. In the present case the patient developed toxic epidermal necrolysis due to isoniazid.

Case Report :

R.D., a 27 years old female, was admitted in emergency on 8.7.74 with severe exfoliation of skin with marked itching, swelling of face and extremities, high grade fever, ulceration in the mouth, burning in micturition, mild jaundice and alopecia. Before hospitalization she was receiving injections of streptomycin, INH and PAS. Six days after starting the treatment, erythematous rashes developed all over the body with itching and all the drugs were withdrawn. After the rashes had subsided the same treatment was started again but she developed the same symptoms again.

On examination pulse was 156/mt., temperature 103° F. and blood pressure 126/82 mm. of Hg. Mild jaundice was present. Skin revealed vesiculobullus lesions all over the body with peeling of the skin at several places (Fig. 1). Skin colour as a whole had become red. Scale formation at places was seen. There was marked itching in the lesions. She was quite toxic looking. Mucosal ulcerations were seen at lips and in the buccal mucosa. There was also watery discharge from both ears and both ear drums were found inflamed. No ocular defect could be noticed. Chest examination revealed medium pitched bronchial breathing with crepitations in right supra and interscapular region. Other systems were found normal.

Investigations revealed raised ESR, low haemoglobin level and moderate polymorphonuclear leucocytosis. Sputum was positive for AFB. Serum bilirubin was 1.6 mg per cent and thymol turbidity 6 units. Plasma proteins and A.G. ratio were normal. Urine was sterile on



Fig. 1.

Showing toxic look of the patient with vesiculo-bullous lesions over limbs and face. Peeling of skin is seen and scab formation is visible at places.

culture for secondary organisms. Skiagrams chest showed a small cavity with exudative lesions in right upper and middle zones.

The patient was put on broad spectrum antibiotics and antihistamins, a sedative and systemic corticosteroids. Lotion zinc calamine was applied to the skin. All antitubercular treatment was withheld. When she had improved, and the lesions subsided a single dose of INH 25mg. was administered but she developed high grade fever, vesicular rashes all over body, redness and swelling of face and severe itching again. Antihistaminic drugs and corticosteroid were restarted. When the lesions subsided, unfortunately she took a tablet of INH 100 mgm. accidentally after a few days and was again ill with all the symptoms. She is now well and is on ethambutol, ethionamide and pyrazinamide,

because she did not seem to accept streptomycin very well.

Discussion

Toxic epidermal necrolysis was described by Lyell in 1956. It is rare with antitubercular drugs and only a few cases have been reported with PAS, streptomycin and thiacetazone (Sehgal *et al.*, 1973) but as far as known never with isoniazid. In the present case it occurred with isoniazid.

Lyell 1967, in his study of 128 cases of TEN divided them in three groups: drugs, idiopathic and infective. Females were more affected than males in all the groups. The drugs involved were sulphonamides, phenylbutazone and antibiotics in order of frequency. In idiopathic group no explanation could be given although some patients were suffering from viral disease e.g. small pox, herpes, measles; urinary tract infection; peritonitis; lymphoma; hodgkins disease and respiratory aspergillosis. It was also associated with certain poisoning like barbiturate, cocaine and alcohol. In the infective group usually staphylococcus aureus was cultured.

Many workers are of opinion that TEN is an infective process caused by staphylococcus aureus phase type 71 (Lyell, 1967; Tyson *et al.*, 1966; Samuels, 1967; Holzel & Jacobs, 1966) while Walker (1962) thought it to occur due to allergy. In Lyell's series of 128 cases, 35 were due to drug allergy. A case of allergy to streptomycin and thiacetazone was reported by Sehgal *et al.* (1973). They could not find any infective etiology.

In the present case TEN occurred with isoniazid and even a very small dose (10 mg.), produced the clinical features. Surprisingly she tolerated even PAS, thiacetazone and streptomycin, while so far workers have reported it to occur with these drugs. We think that it was only as a result of allergy to INH and no evidence of an infective etiology could be found. The development of mild jaundice and watery discharge from ears was also thought to be due to allergic process as they disappeared after withdrawal of INH.

Summary

A young tubercular female patient developing toxic epidermal necrolysis with severe constitutional symptoms, marked vesiculobullous,

eruptions all over body with peeling of skin, severe itching, otorrhoea, mild jaundice and alopecia occurring due to isoniazid is reported. It was thought to be as a manifestation of drug allergy to INH and no evidence of infective etiology could be found. The patient did not have such manifestations with any other antitubercular drug including PAS and streptomycin.

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LYELL SYNDROME DUE TO THIA CETAZONE

R.P. BHAGI, S.S. GHAI and V.P.S. NIRVAN

(From Municipal T.B. Clinics, Delhi)

Thiacetazone has been accepted as primary drug and is widely used in India. It is very well tolerated by the patients. It is reported that major toxic reactions occur in about 4 per cent of cases (Pamra., 1971). The main toxic reactions during thiacetazone therapy are exfoliative dermatitis and jaundice (Gothi *et al.*, 1966). Death has also been reported due to thiacetazone toxicity (Khanna *et al.*, 1973). Occasionally T.B. Drugs have been incriminated in causation of Lyell Syndrome and Stevens = Johnson Syndrome. Recently we encountered a case of pulmonary tuberculosis who on administration of Thiacetazone developed acute epidermal necrolysis — (Lyell's Syndrome). This is of rare occurrence after anti-tubercular drugs and hence it is being reported.

