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## BCG VACCINATION

No sooner had Robert Koch proved tuberculosis to be an infectious disease and demonstrated the causative micro-organism, the search was on for a suitable immunising agent. Calmette and Guerin finally succeeded in attenuating the virulence of a bovine strain to such an extent that it (BCG) failed to produce disease in animals but conferred substantial protection against the development of disease when infection with a virulent strain occurred subsequently. The resultant wave of euphoria and promise was natural. Many thought that B.C.G. would, in due course, lead to victory over tuberculosis, the great killer, but that was not to be.

Ordinarily, either the efficacy of a therapeutic or a prophylactic agent is established within a few years or it is abandoned altogether. In the case of BCG vaccination, 60 years have passed since it became available but its role in tuberculosis control is still far from settled and the protection conferred by it is still steeped in controversy.

It is often argued that BCG was introduced on the basis of observations and impressions of pioneers like Wallgren, Heimbeck and others without proving its efficacy by a scientifically controlled trial. It is usually forgotten that the importance of controlled trials, universally accepted today, had not been realised at the time BCG was introduced. Further, it is not easy to organize a valid controlled trial on BCG. Everyone after infection does not develop disease. The small minority, say 3-5 percent, who develop disease may do so after a long lag period extending even up to 20 years or more. The longer the period of surveillance, the greater the withdrawals from study population and consequent vitiation of inferences. And lastly, unlike other infectious diseases, certain characteristics of tuberculosis e.g. dormant bacilli, endogenous reinfection, many and variegated predisposing factors, etc., make assessment of the protective effect of BCG vaccination difficult and uncertain.

Baily's review article published in this issue gives a critical account of the important BCG trials. Marked disparity in their results has kept the controversy alive. Even the Chingleput trial, which was expected to end the controversy once for all, has failed to do so.

Academicians have put forth new hypotheses and recommended studies to identify, as far as possible, the various factors which could have influenced the protective effect of BCG and thereby led to disparity in the overall results of earlier studies. But the more pressing issue today is: Should we

scrap BCG vaccination altogether or modify or continue unchanged the present programme?

Contribution of BCG to tuberculosis control can be assessed from two different angles. One is in respect of its ability to reduce the transmission of disease in the community, i.e., its effect on the incidence of bacillary pulmonary disease. The Chingleput trial has shown that BCG could not play any role in this respect in that population. Even if BCG did confer some protection in respect of bacillary pulmonary disease, its actual overall contribution towards problem reduction in any population would depend on the proportion of bacillary cases which arise from the tuberculin reactors and non-reactors. Since, in the Chingleput trial, nearly 90% of the bacillary pulmonary cases arose from amongst the reactors, BCG would not have made any significant contribution to the problem reduction even if it had conferred (for argument's sake) 80% protection, since it could have prevented fresh cases developing amongst the non-reactors only.

The second criterion for assessment would be the number of primary and early post-primary cases prevented by BCG. These manifestations were, unfortunately, not studied in the Chingleput trial. It is therefore imperative to mount another trial to study the protective effect of BCG, if any, in respect of *all* manifestations of tuberculosis, more particularly the serious early post-primary manifestations of haematogenous dissemination. This trial need not cover as large a population as the Chingleput trial. Vaccination of children upto 12 or 14 years in age with proper controls, followed for a period of about 5 years should provide authentic evidence for or against this aspect of the problem. We owe this trial to ourselves, to the administrators and to the people in general.

And till the results from this trial become available, continuation of the vaccination programme as heretofore appears to be logical. The balance of the conflicting evidence available so far appears to be in favour of BCG vaccination conferring some protection against the development of primary and early post-primary disease, even if the quantum of protection may vary from one epidemiological situation to another.

## REVIEW ARTICLE

### PRESENT STATUS OF IMMUNISATION AGAINST TUBERCULOSIS

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The discovery of the tubercle bacillus by Robert Koch in 1882 and his classical demonstration, in 1891, of the effect of a second infection with tubercle bacilli in an already tuberculous guinea pig, which later came to be known as the 'Koch phenomenon', heralded scores of attempts to develop a specific immunising agent against tuberculosis, derived from the tubercle bacillus. The attempts were indeed inspired by the observations of Edward Jenner who about a hundred years earlier, in 1798, had also noticed the increased reactivity to vaccinia virus occurring in persons who had been previously vaccinated or who had had smallpox.

In animal experiments conducted over the years, the immunising capacity of four distinct types of 'vaccines' were studied: preparations consisting of small numbers of living tubercle bacilli; preparations containing mycobacteria that are non-pathogenic to man but pathogenic to certain animals or birds; products of tubercle bacilli or tubercle bacilli themselves, killed by a variety of physical and chemical methods and finally, preparations containing attenuated variants of originally virulent strains of tubercle bacilli pathogenic to man (Weiss 1959, a, b, c).

The first was never widely tested and discarded as too hazardous. The second i.e. several mycobacteria that are non-pathogenic to man, were shown to be ineffective until the discovery of the effect of the Vole bacillus (*M. microti*) which causes naturally occurring disease among field rats (Wells, 1937) and is also pathogenic to certain other species of animals including the guinea pig. Vaccine prepared from the vole bacilli was shown to offer significant and a measurable degree of protection in man (Medical Research Council, Great Britain, 1972). The first attempts to induce immunity with killed tubercle bacilli or their products were initiated soon after the discovery of the tubercle bacillus. For instance, Daremberg in 1889 reported that several rabbits which had been inoculated with cultures of tubercle bacilli sterilised by heating for 15 minutes at 115°C or for six hours at 70°C survived longer after virulent challenge infection. Later his claim was not substantiated by others. Since then scores of animal experiments using non-living vaccines have been reported (Weiss 1959, a, b, c) with conflicting results. One of the possible reasons for these

conflicting results could be the fact that the test-systems used for testing the vaccines in animal models varied from experimenter to experimenter, as is seen in the varying results in the potency assay of the same BCG vaccines in different BCG laboratories (Smith, et al 1971). Thus, non-viable vaccines have never been employed though interest in these vaccines has not ceased even to-day. Although Vole vaccine has been shown to confer a significant degree of protection, vaccination with Vole vaccine causes some unpleasant reactions at the site of vaccination and as such has never been practised on any large scale. Thus, the only vaccine that has been used, and used extensively throughout the world, is the BCG (bacille Calmette Guerin) which is an attenuated variant of *M. bovis*. BCG vaccine does not cause progressive disease in man except in the extremely few recorded cases and under exceptional circumstances. It is also avirulent in experimental animals except the Syrian golden hamster.

Virtually since BCG vaccine was introduced by Calmette and Guerin in 1921, it has been a subject of controversy. It was introduced in Europe at a time when Europe was just recovering from the ravages of a war and tuberculosis was quite common, and interest in BCG, considerable. With greater 'experience' which was not uniform, interest in many countries including United States and Britain waned. Scandinavian countries however have always been very enthusiastic about BCG vaccination. In the post second world-war years, massive BCG vaccination campaigns were organised in Europe through the International Tuberculosis Campaign with Headquarters in Copenhagen. Tuberculosis at that time was still relatively common and the privations of war had aggravated the situation in many countries. Soon after, BCG was introduced in many developing countries of the world and in India, it was first tried out in 1948 and vaccination programme started on a large scale, as a mass campaign, in 1951.

By 1950, even though BCG vaccination was in use for nearly 30 years and several BCG campaigns had already started, the opinion about BCG in many developed countries, especially Britain and United States could only be

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considered as lukewarm. This was best stated by D'Arcy Hart et al as "...moderate opinion on BCG in Britain and in the USA in 1949 might have been summarised as follows: (1) it gave some protection in those specifically exposed to tuberculous infection in their homes or at work; (2) it could be expected, at least in general populations with low standards of living and high tuberculosis rates, to reduce the incidence of tuberculous disease appearing within a few years of a natural first infection with tubercle bacillus ....." (Hart, Pollock and Sutherland, 1957).