Case Report :

S.K. 25 years, female, Bank employee complained of low grade fever of 20 days' duration. Then she had frank haemoptysis, which motivated her to seek advice at T.B. Clinic, Moti Nagar. Patient was investigated. Skiagram chest showed infiltration right upper and middle zones. Sputum was positive for A.F.B. Patient was put on anti T.B. Drug i.e. S.M./I.N.H. for 11 months, after which the drug regimen was changed to THI/INH. The total daily dosage was 150 mgm of thiacetazone and 300 mgm of INH to be taken in a single dose at bedtime.

On 15th day of Thiacetazone/INH regimen patient noticed multiple blisters over the body, extremities neck and face. Eyes were red and angry-looking with watery discharge. A raw area involving the mucous membrane of the mouth developed and blood started oozing out from the ulcerated area. The lips and tongue were markedly swollen. The patient was unable to take any solids but could take fluids. Later, large areas of skin peeled off. Patient felt burning sensation all over the body, and had fever ranging upto 103°. Nikolsky's sign was positive.

The drugs were stopped and the patient was immediately treated with parental steroids and anti-allergic drugs. Local steroids (Efcorlin Pellets) for the mouth and high doses of B. complex were also given. Plenty of fluid was administered orally. Patient recovered fully in 1½ months' time. She was subsequently put on I.N.H./PAS and is progressing well.

Discussion

In 1956 Lyell described four cases of Bullous Epidermal Necrolytic Eruption. This is most frequently associated with long acting Sulpha, Pencilline, Pyrazalone derivatives and Hydantoin etc. Only few cases have been reported due to anti-microbials particularly thiacetazone (Sehgal *et al.*, 1973, Bedi *et al.*, 1974).

In the above reported case it is evident that soon after thiacetazone started, hypersensitivity reaction to the drug occurred. Only timely intervention and stoppage of drug was able to avert the fatal incident.

Since thiacetazone is being used extensively in the treatment of pulmonary tuberculosis in our country, it is desirable that this fatal side effect produced by the drug be kept in mind. A careful supervision after the start of treatment with thiacetazone is necessary.

ACKNOWLEDGEMENT

We are grateful to Col. S.L. Chadha, Municipal Health Officer, for kindly permitting us to report this case and to Mr. Sardana for typing the manuscript.

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23rd INTERNATIONAL TUBERCULOSIS CONFERENCE

S.P. PAMRA

The 23rd International Tuberculosis Conference was held in Mexico City from 22nd to 26th September, 1975. Over 3,000 participants including accompanying persons attended the conference. The following persons from India attended the conference:

Dr. R. Viswanathan
Dr. Nagappa Alva, M.P.
Dr. H.B. Dingley
Dr. S.P. Tripathy
Dr. Raj Narain
Dr. M.L. Mehrotra
Dr. S.P. Pamra

The conference this year was different from the previous ones to the extent that non-tuberculous chest diseases figured prominently in the programme for the first time in this conference in accordance with the decision of the Council of International Union taken in 1973. In all, 40 scientific sessions were held during the 5 days of the conference and of these, 13 were devoted to non-tuberculous chest conditions. A large number of workers involved in the latter were also seen for the first time among the delegates. The conference was held in the Auditorium of the National Medical Centre and the arrangements were excellent.

The inaugural session was held on the 22nd September, 1975 at 9 A.M. when in addition to the Minister of Public Health & Welfare, the President of the Republic of Mexico also graced the occasion and addressed the delegates. The conference was presided over by Prof. M. Jimenez of Mexico who is the current President of the International Union Against Tuberculosis and Director of the N.T.I, of Mexico. The inaugural session was followed by two short sessions, in one of which the WHO representatives addressed the delegates on the current status of the tuberculosis problem in the world and the WHO policies in relation to tuberculosis control. The IXth report of the WHO Expert Group was also referred to in this connection and commended to the delegates. The other morning session was addressed by the Minister of Public Health and Welfare, Director of the Institute of Security and Social Services and chief of the national campaign against tuberculosis. The three speakers dealt with the health problem in general and the tuberculosis control in Mexico.

General Health Programme in Mexico

The state of Mexico had a population of about 57 million in 1974. The current birth rate is among the highest in the world, viz., 46 per 1,000. With a death rate of about 10, the annual rate of population growth is 3.6 per cent. The country consists of 31 states with one federal unit comprising the capital city. The population of the capital city is nearly 8 million and it is the sixth largest city in the world. The bulk of the remaining population lives mostly in small communities, 40 per cent of which have a population of less than 100 inhabitants. Infectious diseases are the biggest killers being responsible for 39 per cent of all deaths in the country. Gastro-intestinal diseases are next in the list of killers, followed by cardiac conditions. Small pox, cholera and yellow fever have been completely eliminated. Infant mortality is about 62 per 1,000 and mortality amongst pre-school children is nearly 9 per 1,000. Life expectancy was 39 years in 1940 but it is 63 years now. 76 per cent of the population over 10 years of age can read and write.

Although industrial sector now contributes an increasingly large share to G.N.P., agriculture continues to employ the largest sector of the population. Maize, beans, wheat, rice, cotton and coffee are the main agricultural produce. Not only is Mexico self sufficient in food, it also exports food grains. It is self sufficient in oil also. Oil production is being stepped up and in a short time Mexico will also be an oil exporting country. It is the third largest producer of silver, fifth of zinc, fourth of lead and second of sulphur in the whole world. It is one of the leading countries in the world which manufacture hormones.

Health planning in real earnest started in the country in 1935. The latest document of the Ministry of Health, while presenting the national health programme declares that "a society without health education identifies itself with primitive state unworthy of man, anti-social, anti-aesthetic, anti-economic, immoral and capable of creating situations dangerous to social health and well being."