Opinions on the efficacy of BCG Vaccine were formed, in addition to the demonstration of its effects in animal models, in several ways: Observations based on 'experiences' with the use of BCG, early uncontrolled observations and studies on the protective effect of BCG and, the results of controlled trials. While the first two could be considered to be easily influenced by several factors, more recent observations indicate that conflicting results obtained even in well controlled trials could have been due to one or more factors as yet unidentified.

#### **Protective Effect of BCG Vaccine**

Though all BCG vaccine produced in the world in dozens of BCG laboratories to-day, comes from the original BCG culture produced by Calmette and Guerin, characteristics of the vaccines produced in different laboratories vary. This is because with repeated subculturing, the genetic characteristics of BCG (or, for that matter, several micro-organisms) undergo change. As a result of repeated sub-culturing, the changes in the BCG produced in one laboratory may not be the same as the changes obtained in another. In one instance, only the morphological characteristics of the bacilli may have changed with no changes in the protective effect. In another, while the morphological characteristics are not affected, the protective effect may have changed considerably. It is therefore, common practice to refer to BCG produced in different laboratories as 'strains' of BCG. Thus, BCG produced in Madras is referred to as 'BCG-Madras' (strain 1331) and BCG produced in Paris as 'BCG-Paris' (strain 1173) etc. In animal experiments, most strains of BCG show a higher or a lower protective effect measured as the survival time of the animals (guinea pig, mice etc) which have been vaccinated and later challenged, i.e. infected, with virulent tubercle bacilli, as compared to those that are not vaccinated but are only challenged. (Ladefoged, Bunch-Christensen and Guld, 1970),

In man, however, evidence of the protective effect of BCG vaccination can be obtained through clinical observation, or better still, through controlled trials. Literature is replete with reports on observations and controlled trials but most of these cannot be considered as statistically valid.

The first controlled trial which can be considered as statistically valid was started by Aronson and others (1958) in 1935. Prior to this study, most of the evidence in favour of a protective effect of BCG in man came from clinical observations. Some of these observations were more solid than the evidence available for several other prophylactic measures and are discussed below.

#### **The earlier observations and studies**

Heimbeck's studies :

One of the earliest observations and studies on BCG were those by Heimbeck in Norway. In 1924, Heimbeck (Heimbeck, 1948), started tuberculin testing the staff of the Oslo municipal hospital in Norway. The hospital then had about 2,000 beds and about 300 of those were occupied by patients suffering from tuberculosis. He had observed that many nurses developed tuberculosis within a few years after joining nursing. Table 1 presents the fate of the nurses joining in 1924, 1925 and 1926. Of the 109 nurses joining in 1924, 58 were tuberculin positive and 51, tuberculin negative. By the end of three years, only one of the 51 nurses who was tuberculin negative continued to be tuberculin negative and all the others had converted to the tuberculin positive state. Over the next few years whereas only 1 case of tuberculosis developed among the initially tuberculin positive, among the 51 initially tuberculin negative nurses, 18 cases developed with 7 deaths. The fate of the cohorts admitted in 1925 and 1926 was also similar except for deaths in the tuberculin negatives.

Observing this striking fate among those initially tuberculin negative nurses, Heimbeck offered, from 1927 onwards, BCG vaccination to all tuberculin negative new entrants. He, however, did not compel them too much to get vaccinated with the result that of the 899 nurses (Table 2) admitted between 1927 and 1934, 436 were tuberculin positive, 95 were tuberculin negative but refused vaccination, and 368 were tuberculin negative and BCG vaccinated. Whereas 42 cases of tuberculosis developed among the 95 unvaccinated tuberculin negatives, 37 cases developed among the 368 vaccinated tuberculin negatives during the following few years after

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Table 1

*Heimbeck's observation among student nurses in Oslo*

Year of admission	Tuberculin Positive			Tuberculin Negative		
	Total	Cases of TB	Deaths	Total	Cases of TB	Deaths
1924	58	1	0	51	18	7
1925	42	1	0	72	26	1
1926	52	1	0	62	18	0

Table 2

*Heimbeck's BCG study among student nurses in oslo: 1927-1934*

Tuberculin and BCG status on entry	Nos.	Cases of Tuberculosis	Percent
Tub. Positive	436	27	6.2
Tub. Negative, Not vaccinated	95	42	44.2
Tub. Negative, BCG vaccinated	368	37	10.1

vaccination—a reduction of about 76 percent among vaccinated. This early observation of Heimbeck cannot be considered as absolute proof of the protective effect of BCG mainly because the 95 'controls' were self-selected and thus the allocation was far from blind. Even so, since the study population was all uniform i.e. all women aged about 20 and all belonging to urban middle class families, of similar socio-economic status and exposed to similar risk of infection, the study can be considered as of interest and provided one of the first evidences of the protective effect of BCG in humans.

Hyge's study :

An epidemic of tuberculosis in school girls aged 12-18 years, has been described by Hyge (Guld, 1980). The epidemic occurred in a blacked out air-raid shelter where all the pupils were exposed to infection by chance. This occurred 1-3 months after routine tuberculin testing (Mantoux 100 unites) and x-ray examination of

all pupils and one year after BCG vaccination of the majority of tuberculin negatives.

The fate of the pupils is shown in a summarised form in Table 3. While of the 94 who were tuberculin negative and were not vaccinated, 41 cases of primary tuberculosis occurred, among the 106 tuberculin negatives vaccinated with BCG, no case of primary tuberculosis occurred. The development of progressive primary disease is also presented. Though this is a retrospective study, and again, not statistically fully valid, the complete absence of primary disease among the vaccinated is striking and can scarcely be explained as being entirely due to bias. Indeed the above two studies gave strong indications of the protective effect of BCG in man and provided an impetus for planning statistically valid studies to obtain irrefutable proof of the protective effect of BCG.

Table 3

*Hyge's study: An Epidemic of Tuberculosis among school girls during the second World War*

Status before epidemic	Students exposed	Cases of tuberculosis (Primary)	Progressive Pulmonary T.B. over 12 years
Tub. Negative	94	41	20
Tub. Negative, BCG vaccinated	106	0	4
Tub. Positive, Not vaccinated	105	1	14

### The controlled trials

Controlled trials have come to be recognised as the most reliable methods of establishing the efficacy of therapeutic or prophylactic measures in man and confirm what has been studied in animal models as also from 'experiences' from Application in humans. The trials are meant to establish not only that a curative or a prophylactic measure is effective, but the actual degree of efficacy. In these trials, after the safety of the measures is assured and ethics of the study examined, the hypotheses are clearly laid down, subjects (persons) among whom the studies will be conducted are carefully identified, the appropriate design selected and meticulous care is exercised in the follow-up of all subjects for the same period of time. Possibly, the most important characteristic of these trials is that, neither the person who administers a measure nor the subject to whom it is administered decides which measure is applied to whom. Subjects are allocated to the measures through a double-blind randomised scheme.

In the BCG trials, following an appropriate

randomisation scheme, subjects are allocated either to 'BCG vaccination' or to 'no BCG vaccination' (controls) blindly. All the subjects are followed-up for a specified and the same duration of time, to identify the new cases of tuberculosis arising from among them. (It will be obvious that preliminary investigations are carried out to exclude from analysis of the protective effect, persons who at the time of allocation are either infected or are actually suffering from tuberculosis). The protective effect of BCG is expressed as the proportion by which the incidence of new cases is reduced among the vaccinated as compared to the controls.

A very large number of BCG trials have been reported in the literature. Most of these trials, for one reason or another do not satisfy the criteria mentioned above and are thus statistically not valid. As upto the time that the Chingleput study of the protective effect of BCG vaccination was started, the studies indicated in Table 4 can be considered as some of the studies that are statistically valid and conducted in the general population.