There is a total of 35,000 doctors in the whole country but as in our country, the medical coverage is unequal. In Mexico City alone there are 14,500 doctors (one for every 500 population or

per 10 sq. km.). In the moffusil, the ratio is one per 4,600 population or per 216 sq. km. In all, there are 90,000 hospital beds and 5,253 medical units out of which 2,091 are in the rural areas, corresponding to something like our primary health centres. Annual per capita expenditure on health was \$29.5 in 1971 and has gone up to \$55.8 in 1974.

15 per cent of the population is covered by health and social security insurance. This aspect of the problem is taken care of by the Institute of Social Security, which is a joint venture of the Government and the public. One-third of its finances are provided by the state, one-third by large employers in the country and one-third by the public. Like ESI in our country, it runs its own hospitals and clinics.

Tuberculosis and its Control in Mexico.

It has been estimated that the total number of cases of tuberculosis in the country is about 120,000 at any one point of time giving a prevalence rate of 2.3 per 1,000 of bacillary disease. (In Mexico only those persons whose sputum is positive are notified and are considered as cases of active tuberculosis). Nearly 36,000 new patients are diagnosed every year giving a new notification rate of 0.68 per 1,000 per year. The mortality rate in 1973 was 17 per 100,000 for all forms of tuberculosis, out of which pulmonary tuberculosis accounted for 15. Mortality rate for tuberculous meningitis was 1.3. 15.3 per cent of children below 15 years are tuberculin reactors. Active case-finding was carried out in the country in 1971 and it was found that half of the total number of cases in any community were undiagnosed. There are three tuberculosis hospitals, the biggest of which with 680 beds was converted into National Institute for Pulmonary Diseases in 1975.

There is a separate section of the Health Ministry which deals with tuberculosis control in the country. Tuberculosis services are integrated completely with the general health services at all levels except in the Mexico City which has a special tuberculosis control service. This service is available in 36 of the 48 health centres in the city and each of the 36 centres has on its staff a specialist in tuberculosis and chest diseases. All sputum examinations are carried out in a single laboratory. All positive slides and 10 per cent of negative slides from peripheral centres are re-checked centrally. 80 per cent of the population with cough and expectoration of about 2/3 weeks duration is found tuberculous. Intermittent chemotherapy is very popular. The defaulter rate before 1971 used to be very high (only 50 per cent completed one year's

treatment). In 1971, a study based on 9 health centres which were the first to integrate tuberculosis control into their routine work showed that 83 per cent of the patients in 1971-72 completed treatment regularly. The defaulter action was taken by the para-medical staff of the health centres.

BCG vaccination is compulsory. Thirty five special nurses carry out BCG vaccination in Mexico City whereas in the rural areas BCG vaccination is integrated with the general immunization programme. Massive BCG campaign was carried out in 1970 and another one 4 years earlier. It is estimated that by 1976, 80 per cent of all children would be vaccinated. The BCG laboratory produces 8 million doses of freeze-dried vaccine per year, out of which nearly 5 million doses will be exported by 1976 when bulk of the children would have been vaccinated and the country will need only about 3 million doses for the new births per year.

Tuberculosis Association of Mexico

A very active Tuberculosis Association is functioning in Mexico. A unique feature of its working is that the salary of the staff (comprising about 30 persons) is paid by the Government and the money that the Association raises itself is spent on health education, publicity and social and economic relief to poor patients. The total collections of the Association amount to about \$800,000 per year out of which the proceeds of TB seals are \$666,000 and the remaining comes from donations etc.

Future Targets

The Ministry of Health has laid down specific targets which have to be met by 1983. The post-natal mortality is to be reduced by 37 per cent, infant mortality by 35 per cent, mortality in the pre-school children by 52 per cent. The birth rate by that time is expected to come down to 32 with an annual population growth of only 2.3 per cent. Morbidity in case of malaria, diphtheria, and tetanus is expected to come down by 95 per cent, diarrhoea, amoebiasis etc. by 60 per cent and leprosy by 90 per cent. Total new cases of tuberculosis are expected to go down by 50 per cent and the mortality by 80 per cent in 1983. Life expectancy is expected to go up to 68 years. Health care will be available to 85 per cent of the population within easy distance.

Scientific Sessions

As mentioned already, 40 scientific sessions were held during 5 days. Apart from one main session each day in the morning, the scientific

sessions were being held simultaneously in 3 rooms after the main session, with the result that one could attend only about 1/3rd of the sessions. In all 230 papers were presented during the 5 days. Out of the 27 sessions on tuberculosis, as many as 13 dealt with various aspects of chemotherapy and the remaining 14 covered epidemiology, microbiology, BCG, chemoprophylaxis, etc. The main subjects covered in 13 sessions on non-tuberculous chest diseases were the problems of air pollution, smoking, chronic bronchitis and asthma. Three sessions were devoted to defence mechanism of the lung and its response to invasion. Some of the important sessions attended by the reporter are summarised below :

Preventive treatment in persons with fibrotic lesions of the lung

Preliminary results of this co-operative trial being conducted by the International Union Against Tuberculosis in 7 countries were presented at the Tokyo conference (Indian Journal of Tuberculosis, 1974,21,41). Nearly 2,800 patients with fibrotic lesions were randomly allocated to 3 treatment groups and to the 4th placebo group. The 3 treatment groups were given INH for 12, 24 and 52 weeks. About 90 per cent of the persons in each group had a regularity of over 75 per cent. The breakdown rate in the placebo group was 4.3 per 1,000 per year. Till 1973, INH had reduced the expected number of cases (based on the behaviour of placebo group) by 75 per cent in the 12 weeks group and 96 per cent in the 24 and 52 weeks groups. In the subsequent 2 years of follow up the protection given by INH was reduced, the advantage being 43 per cent in 12 weeks group, 70 per cent in 24 weeks group and 76 per cent in 52 weeks group, thus proving that as time goes on, the advantage of chemoprophylaxis in such persons goes on diminishing and INH treatment for 12 weeks does not confer significant protection. The breakdown rate did not differ in relation to the time that the lesions were known to have been inactive before being inducted into the study. However, the bigger the lesions the greater was the breakdown rate.