Table 4  
*Results of Six controlled trials of BCG vaccination Against Tuberculosis*

Trial and age of subjects	Intake period	Duration of follow-up yrs.	Vaccination group	No. of subjects	Cases of tuberculosis	Protective effective %
North Amer.* Indians (9) 1-18 yrs.	1935-38	9-11	Control BCG	1457 1551	238 64	80
Georgia (14) 6-17 yrs.	1947	12-23	Control BCG	2341 2498	3 5	None
Puerto Rico (13)	1949-51	5½-7½	Control BCG	27338 50634	73 93	31
Georgia, Alabama (21) 5+ years	1950	14	Control BCG	17854 16913	32 26	14
Great Britan (5) 14-15½ yrs.	1950-52	15	Control BCG	12699 13598	240 56	78
Madanapalle (15) All ages	1950-55	9-14	Control BCG	5808 5069	46 28	31

\*Figures in brackets indicate the reference nos. of the reports on these studies.

The first of these studies was conducted among the North American Indians (Aronson, Aronson and Taylor, 1958). The study population was characterised by low socio-economic conditions and a high risk of tuberculous disease. At about the 10th year of follow-up the incidence of tuberculosis cases among the vaccinated was 80 % less than the incidence among controls. At the time of the final follow-up i.e. at about the 18th year, the protective effect was still of the order of 72% since there were 42 cases of tuberculosis among the BCG vaccinated compared to 185 cases among the controls. In this study not only the emergence of new cases was evaluated but also, the deaths were carefully assessed. As at the end of follow-up, there were 13 tuberculous deaths among the BCG vaccinated compared to 68 tuberculous deaths among the controls giving a protection of 82%. Acid fast bacilli could be demonstrated among 5 deaths vaccinated and among 27 deaths that were not vaccinated again giving a protection rate of 82 %. On the whole, this early but well conducted study indicated a protective effect of about 80 %.

Similarly, three other studies were started in different parts of United States of America during the late forties. In the study in Puerto Rico, started in 1949, the protective effect of BCG has been assessed in 27,338 controls and 50,634 vaccinees. As at about 6 years the protective effect was 31 % (Palmer, Shaw, and Comstock, 1958) while at the 18th year of follow-up it still was the same i.e. 28.7% (Comstock, Livesay and Woolpert, 1974). The effect was similar in different age groups. In another study in Georgia in a population of about 5,000 children aged 6-17 years, no protective effect was observed. In the third American study in Georgia and Alabama a very modest protective effect of about 14 % was observed. (Comstock and Webster 1969).

The Medical Research Council (MRC), Great Britain carried out a study among British school leavers (all aged 14-15½ years) wherein 12,699 were unvaccinated and 13,598 were offered BCG vaccination (Medical Research Council, Great Britain, 1972) The protective effect was assessed at various intervals for 15 years and it was found that it was almost constant at about 80%. This was also true when the effect was assessed against different manifestations of tuberculosis. In the same trial, another section of the study subjects had been vaccinated with Vole vaccine and in them also the protective effect of Vole vaccine was similar to that of BCG, i.e., about 80 %. In a small study in a general population of about 10,000 persons in Madanapalle in South India, the protective effect as at about 9-14 years after vaccination was assessed

to be about 30% (Frimodt-Moller, Acharyulu and Parthasarathy, 1968).

It will thus be observed that while animal models almost always showed a measurable degree of protection by BCG, experience in humans varied considerably. In the words of Ian Sutherland, who was always associated with the MRC trial in Britain, “\_\_ the instinctive reaction of any scientific worker, when he finds that his results differ from those of another scientific worker, is to mistrust the other man’s results, and so it was not surprising that there was a good deal of coming and going across the Atlantic between the MRC workers and the U.S. Public Health Service Workers, each group prepared to be very critical about the other’s investigations. The results of this exercise have, however, been entirely beneficial in that our mistrust has been dispelled...” (Sutherland, 1971). After considerable deliberations, they agreed that, of the many reasons that can be associated for the lack of protective effect in American studies, two reasons might be the most relevant; firstly, the vaccine used in some of the American studies could have been prepared from poor strains of BCG and secondly, that infection with atypical mycobacteria prevalent in the United States may have itself offered some degree of protection which masked the protection offered by BCG. When the Chingleput study was planned and started in 1968, this was the state of knowledge regarding the protective effect of BCG vaccination.

#### The Chingleput BCG trial

In 1963, the Government of India took up the question of conducting a BCG trial in India. There was still some controversy in the country about the use of BCG and it was felt that the problem had to be settled by a controlled field study under Indian conditions. The study (Tuberculosis Prevention Trial, Madras, 1980) was planned in collaboration with the World Health Organisation and the Centre for Disease Control, United States Public Health Service and conducted by the Indian Council of Medical Research as a separate project.

The study was undertaken in Trivellore taluk of Chingleput district in Tamil Nadu. The intake (i.e. admission of population to the study) was started in July, 1968 and completed in March, 1971. During this period, a total population of about 3,60,000 persons in 209 contiguous villages and one town were registered on individual cards. All persons aged one month and above were offered one of two doses of BCG vaccination (0.01 mg or 0.1 mg) or a placebo on a random basis. Two strains of

BCG, the Copenhagen and the Paris strains were used. At the same time, all persons aged 1 year and above were tested with Tuberculin (PPD-S) and an antigen prepared from an atypical mycobacteria (PPD-B), the former, to elicit the status of infection with *M. tuberculosis* and the latter to elicit infection with atypical mycobacteria. All persons aged 10 years and above were also X-rayed and for those in whom X-rays showed any abnormality sputum examination by direct smear and culture was done.

The study population was systematically and intensively followed up by X-ray and sputum examinations in an effort to diagnose all new cases of pulmonary tuberculosis occurring in the community. In addition, representative samples of population were tuberculin tested using PPD-S in order to elicit the status of tuberculin sensitivity after BCG vaccination.

The population was characterised by high prevalence and incidence of tuberculous infection as well as high prevalence of non-specific sensitivity. The overall prevalence of tuberculous disease (pulmonary) was also high being very much higher in males than in females.

Table 5 presents, in brief, the main results regarding the protective effect of BCG vaccination in the prevention of pulmonary tuberculosis as observed in the study.

Table 5

*The Chingleput BCG trial: Results\* (7½ Years)*

Tuberculin reaction at intake	Given Standard Dose BCG (0.1 mg.)	Given Standard Dose BCG (0.01 mg.)	Placebo
0-7 mm	37	37	28
8-11 mm	14	17	17

- (i) Distribution of definite bacillary cases of pulmonary tuberculosis only.
- (ii) **Results** similar for less definite bacillary cases (**culture** negative on one specimen only) and cases positive on X-ray only.
- (iii) Nos. vaccinated are similar in all three groups.

The table shows the distribution of new cases of pulmonary tuberculosis that were positive on culture of at least two specimens of sputum

i.e. in all probability, these were definite cases of tuberculosis. The protective effect is studied among those who were initially tuberculin negative i.e. reacting with 0-11 mm to PPD-S. These are again divided into two groups, one reacting with 0-7 mm i.e. definitely not infected at intake and the other reacting with an induration of 8-11 mm. Some of the latter could be considered to have been infected with *M. tuberculosis*. Because of the large size of the study population the denominators can be taken as similar. The difference observed between the three groups do not attain statistical significance. Thus, BCG gave no protection against the development of bacillary pulmonary tuberculosis in this study. The results were similar when analysis was done for less definite bacillary cases as well as X-ray positive but abacillary cases.

### Current Status of Immunisation Against Tuberculosis in India Based on the Results of Well-Conducted BCG Trials

The Chingleput study was conducted on the hypothesis that BCG offers protection against tuberculosis and one of the objectives was to measure the exact degree of protection offered by BCG. With the present result in hand it is scientifically appropriate to examine the possible reasons for this result.

The study was meticulously conducted and the procedures followed were constantly monitored in order to obtain accurate results. Even so, a committee of experts was appointed to scrutinise the methodology and it, concluded that no errors could have been introduced. In further "discussing the possible reasons for this result in the Trial in India, one major assumption is made. That all trials listed in Table 4 and the present one are scientifically valid. Only those hypotheses that are *amenable to testing* are presented.

One of the reasons put forward by the American workers was that the low protective effects observed in the trials conducted in the U.S. were due to the masking of the protective effect of BCG by the protection afforded by previous infection with atypical mycobacteria. Examining the problem in animal studies, Palmer and Long (1966) found that atypical mycobacteria do give some protection against tuberculosis in animals. While BCG confers about 81% protection, photochromogens confer 68%, Scotochromogens and non-chromogens 56% and rapid growers 15%. Further, if animals which have been previously infected with photochromogens, are injected with BCG the protection is not additive but goes up to 80% as in the case of BCG. Thus—in an animal study, if animals are first infected with photochromogens and

then vaccinated with BCG the protection that will be attributable to BCG would be only 12%=(80 %-68 %). If what is observed in animals is true of man, then in areas with high prevalence of non-specific mycobacteria in the environment, only the *residual* protection would be observed in the BCG trials. As has been said earlier, the prevalence of nonspecific sensitivity was very high in the study area indicating a high prevalence of environmental atypical mycobacteria,

A rough estimate of the type (photochromogens, scotochromogens, etc) of environmental mycobacteria; prevalent in the area of the study can be obtained from cultures of sputa collected from study subjects, usually in a survey such as this, at their homes. From the sputum samples collected under field conditions, such environmental mycobacteria would be grown as contaminants. In the over 2,00,000 sputum samples collected and cultured during the study, in nearly 6% such contaminants were grown indicating the very high prevalence of environmental atypical mycobacteria. However, it was observed that most of the mycobacteria were those that gave only a low degree of protection. In effect, only 1% of all the atypical mycobacteria isolated were typed as photochromogens which were shown by Palmer and Long to confer a protection close to that of BCG. If BCG were to confer a high degree of protection of the order of 80 %, one should have observed some residual protection in the study population since most infections with atypical mycobacteria would probably be caused by organisms that confer low degree of protection. Thus infections with atypical mycobacteria may not, at least fully, explain the zero protection observed in the study.

Disease occurring as a direct extension of the first infection (primary) itself is most common in children and the forms of disease can be termed as childhood forms of tuberculosis. These include, besides the primary complex, complications such as miliary, meningitis, bone and joint tuberculosis etc. In contrast, adult forms of tuberculosis represented mainly by cavitating bacillary pulmonary tuberculosis is considered to be mainly a result of later endogenous reactivation of a healed primary complex, and not as a result of another exogenous reinfection with tubercle bacilli. Since Koch demonstrated that a second infection with tubercle bacilli in a guinea pig is far more difficult than the first, it has occurred to most workers that much of adult forms, of tuberculosis occurs as a result of endogenous reactivation. The role of BCG was based on this hypothesis as it will be obvious

that if exogenous reinfection is the main cause of adult type of tuberculosis, BCG obviously cannot help.

In Chingleput area, infection with tuberculosis is very high and the virulence of *M. tuberculosis* isolated in the area is probably low. If the high incidence of tuberculous infection results in exogenous reinfection being the prime cause of adult forms of tuberculosis, BCG may not be expected to protect against such disease. This hypothesis appears promising in explaining the *complete lack* of protective effect in Chingleput study. Attempts are being made to investigate this hypothesis. This is relevant not only for the explanation of the failure of BCG to protect in this study but also for the Tuberculosis Programme in general.

Several other hypotheses can be put forward. Two of these are: the differences in immunological responses in different population groups; the effect of nutrition on immunological responses in the body. While the former could be investigated, the latter appears to be not relevant because one cannot classify the entire population of the study area as undernourished or malnourished. Further, tuberculin sensitivity, which is an immunological response to antigens derived from the tubercle bacilli, is not influenced by the state of nutrition in the population. In a study by Ganapati and Chakraborty (1981) where the state of under-nutrition was classified into 4 grades depending on the severity of under-nutrition, tuberculin sensitivity status was similar in children in all the four grades of undernutrition as also in children classified as normal.

The present status of BCG vaccination stems from the knowledge as it stands to-day. BCG offered no protection against pulmonary tuberculosis. At the same time, one cannot assume that BCG may not protect against childhood forms of tuberculosis which were not investigated in the trial. It is however quite likely that BCG would protect against such disease for the following reasons: disease forms in animal studies, where BCG almost always conferred a measurable degree of protection, resemble more closely childhood forms of tuberculosis rather than adult forms. Secondly, several controlled trials wherein protection against other forms of tuberculosis has been investigated (Medical Research Council, 1972; Rosenthal et al 1961) have shown that BCG offers protection against childhood forms of tuberculosis. It is thus appropriate that BCG vaccination, at present in India, is limited to the prevention of tuberculosis in childhood.

In all studies, except the small study in Madanapalle, where BCG was shown to be protective, it was demonstrated that the Protection was durable i.e. it lasted as long as the follow-up of the population was continued. This is true irrespective of the degree of protection as evidenced in the British trial where the protection was high, and Puerto Rico where the protection was low. On this basis, if a good vaccination is offered at an young age, revaccination may not be indicated as, in those studies protection lasted from 5 to 20 years. Primary Infection is most frequent in the younger ages and so is primary disease. Thus if BCG vaccination has to be given to prevent primary disease, it should be given before primary infection occurs i.e. in India well before the age of 5 years. After 20 years of age, primary infection is less frequent in India and risk of primary disease even less frequent. Revaccination is indicated only when the first vaccination has not been satisfactory—i.e. given either with a poor vaccine with a poor technique. It may however be remembered that post vaccination allergy tends to wane with time (Tuberculosis Prevention Trial, 1980) and deciding on revaccination on the basis of waned post-vaccination allergy may not be Quite appropriate. In animal experiments it has been shown that BCG induced allergy wanes very fast but can be restored by repeated tuberculin testing. With the waning of allergy, the acquired resistance does not wane nor, at the same time, with restoration of allergy by repeat 'tuberculin test' is the acquired resistance enhanced (Magnus, 1957). In a study in children it was shown that BCG induced allergy wanes with - time but can be restored by repeated tuberculin testing (Guld et al. 1968). Thus, revaccination may be practised only if a group of children vaccinated very early in life show poor post-vaccination allergy shortly after vaccination—say between 2 to 6 months. For all practical purposes, revaccination is not indicated if the first vaccination has been good.

Discussed above is the status of immunisation against tuberculosis in India to-day. In developed countries, with the sharp decline of tuberculosis, interest in immunisation has also declined. However, developing countries like India, which have missed those winds of change, may have to continue their interest in immunisation. The story of immunisation against tuberculosis is not yet over.

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# SYMPTOM AWARENESS AND ACTION TAKING OF PERSONS WITH PULMONARY TUBERCULOSIS IN RURAL COMMUNITIES SURVEYED REPEATEDLY TO DETERMINE *THE* EPIDEMIOLOGY OF THE DISEASE

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**Summary** : Fifty one persons aged 20 years and above classified by X-ray as 'probably tuberculosis, possibly active' and 'probably tuberculosis and active' in the fifth round of the Longitudinal Survey in 22 villages, were interviewed on a structured questionnaire to elicit the awareness of symptoms and details of action taken to seek relief.

Almost all of those bacteriologically positive were aware of symptoms suggestive of tuberculosis, thus registering a higher percentage of awareness than the X-ray positives.

Of those with symptoms, 58.8 % sought relief, many of them at multiple agencies such as Govt. hospitals and private practitioners and some at tuberculosis hospitals, on being referred there. Most had obtained services free of cost and appreciated the available intrinsic benefits. Prior personal or family associations were the main reasons for seeking the services of private practitioners. Only 23 % had gone to the nearest health facilities. Lack of proper facilities for good treatment and preference to be treated at urban centres were the main reasons for not availing of the services at the nearest health facilities.

## Introduction

Epidemiological studies undertaken by the National Tuberculosis Institute, Bangalore, often have had sociological counterparts wherein the prevalence of symptoms and action taken have been studied with respect to sputum positive cases, X-ray suspects or the general population<sup>1,2,8</sup>. The fifth round of the longitudinal survey provided yet another opportunity to study symptom awareness and action taking of people suspected to be having pulmonary tuberculosis as evident in radiological shadows suggestive of tuberculosis.