The incidence of hepatitis in this study was also reported in the Mexico conference, it was reported that the incidence of hepatitis was significantly more in the treated group; highest in persons above 45 years in age and with a previous history of liver disease. The risk of developing hepatitis is much higher in alcoholics. Hepatitis usually occurs early after the start of INH (maximum cases in the first 8 weeks of drug taking); there was no difference with INH of different brands but there were two cities where the incidence was the highest. The authors

concluded that the exact cause of liver damage was probably not known though simultaneous administration of INH increases the risk.

In another study on the same subject from Baltimore it was reported that out of 20,000 persons on INH prophylaxis, there were 13 deaths following liver damage. There was a preponderance of deaths among post-menopausal women, usually black women and in those with pre-existing liver disease.

In another study reported from Minnesota based on 7,000 persons, mostly males, who had had inactive lesions for over 5 years, INH was given for one year to 1/3rd of the patients, for 2 years to another 1/3rd and the remaining 1/3rd were on placebo. In this study there was no significant difference in the breakdown rate in the 3 groups even though 75 per cent of the persons in the treatment group took INH regularly and for the entire duration.

A review of diagnostic & treatment procedures and results

A number of papers were presented from different countries reviewing the diagnostic and treatment procedures. In Netherlands the study was based on 662 bacillary cases diagnosed in one year. Three hundred of these were positive by direct smear and the remaining 362 who were negative by direct smear were positive by culture. Active case-finding contributed 15 per cent, passive case-finding in chest clinics 71 per cent, other health facilities 12 per cent and miscellaneous 2 per cent. Out of the cases diagnosed in chest clinics (passive case-finding) 41 per cent attended voluntarily because of symptoms. Of the total 662 cases, 75 per cent had cough, 17 per cent other symptoms and 9 per cent had no symptoms referable to the chest. 43 per cent of the patients who were positive only by culture and 6 per cent of those who were positive by direct smear also were treated with two drugs. 91 per cent of the smear positive and 85 per cent of the culture positives completed the treatment. Only 1 per cent and 3 per cent respectively gave up treatment prematurely. All except 3 smear positives and 2 culture positives were converted.

In the Federal Republic of Germany 71 per cent were positive by smear and 29 per cent by culture alone. Relapse accounted for 36 per cent of the new cases. 8 per cent of the smear positives and 34 per cent of the culture positives had no symptoms. Three-fourth of the smear positives were diagnosed among the direct smear positives, symptoms had persisted for less than 2 months before diagnosis in 60 per cent, 2 to 4 months in 25 per cent, 4 to 6 months in 8 per cent and

more than 6 months in 7 per cent. In the last group the patients had consulted more than one doctor before diagnosis.

In U.K. men in older age groups predominated. There were a total of 53 deaths in 865 patients; 34 died of pulmonary tuberculosis and 19 from other causes unrelated to tuberculosis. Initial drug resistance was 1 per cent. 80 per cent of the patients were treated with 3 drugs. Duration of treatment was less than 12 months in 5 per cent, 12 to 18 months in 15 per cent, 18 to 24 months in 37 per cent and more than 24 months in 43 per cent. Average duration worked out at 22 months. 0.8 per cent required surgical treatment. 7.5 per cent were given steroids also. 4 per cent never stopped work. 18 per cent never returned to work. 19 per cent returned to work after 10 months. On an average 6 x-ray and sputum examinations were carried out per patient per treatment year. All positive patients were admitted to hospital. 30 per cent of them stayed for more than 6 months. The incidence of drug toxicity was 2.6 per cent. Drug default was insignificant i.e. in 5.5 per cent only.

In a study from Kenya based on 1,886 new patients diagnosed in 6 months in 1969, 88 per cent were pulmonary, 10 per cent extra-pulmonary and 2 per cent both pulmonary and extra-pulmonary. 96 per cent were fresh cases and 4 per cent relapses. Sputum was positive by direct smear in 50 per cent. In 6 cases the strain was atypical and in one it was bovine. Initial drug resistance was seen in 9 per cent; INH 5 per cent, streptomycin 3 per cent, both INH and streptomycin 1 per cent. 76 per cent of the cases were cavitary. 22 per cent were minimal and 37 per cent far advanced. After one year, 75 per cent were alive, 12 per cent had died and 12 per cent were lost to follow up. Death and maximum loss of patients (60 per cent) occurred in the first 3 months and 20 per cent in the next 3 months. After one year, 8 per cent were still positive, 80 per cent were negative and the sputum results were not available for 12 per cent. 2 per cent out of 420 originally sputum negative cases became positive during treatment. 34 per cent of the patients took drugs as advised for 12 months and 33 per cent for less than 6 months. 80 per cent of the patients were treated with INH and thiacetazone, supplemented with streptomycin for the first 4 to 8 weeks.

In another interesting study the cost of diagnosis and treatment in various countries was compared. It was calculated that the expenditure in France was \$24,900, in USA, \$12,525, in Netherlands \$10,106, and in Japan \$7,800. The cost did not include social and financial

assistance. The differences are mainly due to the difference in policies in relation to hospitalization and the total duration of treatment.