Starting from 1961 the community had come under epidemiologic survey five times. The second survey was after an interval of one and a half years, the third after yet another one and a half years of the second survey, the fourth after two years of the third and the fifth in 1977 after eleven years of the fourth. Since 1974 the community was covered by the district tuberculosis programme, by which diagnostic and treatment services for tuberculosis became available at the peripheral health institutions located in the rural areas also.

It therefore seemed desirable to study the awareness of symptoms and action taking of persons in the 'community where repeated surveys consisting of tuberculin testing, X-ray examination and sputum microscopy had been carried out and where facilities for diagnosis and treatment were available subsequently.

## Objectives

The objectives of the study were as follows:

1. To estimate the awareness of symptoms suggestive of tuberculosis by direct, elicitive interviews of those classified by X-ray as 'probably tuberculosis, possibly active and probably tuberculosis and active' by at least one of the X-ray readers.
2. To determine the proportion of the above who have taken action and the type of services obtained, specially at modern medical facilities,
3. To determine the factors that encourage or discourage them to seek treatment at centres readily accessible to them.
4. To determine why, though aware of symptoms no action was taken.

## Study Population

The study was undertaken in the 22 villages of Nelamangala Taluk, Bangalore District Karnataka where the epidemiological surveys were carried out. All radiological positives aged 20 years and above in the category 'probably tuberculosis and possibly or definitely active' detected in the *fifth round of the survey* were included in the study.

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Table I

*Interview Status by X-ray Classification  
(Coverage)*

Interview Status

X-ray Classification	Satisfactorily Interviewed	Temporarily Absent	Temporarily present	Dead	Migrated	Total
Active by both	7	—	—	1	—	8
Active by one	13	—	—	2	—	15
Probably active by both	14	1	1	1	1	18
Probably active by one & not active by the other	17	3	—	1	—	21
Total Percentage	51 82.26	4 6.45	1 1.61	5 8.06	1 1.61	62 100.00

**Methods**

The identification details of the eligible persons were made available to the social investigator within about two weeks of completion of the epidemiological survey of each of the twenty-two villages. Each person was interviewed at his residence by the social investigator directly on the basis of a structured questionnaire.

**Coverage**

Of the 62 persons referred as X-ray positives to the social investigator, 51 (82.26%) were satisfactorily interviewed. Of the remaining, four were absent from the village during the period of investigation and one had been at the village only during the epidemiological survey, one had migrated and *five had died* during the interviewing period.

**Presence of symptoms**

Table II shows that of the 51 satisfactorily interviewed 80.4% had symptoms suggestive of tuberculosis recently, i.e., at the time when the epidemiological survey which obtained evidence of his X-ray positivity had been done. 84.3% were aware of having had the symptoms at sometime or the other. 31(75.6%) out of the 41 X-ray positive persons with symptoms recently said that they had been worried about the symptoms.

Table II

*Presence of symptoms suggestive of tuberculosis of any duration (Recent, Anytime) by X-ray and Bacteriological classification*

Category	No. Satis. Intd.	Symptoms present	
		Recent	Anytime
Active by both	7	5	5
Active by one	13	13	13
Probably Active by both	14	11	13
Probably Active by one not Active by the other	17	12	12
Total (Active or probably active by at least one) Percentage	51	41 80.39	43 84.31
Total (Sputum positive by any method) Percentage	20	19 95.00	19 95.00

Table III

*Prevalence of Symptoms Suggestive of Tuberculosis by X-ray & Bacteriological Classification*

Category	Number Satisfactorily interviewed	Symptoms present				Presence of at least one of these symptom
		Total with cough %	Total with chest pain %	Total with fever %	Total with haemoptysis %	
Active by both	7	57.14	42.86	14.29	—	57.14
Active by one	13	69.23	84.62	30.77	23.08	92.31
Probably active by both	14	57.14	50.00	14.29	21.43	57.14
Probably active by one and not active by other	17	58.82	35.29	17.65	5.88	70.59
Active or probably active by at least one	51	60.78	52.94	19.61	13.73	70.59
Sputum positive by microscopy & culture	12	91.67	75.00	50.00	25.00	100.00
Sputum positive by microscopy alone	—	—	—	—	—	—
Sputum positive by culture alone	8	37.50	37.50	12.50	—	50.00
Sputum positive by any method	20	70.00	60.00	35.00	15.00	80.00

Of the bacteriologically positive cases 95.0% were aware of symptoms both at the time of interview and at any time of recall. 18(94.7%) out of the 19 bacillary positive with symptoms said they worried about their symptoms.

#### Prevalence of symptoms

Table III shows the prevalence of each of the four cardinal symptoms—cough, fever, chest pain for one month and haemoptysis analysed in terms of the X-ray and microscopy classifications.

Cough is the predominant symptom in all but one category of X-ray positives, next in importance being chest pain, then fever and lastly haemoptysis.

When these symptoms are analysed in terms of those with sputum positivity, higher percentages are obtained except in the category who are only culture positives.

#### Action taken by the symptomatics

Out of the 41 persons radiologically positive who had symptoms suggestive of tuberculosis, 36 had cough, fever and chest pain for more than a month while the rest had these symptoms for lesser duration of time. Six persons out of the 36 had not, taken any action, while 30 (73.2%) or 58.8% out of the total interviewed satisfactorily had taken some action to find relief of symptoms.

Table IV shows the action taken because of symptoms experienced recently and the recall of action taken for similar symptoms occurring earlier.

Of those who experienced the symptoms recently and had taken action, 16.7% had gone to tuberculosis hospitals, 56.7% to government hospitals and 50.0% to private practitioners; of those who recalled actions taken earlier, 13.3% 13.3% and 33.3% had gone to the above facilities

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Table IV

Proportion of action taking among chest symptomatics by facility and judgement of treatment

Number Action Taken = 30 (58.82 %)

Facility	Judgement of Treatment							
	RECENT				EARLIER			
	TB TTT Doubtful	TB TTT likely	TB TTT definite	Total %	TB TTT doubtful	TB TTT likely	TB TTT definite	Total %
Indigenous	3	—	—	10.00	1	—	—	3.33
Pvt. Pract.	13	—	2	50.00	5	1	4	33.33
Govt. Hosp.	8	1	8	56.67	1	1	2	13.33
TB Hosp.	—	—	5	16.67	—	—	4	13.33
Total				58.82				58.82

TTT = Treatment  
Pvt. Pract. = Private Practitioners.

respectively. It is seen that some of the patients had gone to more than one health facility, mostly those offering modern health services.

When asked why they had gone to the private practitioner, out of the 21 people 15 said that they had prior personal associations with the doctors, 3 said the treatment was better, 2 mentioned that government hospitals were not good and one had some vague reasons. The places to which the patient went were at distances ranging from 3 km to 80 km, 13 of them having gone beyond 10 kms. Two said that they had obtained services free of cost, 10 people had spent amounts below Rs. 50/, 2 claimed to have spent above Rs. 3,000/-

Similarly, of the 18 who had gone to general health services, 6 had been referred and 12 had gone there because of intrinsic benefits available at these services. For two patients facilities were obtainable within the village and for 9 they were available within 3 to 10 km and the rest further away. Fifteen patients received free treatment while three patients claimed to have incurred expenditure of Rs. 30/- Rs. 400/- and Rs. 2,500/- at the *general health services*.

Out of the 8 persons who went to tuberculosis hospitals, 5 had been referred by other health

facilities while the rest went on the advice of family or other knowledgeable people. These hospitals were beyond 10 kms of their villages. All patients reported having received diagnosis and treatment free of cost.

Three persons had obtained indigenous treatment free of cost and near to their villages on the advice of their families.

Tables on the above and subsequent details on action taking have not been presented as the numbers are small. Not considering the duration of symptoms, 8 persons though aware of symptoms had not taken action. Reasons given for no action were various such as the symptoms being not serious enough. Lack of money, time and help, physical disabilities and infirmity. When asked whether they really wanted to take action three of them said that they had not wanted to take any action.

The 51 persons satisfactorily interviewed were asked to mention the health facilities nearest to the villages. Forty nine private practitioners and 82 general health services were mentioned. Except for one, the private practitioners were within 15 km, 18 (36.7%) of them being within 5 kms. Similarly, except for one, the general health services were within 15km; 5 (6.1 %) were within the villages itself and in

all, 30(36.6%) were within 5 km and (83%) within 10 kms.