Chemotherapy

As already mentioned, maximum number of papers in the conference were on the subject of chemotherapy of pulmonary tuberculosis. Of these a large majority dealt with the results of short-term chemotherapy. This is understandable since the bulk of the research in chemotherapy in practically all countries of the world is to-day aimed at reducing the duration of treatment in order to minimize the problems of drug default and premature stoppage of treatment.

In the beginning of short-term chemotherapy, 4 drug regimens were used. The tendency now is to use only 2 or 3 bactericidal drugs preferably INH and rifampicin, the 3rd drug when used is either streptomycin or pyrazinamide or ethambutol. The duration of treatment is also being progressively reduced to 3 months from the usual 6 to 9 months previously. In some studies intensive treatment with 3 or 4 drugs is given for the first few weeks and thereafter the number of drugs is reduced, usually to 2, during the subsequent less intensive phase of treatment. In some other studies, after an intensive daily phase of a few weeks, the drugs, usually INH, rifampicin and ethambutol are given intermittently during the subsequent phase. The immediate results of these two modifications do not appear to be poorer.

The Tuberculosis Association of India is also conducting a co-operative study on short-term chemotherapy from three institutions in Delhi. The duration of treatment is 20 weeks and 2 short-term regimens are being tried. The interim results* of this study were also reported at the Mexico conference. It is not possible to review the results of the various studies separately in this short summary. The salient points arising from these studies are as follows:

1. The immediate results of treatment in some studies appear to be as good in 3 months treatment as in 6 or 9 months.
2. Regimens based on intermittent treatment in the continuation phase after daily treatment initially seem to be as effective as regimens based on daily treatment all through.
3. If Rifampicin is discontinued after about

* Full paper will be published in the April 1976 issue of the Indian Journal of Tuberculosis.

2 months and the subsequent treatment is without rifampicin, the results do not appear to be significantly poorer.

4. In one study high doses of rifampicin (900 mg) were tried without any improvement in the results.

5. Toxic reactions to rifampicin are more common in once weekly than in twice weekly regimens.

6. Ethambutol alone is not of much use but when used with INH and rifampicin, it enhances the efficiency of the regimen.

7. INH, streptomycin and pyrazinamide in many studies do not give as good results as INH, streptomycin and rifampicin. In one study reported from Hong Kong, the former regimen however gave equally good results. Bad Hi develop resistance to pyrazinamide rather quickly. INH and pyrazinamide eliminate bacilli much more efficiently than either alone.

8. Streptomycin, rifampicin and pyrazinamide in various combinations of any two of these three drugs are not good combinations.

9. Patients with initial drug resistance do not fare as well as those with initially sensitive bacilli, but the difference in results is no more and no less than in the case of conventional therapy in the 2 group of patients in relation to drug sensitive bacilli.

10. Relapse, if it occurs at all, is usually seen soon after stopping the treatment as opposed to conventional long-term treatment where the maximum number of relapses are usually seen 2 years after stopping the treatment.

11. Relapse rates do not seem to have any relationship with extent of disease and/or cavitory status at the start of treatment.

12. Relapse rates on the whole range from 0 to 5 per cent.

Apart from the paper on short-term chemotherapy presented by Dr. Viswanathan, Chairman of the Research Committee of the Tuberculosis Association of India, 5 more papers were presented by members of the Indian delegation. Dr. S.P. Tripathy presented a paper on therapeutic efficacy and adverse reactions of a slow release INH preparation (Matrix-INH). The results of Matrix-INH in doses of 40 mg/kg. with 300 mg of ordinary INH gave as good results in rapid inactivators as ordinary INH given daily in slow inactivators. Dr. Dingley reported on the prevalence of endo-bronchial tuberculosis and bacteriological confirmation of the primary disease in children. Dr. Raj Narain reported on the waning of tuberculin allergy during 4 years following BCG vaccination. He also reported that BCG vaccination in even strong reactors to tuberculin was in no way harmful. Dr. Mehrotra reported on the role of neighbourhood clinics in urban areas in respect of case-finding and management of treatment of pulmonary tuberculosis. All these papers were very well received.

NEWS & NOTES

ANNUAL MEETING

The 37th Annual General Meeting of the Association will be held on Thursday, the 22nd April, 1976, in the Conference Hall of the Association, 3 Red Cross Road, New Delhi-110001.

NATIONAL CONFERENCE

The Thirtyfirst National Conference on Tuberculosis and Chest Diseases will be held in Lucknow (Uttar Pradesh) sometime in October/November, 1976. The exact dates will be announced in due course. Subjects selected by the Programme Committee for discussion at the Conference include (1) Surgery; (2) Air Pollution; (3) Symposium on 'Smoking Hazard'; (4) National TB Control Programme with special reference to the working of peripheral health institutions; (5) TB Seal Sale Campaign; (6) Childhood Tuberculosis; (7) Chemotherapy Including management of resistant cases; (8) Problem of Drug Default-its reasons and management. (9) Fungal infections and (10) Extra-pulmonary Tuberculosis.

Those who wish to present papers at the Conference may send in the titles of their papers along with an abstract to the Secretary-General, TB Association of India, 3, Red Cross Road, New Delhi-1, latest by the 31st March, 1976.

CHAIRMAN, TECHNICAL COMMITTEE

Dr. Tahir Mirza, State TB Officer, Jammu & Kashmir and Honorary Secretary, Jammu & Kashmir TB Association, Srinagar, has been nominated as Chairman of the Standing Technical Committee and President of the 31st National Conference on TB & Chest Diseases *vice* Dr. H. B. Dingley.

DR. S.P. PAMRA

Dr. S.P. Pamra, Director, New Delhi TB Centre and Associate Editor, Indian Journal of Tuberculosis, has been elected a Fellow of the Academy of Medical Sciences.