Only seven (23%) out of the 30 who had taken action had gone to one or other of the nearest health facilities they had mentioned. The others gave various reasons for not having gone to those they had mentioned. Six of them said they get better treatment at private practitioners. Another six persons said that these places had either no proper facilities, could get service only on payment or that they had no confidence in them. Four said that they preferred treatment at urban centres and six others had no particular reason for not going to these centres.

### Discussion

During the period of sixteen years from 1961, the 22 villages under study had been surveyed five times through tuberculin testing, radiological and sputum examination to determine the natural trend of pulmonary tuberculosis. It may be presumed that these surveys had helped to increase the community's awareness and knowledge about the disease. It is found that the awareness of the bacteriologically positive patients questioned specifically mentioning the symptoms was the same as was obtained in an earlier study, indicating that almost all the patients who are sputum positive are aware of one or other of the cardinal symptoms of tuberculosis. Almost all of them are worried about their symptom.

When analysed according to X-ray positivity, 80% are aware of symptoms and 75.6% of the symptomatics expressed worry about their symptoms. The sputum positives showed a higher proportion of those with each of the four symptoms as compared to the X-ray positives.

Out of the total of 51 persons with X-ray positivity interviewed 58.8% or 73.2% of the symptomatics had sought relief for their symptoms which is a higher proportion than obtained in the earlier studies.<sup>3, 8</sup> They had approached more than one treatment agency. Help from private practitioners was obtained on being so advised by others, even when such services in 62% were available at distances beyond ten kms and when, except in two cases, they had to incur much expenditure.

It is observed that 60% had gone to general health services, two thirds having gone because of the intrinsic benefits; most got free treatment and Half of the facilities were within 10 km.

The TB hospitals were beyond 10 kms and.

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all (8) had obtained anti-tuberculosis treatment free of cost. (. Some of those who had gone to private practitioners and government hospitals seem also to have received anti-tuberculosis treatment both for symptoms recently experienced as well as symptoms they could recall.

All were aware of modern health facilities accessible to them even if they be as far as 15 km, the general health services being mentioned almost as many times as private practitioners. 37% of the general health services mentioned were within 5 kms distance and 83% within 10 km. Only 23 % had gone to the facility which according to them was "nearest". The reasons for not having gone ranged from a preference for other facilities to a lack of confidence in the nearest places offering general health services.

Sociological studies of persons detected during community surveys to be suffering from pulmonary tuberculosis do have the disadvantage of having to deal with small number of persons considering the fact that the prevalence of sputum positive cases in the community is 0.4% and of X-ray suspects 1.6%. However, these studies are pointers in understanding the awareness and changes in awareness in comparison and in keeping with the socio-economic development of the environment. They also point out to the different aspects involved in a person's choice of a treatment facility to which he goes to find relief for his suffering.

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## THIO-ACETAZONE SERUM LEVELS IN NORTH INDIAN PATIENTS

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**Summary :** 64 hospitalized patients of pulmonary tuberculosis of North Indian origin were administered thioacetazone in 3 doses along with other anti-tuberculosis drugs. Serum thioacetazone levels were found to be higher in those receiving higher dosages of thioacetazone though the rise in the serum levels was not proportional to the dose administered. Assuming an arbitrary concentration of thioacetazone 0.5 ug/ml for determining the coverage, 2/3rd increase in the exposure was seen when the dose was increased from 150 mg. to 450 mg. Clinical and biochemical parameters to determine thioacetazone toxicity were found to be within normal limits. Minor gastrointestinal irritation, not necessitating the withdrawal of the drug was encountered in 4 patients on 450 mg. dosage of thioacetazone.

### Introduction

Thioacetazone has been used as a primary anti-tuberculosis drug in India for the last 18 years. Large number of clinical studies on its efficacy have been conducted. (Deshmukh and Master, 1962, Patel, 1962, Deshmukh, Master and Kulkarni, 1963, Chandra Shekhar, Maribasappa and Rajasekhra 1964, Patel, 1964, Menon, 1965, Mehrotra, Pande, Grover, Sharma, Bhargava and Gupta, 1965, Tuberculosis Chemotherapy Centre, 1966, Sikand, 1966, Singh, Puri, and Sharma, 1966, Singh and Puri, 1967, Bhatia and Thind, 1967, Dingley and Sehgal, 1967, Khanna, 1969, Shah and Kothari, 1970, Mathur, 1975). Intermittent therapy with thioacetazone and isoniazid has also been conducted. (Krishnaswamy and Ram Chander, 1974).

Indeed, there are only two studies conducted so far on the serum thioacetazone level in patients of Indian origin. One of these was conducted in Singapore (Ellard, Dickinson, Gammon and Mitchison, 1974) and the other in West Bengal (Sen, Chatterjee, Saha and Roy 1974). India is a vast country and is inhabited by over 680 million people belonging to many ethnic groups. Consequently, the results obtained in Singapore and East India may not, necessarily, be applicable to the entire Indian population or even to those living in North India.

This study was, therefore, conducted to estimate the serum levels of thioacetazone, obtained after a single dose administration of the drug, and levels obtained after its use for a period of 3 months in conjunction with other anti-tuberculosis drugs like isoniazid and streptomycin in patients of North Indian origin. Routine liver function test e.g. serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and serum alkaline phosphatase levels were also monitored regularly, besides the clinical observations for

side effects of thioacetazone during the entire period of 3 months of the drug administration.

### Material and Methods

#### Subjects

64 hospitalized patients of pulmonary tuberculosis, who had not been treated previously, were included in the study. They were randomly allocated to either of the two groups given below:

1. Group 'A' : 29 patients received daily therapy.
2. Group 'IT' : 35 patients received intermittent therapy.

This group was further subdivided into two sub-groups :- (B)

Group B<sub>1</sub>: Comprising 16 patients, who received thioacetazone 300 mg. twice a week.

Group B<sub>2</sub>: Comprising 19 patients, who received thioacetazone 450 mg. twice a week.

#### Chemo-therapeutic Schedules Employed

*Daily regimen* : Streptomycin 1 g. I.M.I. once a day, Isoniazid 300 mg. and thioacetazone 150 mg. administered in single dose after breakfast by mouth.

#### Intermittent regimen

Group B<sub>1</sub> Streptomycin 1 g. I.M.I., Isoniazid 650 mg. and thioacetazone 300 mg. orally administered twice a week under the supervision of the hospital staff nurse.

Group B<sub>2</sub> : Streptomycin 1 g. I.M.I., I.N.H. 650 mg. and thioacetazone 450 mg. orally administered twice a week under the supervision of the hospital staff nurse.

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### Investigations Conducted

- A. Estimation of serum thioacetazone level :- 5 patients (control) from each group (Groups A, B! & BJ were selected at random to determine the time of maximum serum concentration of the drug following a single oral dose of thioacetazone (150 mg., 300 mg., 450 mg., respectively).

Following the determination of the time when the peak serum concentration was achieved, serum thioacetazone concentrations were measured from the serum of the subject every month during the subsequent 3 months of study. The venous blood was drawn at the same pre-determined hour after administration of thioacetazone.

- B. S.G.O.T., S.G.P.T., serum alkaline phosphatase: The levels of these enzymes were estimated before the initiation of the study and subsequently at monthly intervals for the next 3 months.

### Techniques Employed

1. Serum thioacetazone level: Ultraviolet method (Ellard, Dickinson, Gammon and Mitchison, 1974).
2. S.G.O.T. and S.G.P.T. (Reitman & Franke 1957).
3. Serum Alkaline Phosphatase (King and Wootton 1964).