HEALTH VISITOR'S COURSE

The 1976-77 TB Health Visitors Course will commence in July 1976. The Course will be of 9 months duration of which five months will be spent in the New Delhi TB Centre, two weeks in L.R.S. TB Hospital, Mehrauli, two weeks for examination (in December) and three months internship which will last from 1st January to 31st March (including two weeks in a rural centre). The minimum qualification for admission to this course is Higher Secondary/Pre-University with Science or Hygiene and Physiology in matriculation. Application for admission to this course should reach the Secretary-General,

TB Association of India, 3, Red Cross Road, New Delhi-1, by 30th April, 1976.

SEAL SALE CAMPAIGN

The 26th Seal Sale Campaign which commenced on October 2, 1975 terminated on 26th January, 1976.

CHANCHAL SINGH MEMORIAL AWARD — 1976

The Tuberculosis Association of India will award a cash prize of Rs. 500/- to a TB worker, below 45 years of age, for an original article not exceeding 30 double-spaced fool-scrap typed pages (approximately 6,000 words) excluding charts and diagrams on a subject relating to tuberculosis. Papers may be sent, in quadruplicate, to reach the Tuberculosis Association of India office latest by *31st August, 1976*. The cash prize will be awarded to the author of the selected paper at the 31st National Conference to be held in Lucknow.

EXPERT COMMITTEE

The Expert Committee appointed by the I.C.M.R. to review the objects, achievements, deficiencies, etc. of the National TB Control Programme in India is understood to have completed its assignment and submitted a draft report to the I.C.M.R.

SEMINARS/CONFERENCES

The Punjab State TB Association organised the Vth TB Conference on 17th January, 1976, at Amritsar. Sri Balbir Singh, Minister for Health & Family Planning, Punjab Government, inaugurated the conference. Drs. H.B. Dingley, J.L. Bhatia, Jaswant Singh and others presented papers in the scientific session of the conference. Shri B.M. Cariappa, Secretary-General, Tuberculosis Association of India, addressed the conference.

The 4th Annual Conference of TB Association of Haryana was held on 24th October at Hissar. Shri L.M. Jain, Deputy Commissioner of Hissar, inaugurated the conference. A large number of medical and social workers in the State participated in the conference.

The Gujarat State TB Association organised the 4th State TB Workers Conference at Ahmedabad on 14th December. Shri Babubhai Patel, Chief Minister of Gujarat, inaugurated the conference. Among others, Dr. G.D. Gothi of N.T.I, and Dr. H.N. Patel, Director of Health Services, participated in the scientific session and panel discussions. An exhibition of Health Education was also organised on the occasion.

The TB Association of Goa has decided to

organise a Symposium on TB in Goa on 7th March, 1976.

The TB Association of Jammu & Kashmir also plans to hold a Seminar on Tuberculosis and Chest Diseases sometime in the last week of June, 1976.

It is understood that the Maharashtra State TB Association will hold its 14th Workers Conference towards the end of February, 1976.

ANTI-TB SHIBIR

The Maharashtra State Anti-TB Association organised its 69th & 70th Anti-TB Shibir at Wai and Bel-Air Sanatorium (Satara District) on 24th and 25th October, 1975. The Shibir was jointly sponsored by the Rotary Club of Bombay, Panchaghani and Wai. The Camp examined 332 persons and administered BCG vaccination to 1,068 persons. The Association also held its 71st and 72nd Shibir at Sinner and Malegaon in Nasik District on 14th and 15th December, 1975. The Shibir at Sinner which was organised in association with Lions Club of Nasik examined 4,343 persons and administered BCG vaccination to 3,657 persons. The Camp at Malegaon helped

by the Lions Club of Malegaon, administered BCG Vaccination to 10,020 persons.

The Maharashtra State Anti-TB Association in collaboration with the Lions Club of Shivaji Park and Indian Medical Association organised a Health Week in Bombay on 23rd and 27th November, 1975. Similar Health Week was also held at Kalyan on 23rd November, 1975 under the joint auspices of the Maharashtra Association, Lions Free Mass Medical Check up, Lions Clubs of Comballa Hill, Kalyan, Marine Drive and Worli and Medical Club of Kalyan.

EASTERN REGION CONFERENCE

The 10th Eastern Region TB Conference of the International Union Against Tuberculosis under the auspices of the Eastern Region is being organised by the Korean National Tuberculosis Association. This Conference will be held in Seoul, Republic of Korea in conjunction with their National Conference on Tuberculosis from the 11th to 15th October, 1976. The Conference Secretariat has informed that they are arranging an interesting Scientific programme.

BOOK REVIEW

WHILE THE LIGHT LIVES.—REMINISCENCES OF A MEDICAL SCIENTIST BY R. VISWANATHAN. PUBLISHED BY ASTHMA & CHRONIC BRONCHITIS FOUNDATION OF INDIA. PAGES 288. PRICE Rs. 25/-.

Lives of great men are a lesson for every one. This autobiography of a great scientist, an excellent teacher and clinician and a charming writer contains many lessons delivered in a refreshingly unconventional yet extremely interesting style. Instead of a laborious chronicle of events as some autobiographies are, it reads almost like a collection of short stories. There is a subtle blending of wit and wisdom, profane and profound, narration and philosophization and anecdotes with scientific facts. Many complex scientific problems that the author has solved during his long innings have been dealt with lucidity, so as to interest both the scientist as well as the layman. Thumb-nail sketches of colleagues contemporaries and associates make the characters almost alive. The book reveals amply the author's sense of humour and a highly sensitive and discerning mind. Innumerable appreciative friends he has all over the globe are a testimony to his popularity and his contribution to the advancement of scientific knowledge.