**Duration of Study: 3 months.**

### Results

TABLE 1  
*Serum Drug level in Control Subjects*  
150 mg. Thioacetazone

Case No.	TZN ug/ml.						
	0 hr.	2 hr.	4hr.	5 hr.	6 hr.	8 hr.	24 hr.
1.	0.52	1.52	1.72	2.00	1.92	1.80	0.56
2.	0.50	1.45	0.90	2.10	1.95	1.77	0.54
3.	0.45	1.35	1.62	1.72	1.62	1.58	0.48
4.	0.48	1.60	1.30	1.74	1.52	1.46	0.48
5.	0.52	1.45	1.55	1.80	1.60	1.56	0.58

The peak serum concentration of thioacetazone with 150 mg. dose was noted five hours after its administration. This finding is in agreement with those obtained by Ellard et al (1974).

TABLE 2

*Serum Drug Level in Control Subjects*  
300 mg. Thioacetazone

Case No.	TZN ug/ml.						
	0 hr.	2 hr.	4 hr.	5 hr.	6 hr.	8 hr.	24 hr.
1.	0.54	1.62	1.84	1.95	2.65	2.24	0.52
2.	0.50	1.72	1.94	2.00	2.40	2.10	0.50
3.	0.48	1.88	1.82	2.10	2.56	2.26	0.46
4.	0.48	1.78	1.90	2.08	2.36	2.24	0.50
5.	0.52	1.98	2.00	2.24	2.40	2.20	0.56

TABLE 3

*Serum Drug Level in Control Subjects*  
450 mg. Thioacetazone

Case No.	TZN ug/ml.						
	0 hr.	2 hr.	4hr.	5 hr.	6 hr.	8 hr.	24 hr.
1.	0.58	1.85	2.32	2.65	2.78	1.95	0.58
2.	0.55	1.70	2.25	2.85	2.95	2.65	0.58
3.	0.48	1.75	2.00	2.59	2.77	2.49	0.52
4.	0.54	1.65	1.95	2.76	3.10	2.66	0.56
5.	0.56	1.75	1.60	2.75	3.00	2.62	0.56

Peak serum concentrations were attained in the 6th hour after the administration of the drug which again is in agreement with the finding of Ellard et al (1974).

It will be evident from tables 2 & 3 that thioacetazone does not accumulate in the serum, so that at the end of 24 hours the amount of drug left in the serum is almost negligible.

TABLE 4

*Geometric Mean Concentrations (ug/ml.) of Thioacetazone after different doses of the drug.*

Dose :	Mean concentration (ug/ml.) of the drug at different periods (hours)							Geometric Mean cone, (ug/ml.)
	0	2	3	5	6	8	24	
150mg.	0.49	1.47	1.38	1.87	1.71	1.63	0.53	1.16
300 mg.	0.50	1.17	1.90	2.07	2.47	2.21	0.51	1.39
450 mg.	0.54	1.74	2.01	2.72	2.92	2.46	0.56	].54

TABLE 5

*Mean Peak Serum Drug levels in various groups i.e. 150 mg., 450. mg., 300 mg., TZN. among male and female subjects*

Dose	No. of Cases concentration	Control Value month	(a) Peak Serum Con- month obtained	(b) after 1 following the initial dose	(c) after 2 months	(d) after 3 months
TZN ug/ml.						
MALES						
150 mg.	16	0.514	1.667	1.655	1.661	1.654
300 mg.	8	0.501	1.950	1.975	1.988	1.976
450 mg.	10	0.515	2.389	2.405	2.425	2.427
FEMALES						
150mg.	13	0.534	1.833	1.856	1.863	1.868
300 mg.	8	0.550	2.337	2.353	2.330	2.350
450 mg.	9	0.534	2.653	2.673	2.681	2.649

It will be evident that although, there is three-fold rise in the dosage, the rise in mean concentration is less than 50%.

The differences between the values obtained under a b c d are not statistically significant by analysis of variance (2 way analysis). Mean peak serum concentration has been taken to be mean of the highest concentration observed. Although

there is a three fold increase in the dosage of the drug, there is a rise by less than 50% in the peak serum concentration. Thus, it might appear that the serum levels of thioacetazone are proportional to the dose of the drug administered orally though the relationship is not linear. This could be due to slow absorption of thioacetazone and to its simultaneous elimination from the serum during the process of absorption.

TABLE 6

Coverage :	
Duration for which 0.5 ug/ml is maintained (coverage) :	150 mg. 25 hrs.
	300 mg. 24 hrs.
	450 mg. 25 hr.

We have taken an arbitrary concentration of 0.5/ug/ml for determining the coverage. If this parameter is applied there is nothing to choose between the three dosages.

TABLE 7

Exposure to thioacetazone :	
Exposure : Area under the time concentration curve above 0.5 ug/ml.	150 mg. 15.2 ug/ml x hrs. 300 mg. 21.5 ug/ml x hrs. 450 mg. 25.2 ug/ml x hrs.

This actually is a true reflection of

- The concentration at different hours and
- The time for which the concentration is maintained.

It can be seen from above table that there is "approximately 2/3rd increase in the exposure when the dose is increased from 150 mg. to 450 mg.

#### Clinical toxic manifestations of Thio-acetazone

The patients were clinically examined and questioned regarding the appearance of nausea, abdominal discomfort, anorexia, vomiting, diarrhoea, constipation, cutaneous hypersensitivity reaction and jaundice. Only 4 patients out of a total of 19 receiving 450 mg. of thioacetazone twice a week (group B<sub>2</sub>) demonstrated evidence of nausea, abdominal discomfort and anorexia following its ingestion.

#### S.G.O.T., S.G.P.T. and Serum Alkaline Phosphatase Levels

During 3 month's observation the serum levels of these enzymes were found to be within normal limits; although an occasional patient would exhibit minor rise in the level of

these enzymes. The rise noted, even in these cases, was considered to be of no clinical significance primarily because the levels were still within normal limits and the rise was not consistent.

#### Discussion

##### *Serum concentration of thio-acetazone*

Out of 24 patients of North Indian origin highest serum concentration of thio-acetazone was obtained in the 5th hour in group A and in the 6th and the 7th hours after the administration of the drug in Group B. These findings are in agreement with those obtained by Ellard, Dickenson, Gammon and Mitchison (1974). This is due to slow absorption of the drug from G.I. Tract, as evidenced in the delay of peak concentration and its simultaneous elimination from the serum.

##### *Peak serum thio-acetazone concentration*

Mean peak serum concentration (Mean of the highest concentration observed for 150 mg. group, 300 mg. group and 450 mg. group) worked out to 1.87 ug/ml., 2.47 ug/ml. and 2.92 ug/ml.

Geometric mean serum concentrations for the same doses of thio-acetazone have been shown in table 4. Thus it will be observed that increasing the dose of thioacetazone leads to a rise in the level of serum thioacetazone, though, the rise in the level is not mathematically proportional to the dose of the drug administered. Again, these findings are in agreement with those obtained by Ellard et al (1974).

##### *Exposure to thio-acetazone*

(As can be seen from table 7), this is probably the better index of the effect of thio-acetazone concentration on the bacilli in the lesions. It can be seen that there is about 2/3rd increase in the exposure when the dose is increased from 150 mg. to 450 mg. Although the increase in the exposure is much smaller than the increase in the dosage of thio-acetazone, one cannot rule out the possibility that a coverage of 25.2 units, will not be more effective than a coverage of 15.2 units in intermittent chemotherapy. One could also argue that even the coverage of 15.2 units might be adequate in intermittent chemotherapy. It is difficult to say which of the two is a correct picture. Only a controlled clinical trial of therapy in patients receiving the different dosages of thio-acetazone intermittently would resolve this question (Tripathi 1979).

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## B.C.G. TEST

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**Summary :** In our previous study, the value of B.C.G. as a diagnostic test vis-a-vis P.P.D. 1TU and 5 TU was studied and the former was found to be no superior. In the present study, a higher strength of 10 TU PPD RT 23 with Tween 80 has been compared with BCG.

The proportion of BCG Positives on the 5th day was found to be comparable to Tuberculin Positives on the 3rd day, the optimum level of induration size as an index of infection being 10 mm or more for both BCG and Tuberculin tests. The highest values of both Relative Sensitivity and Relative Specificity are 78.4 % and 73. %. Of the cases detected radiologically among the less than 20 year old subjects of the study, 25.71 % were non reactive to B.C.G. against only 8.5% being non reactive to 10 TU. the difference being statistically significant, four cases were bacillary and they were reactive to both BCG and PPD.