Great men are great partly because they set their aims too high and strive consistently to achieve these. If in spite of a rich and successful life, during which many highly coveted honours

and awards, both national and international, have been conferred so deservedly on him, he still thinks his life has been a *failure* to the extent that he has not been able to achieve fully the aims he set for himself, it is only a measure of his own greatness. Candid self-analysis and assessment given towards the end of the book is another index of his greatness.

Any one who cares to read this book will find it instructive and thoroughly enjoyable and yet the book is not without a blemish. Long list of errata given in the beginning of the book is not exhaustive and there are many more printing errors, which with a little more careful scrutiny could and should have been avoided.

The book was released by Dr. Karan Singh, Union Minister of Health & Family Planning, at the inauguration of the Joint Annual Conference of Physicians and Chest Physicians of India on 22nd January, 1976. The entire sale proceeds of the book will be credited to the funds of the Asthma and Bronchitis Foundation of India of which the author is the Founder and President. Thus the readers will not only get full worth of their money but, incidentally, will also help thereby a very worthy cause.

S.P. Pamra

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ABSTRACTS

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Abst. No. 1

Diabetic acidosis and abnormal chest roentgenogram

Paul J. Myerson et al. Chest; 1974, 66, 434.

Pneumomediastinum in diabetic Keto-acidosis without evidence of pulmonary disease has been reported. Increased intra-alveolar pressure in diabetic Keto-acidosis occurs both with Kussmaul respirations and with emesis and either may cause pneumomediastinum. Intra-alveolar pressure results in alveolar rupture causing interstitial emphysema. The air then dissects along the peri-vascular sheaths to the mediastinum. Concomitant subcutaneous emphysema and pneumothorax may or may not be present. The interstitial air usually clears spontaneously.

S.P.P.

Impairment of hepatic uptake of Rifampicin antibiotics by probenecid and its therapeutic implications

S. Kenwright & A.J. Levi. Lancet; 1973, ii, 1401.

Rifampicin is largely metabolised by the liver. The possibility that the hepatic uptake of Rifampicin could be depressed by treatment with probenecid was investigated in rats and man. Rifampicin and probenecid were shown to have similar effects in depressing hepatic uptake of bromsulphthalein and bilirubin in rats. These effects were not due to competition for binding but possibly involve competition at the plasma membrane. Probenecid significantly depressed the hepatic uptake of Rifampicin in rats. In man, peak serum-rifampicin levels were raised by 86 % after oral probenecid. Mean serum increases of approximately 100% were also found at 4, 6 and 9 hours. These studies may have considerable therapeutic implications because the use of Rifampicin is often limited by cost. The results also throw fresh light on the mechanisms of selective hepatic uptake in general.

S.P.P.

Tuberculin reaction in adult Nigerians with sputum positive pulmonary tuberculosis

B.D.W. Harrison, P. Tugwell & I.W. Fawcett, The Lancet; 1975, i, 421.

Forty six out of 48 rural Nigerian Adult patients with sputum positive pulmonary tuberculosis had skin reaction of less than 10 mm to 4 or 5 TU of P.P.D. The size of the reaction correlated significantly with serum albumin and transferrin concentrations. Persons with less than 10 mm reaction had not only lower initial albumin and transferrin levels but a greater increase in concentration of both proteins 4 weeks after starting treatment. This suggests that the poor reactors were initially more severely under-nourished than those with reactions of 10 mm or more. The diminished reaction in these patients seems to be part of a generalized depression of cell-mediated immunity associated with under-nutrition rather than a specific depression of P.P.D. reaction associated with overwhelming antigen load.

The poor reactors also showed a slower rate of sputum conversion during the first 4 weeks of treatment though initially there was no correlation between degree of positivity of sputum and tuberculin reaction. Comparison of initial chest skiagrams showed that poor reactors had slightly more extensive disease with more cavities which tended to be smaller and have thinner walls, although none of these differences were marked. It is concluded that negative tuberculin test is of no value in the diagnosis of pulmonary tuberculosis unless it is combined with a bio-chemical assessment of the persons nutritional status.

S.P.P.

Studies on surgical treatment for chronic empyema with special reference to treatments before and after the radical operation

Hiroshi Anno. Medical Research Report of the Japan Anti-TB Association, 1974, 22, 7.

The results of treatment before and after the radical operation in 201 cases of chronic

empyema who were operated during the period 1962 to 1972 are presented. The treatment was successful in 85% of the cases. 7.5% died and in another 7.5% the end result was unsuccessful. The relapse rate was about 10%.

Preparatory treatment was carried out in 41.2% of all cases, tube drainage in 22.5% and open drainage in 18.7%. In the remaining 58.8% radical operation was not preceded by preparatory treatment. The pus was converted from positive to negative in about the same number of patients (approximately 75%) in both types of preparatory treatment. However, open drainage led to spread of disease in a significantly larger number of patients than in the case of tube drainage. In 35 cases continuous irrigation of the chest space with saline solution was carried out after pleuro-pneumectomy with promising result.

A study on the mode of detection of newly registered pulmonary tuberculosis patients with special reference to their symptoms

Tadao Shimao, Mutsu Homma & Fumiro Iriyama & Hiroto Misawa. Medical Research Reports of the Japan Anti-TB Association, 1974, 22, 17.

A study was made on the mode of detection of newly registered pulmonary tuberculosis patients in the Niigata Prefecture, Japan. The proportion of cases found by mass survey was 37.6%; by other group examinations 5.6% and during examination for other diseases 9.8%. The remaining 46.7% were detected during a visit to the general practitioner because of symptoms. Proportion of cases found through symptomatic visit was lower in the villages than in the cities and towns. In the case of villages, the proportion of patients detected through mass surveys was higher. The percentage of bacillary cases was higher among patients reporting with symptoms at the clinics and there was no difference in this respect in patients from cities, towns or villages. The proportion of cases found by symptomatic visit was higher in females than in males whereas the reverse was the case in patients detected during mass surveys. A much larger proportion of the bacillary cases (as against abacillary cases) had not been x-rayed previously during one year, as well as 3 years preceding the final diagnosis. The most important symptoms reported were cough 28%, fever 15%, chest pain 10%, tiredness 8% and haemoptysis 5%. The duration of symptoms from their appearance to the time of diagnosis was shortest in haemoptysis; next came chest pain, fever and cough. In nearly 30% of the cases of cough with expectoration the time lag between appearance of symptoms and diagnosis was 3 months or more. Approximately

half of the cases had visited other physicians due to the same symptoms prior to final diagnosis and more than half of them had even been x-rayed. In only 23% of those examined by x-ray, tuberculosis was suspected. Of all the symptomatics, tuberculosis was suspected in only 14% at the visit to the practitioner prior to the diagnosis. As a result of this study, emphasis in Japan is now on case-finding amongst symptomatics with mass survey confined only to those with a high risk.

S.P.P.

The effect of radiation on microbiologic characteristics of M. Tuberculosis

Michael B. Zack et al. Chest; 1974, 66, 240.

The effect of irradiation on mutation (expressing itself as drug resistance) and on viability of *Mycobacterium tuberculosis* was studied *in vitro*. Forty two identical cultures of H-37-Rv (*M. Tuberculosis*) were exposed to different levels of cobalt radiation (10, 100, 1000, 2,500, 5,000, 10,000 and 20,000 rads) with six samples used for each of the seven radiation levels. Equivalent samples exposed to zero rads and samples handled and stored identically formed the controls. The viability of organisms began to decrease at radiation levels of 1,000 rads and decreased linearly with higher levels of radiation. Three of the 42 radiated cultures developed drug resistant organisms (one to 1NH, one to PAS and the third to streptomycin). This drug resistance occurred at levels of clinical significance as well as in amounts exceeding probability values for chance resistance mutation. Common belief that irradiation to the lungs leads to exacerbation or reactivation of tuberculous process is not substantiated by the study. On the other hand, if *in vitro* data could be extra-polated to *in vivo* setting, moderate to high dose radiations may in fact have a salutary effect on pulmonary tuberculosis, at least by decreasing the number of viable organisms in pulmonary lesions.

S.P.P.

Mediastinal masses in infants and children

William J. Pokorny, Joseph O. Sherman—Journ. Tub. Surg.; Vol. 68, No. 6 Dec. 74.

The results of treatment in 109 children age range from 2 years to 16 years between 1954 and 1972 have been reviewed. Preoperative evaluation of the child with a mediastinal mass depends on its localization for which the mediastinum is classified into three compartments: the anterior mediastinum, the middle mediastinum, and the para vertebral salcus.

Most of the tumours found in the anterior mediastinum are teratomas and tumours of thymus. Most of the middle mediastinum tumours are lymphomas or duplication cysts. The para vertebralsalcaus, which is located posterior to the anterior border of vertebral bodies is not part of the mediastinum but is included because the neurogenic tumours arise in this area.

The neurogenic tumours which arise from the nerve roots and sympathetic ganglion in the paravertebral gutter are well circumscribed masses on chest roentgenograms. Spicules of calcium may be seen in the blastomas and ganglioneuroblastomas. Due to their proximity to the vertebral foramen, they may extend into the closed space of the vertebral column and produce signs of spinal cord compression. An oesophagogram confirms the extrinsic compression of a posterior mediastinal mass. Broncho-oesophagoscopy and mediastinoscopy are of little value. The level of urinary vanillylmandelic acid is only occasionally elevated in patients with neuroblastoma of the mediastinum. Lymphomas and duplication cysts were the most common masses and were seen in children over 2 years of age.

Lymphosarcomas and Hodgkins present bilateral mediastinal widening on X-rays, the lymphosarcoma tend to be larger and more lobulated masses. The diagnosis of lymphosarcoma can be established by cervical lymph node biopsy.

The children with Hodgkins have non-specific symptoms such as malaise and fever. The physical examination presents peripheral adeno-

pathy or hepatomegaly. The diagnosis can be confirmed by lymph node biopsy.

Duplication cysts and oesophageal duplications occur in middle mediastinum and may cause respiratory distress.

H.B.D.

Use of B.C.G. as an Immunostimulant in the surgical Treatment of Carcinoma of the lung.

F. Ronald Edwards and Francis Whitwell. Thorax (1974) 29, 654.

Cell mediated immunity to cancer cell would appear to exert some control over the extension of tumour growth and stimulation of this factor might result in increased survival after surgical treatment of the tumour. Of the various agents used as stimulators, a single dose B.C.G. = Glaxo (5,00,000 organisms) was given subdermally 10 days after excision of lung carcinoma. The length of survival was used as the index of the effect of the B.C.G.

The aim of the study was to assess the safety of B.C.G. and a survival study of 120 consecutive cases (60 used as controls). At the end of two years the survival rate increased from 38% in the controls to 52% in the B.C.G. group. In the squamous cell group survival has risen from 50% to 62% and in those with positive nodes from 33 % to 53 %. In the oat cell group, it has risen from 11 % in the controls to 50 % in the B.C.G. group. Although results are encouraging but are not statistically significant.

D.H.B.