It is confirmed that the reaction to BCG approximates closely to that obtained with 5 and 10 TU of PPD RT 23 with Tween 30 and that BCG test is of no superior value.

### Introduction

The use of BCG as a diagnostic tool has been controversial. In our study reported earlier (Krishnaswami, K.V. et al, 1979) reactions obtained with BCG when given to already infected persons approximated closely to those with 5 TU PPD RT 23 with Tween 80. Thus the use of BCG for a diagnostic test has no superiority besides being scientifically unsustainable. In the present study, the results of BCG test have been compared with those to 10 TU PPD RT 23 with Tween 80. The study was carried out at the Institute of Tuberculosis and Chest Diseases, Madras, as a continuation of the previous study.

### Materials and Methods

283 persons were included in the study. None of the subjects showed evidence of gross malnutrition. 10 TU PPD RT 23 with Tween 80 was used for the tuberculin test and freeze dried BCG of the same batch as was used in the previous study was used for the BCG test. The persons who carried out the tests were also the same as in the previous study. The criteria for selection and procedures for the study were the same as in the previous study (Krishnaswami, K.V. et al, 1979). Briefly they were :

- a. New chest symptomatics irrespective of age;
- b. Without BCG Scar;
- c. From the feeder area of the Institute; and

- d. Co-operative and willing to attend daily for 7 days.

Persons with complications and concomitant diseases were excluded.

A proforma designed for this study was filled in for every one of the study subjects. All the details including the readings of different days were duly entered. Previous day's readings were not made available to the reader at the time of reading on any day to obviate any bias. The persons included in the study were subjected to radiological and bacteriological examinations. Such of those with positive evidence of disease were put on treatment after the assessments relating to the study. Although subjects of all ages were included in the study, analysis has been carried out separately for the 101 persons under 20 years in age, as in the previous study. Every subject was tested simultaneously with Tuberculin and BCG and the readings of the indurations were recorded as on the third day for Tuberculin and from the third day to the seventh day for BCG in a specially designed proforma individually.

### Results

Table I shows the high coverage of 87.3% achieved in this study. In the previous study also high coverages of 87% and 88.7% were achieved for 1 TU and 5 TU Tuberculin groups respectively.

With 10 TU PPD RT 23 with Tween 80 read on the third day for the 247 persons, the

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\* \* \* Statistician

**TABLE I**  
*Study Data*

Number tested	283
Incomplete data	36
Number analysed	247
Coverage	87.3%

degree of correlation was fairly high with BCG test on the 5th day, comparing the proportions of Tuberculin reactors showing 10 mm and more with the reactors to BCG test, as shown in Table II. It is also observed that the proportions of the third day tuberculin reactors do not approximate closely the BCG reactions read on different days.

**TABLE II**  
*Percentage Infected and Induration Levels*

		Induration Level (mm)			
		≥8	≥10	≥12	14+
PPD 10 TU	III Day	62.8	57.9	48.2	32.4
B.C.G.:	III Day	70.4	63.2	41.3	19.8
	IV Day	70.0	61.5	40.5	23.1
	V Day	65.2	58.7	35.6	20.6
	VI Day	58.3	49.0	28.7	11.3
	VII Day	51.8	42.5	22.3	9.3

Every day's readings of BCG reaction (3rd to 7th days) was duly correlated with the reactions of PPD RT 23 with Tween 80 on the 3rd day by drawing up five correlation tables and deriving the Correlation coefficients. These co-efficients are tabulated in Table III. From this it is seen that the best correlation exists between 10 TU PPD RT 23 with Tween 80 and BCG when the 3rd day's readings of the former (standard) are correlated with the 5th day's readings of the latter.

The findings of Tables II and III confirm

that BCG test should be read on the 5th day, the positive reaction size being 10 mm and more.

**TABLE III**  
*Correlation co-efficients between the 3rd day Tuberculin readings and SCC readings from 3rd to 1th days*

	Correlation Co-efficients
BCG III Day/PPD III Day	0.65
BCG IV Day/PPD III Day	0.67
BCG V Day/PPD III Day	0.72
BCG VI Day/PPD III Day	0.65
BCG VII Day/PPD III Day	0.62

In the previous study also it was observed

In Table IV the Relative Sensitivity and Relative Specificity of BCG and PPD 10 TU at different levels of induration for demarcating the infected were studied. The sizes of BCG and Tuberculin reactions giving the maximal approximation with the highest values for both Relative Sensitivity and Relative Specificity are 78.4% and 73.4% falling at the induration level of 10 mm and more on the 5th day BCG reading. This is indicative of the best level for demarcating the infected, viz., the reaction size of 10 mm and more reckoned as positivity for both Tuberculin and BCG.

In the previous study also the best approximations of Relative Sensitivity and Relative Specificity occurred at the induration level of 10 mm and more for both 1 TU and 5 TU Tuberculin; but this was so between the 6th day BCG reading and 1 TU Tuberculin and 5th day BCG reading at 5 TU Tuberculin, Tuberculin readings of the 3rd day having been taken as the basis in all the three different strengths—1TU, 5TU and 10TU—in both these studies

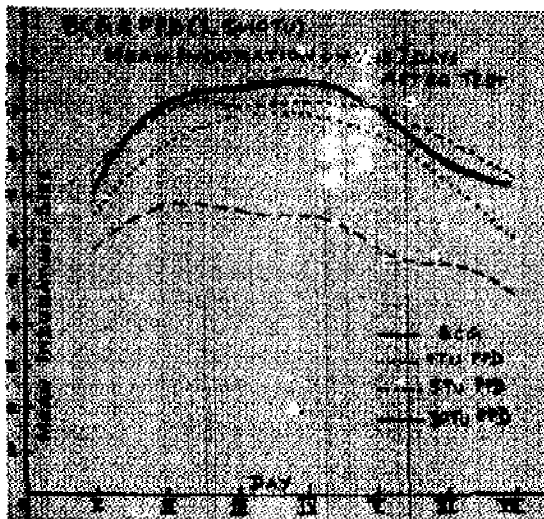
Projecting the mean induration sizes of

**TABLE IV**  
*Relative Sensitivity and Specificity*

		Induration Level (mm)			
		8	10	12	14
B.C.G. :	RS	91.6	85.3	58.7	29.4
	RSP	58.7	67.3	82.7	93.3
III Day	RS	90.1	81.5	55.6	33.1
	RSP	61.5	69.8	83.3	92.7
IV Day	RS	85.6	78.4	50.3	28.1
	RSP	68.1	73.4	88.3	91.5
V Day	RS	83.0	72.3	43.3	18.4
	RSP	74.5	82.1	90.6	98.1
VI	RS	81.1	69.7	37.7	16.4
	RSP	76.9	84.0	92.9	97.6

RS: Relative Sensitivity: Proportion of BCG reactors among Tuberculin reactors;  
RSP: Relative Specificity: Proportion of BCG-non-reactors among Tuberculin non-reactors.

BCG and the different strengths of PPD RT 23 with Tween 80 on the seven days after test on a graph (Fig. 1), it is observed that there is a close approximation between the BCG test and 10 TU Tuberculin test. The best approximation is again found on the 5th day.



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**TABLE V**  
*Comparison of reactions in under 20 years of age*

		B.C.G.			
		Reactors	Non-reactors	Total	
No.	%			No.	%
P	Reactors	42	5	47	46.5
P	Non-reactors	6	48	54	53.5
D	No.	48	53	101	
10	%	47.5	52.5		100.0

There is no statistically significant difference between the proportions of BCG reactors and

Tuberculin reactors. It is also observed that there is no significant difference between the proportions of BCG reactors among Tuberculin non-reactors and vice versa. These findings derived while comparing 10 TU PPD RT 23 with Tween 80 and BCG are similar to 5 TU strength of PPD RT 23 with Tween 80.

Table VI shows that out of 35 cases detected radiologically from among those under 20 years of age, a higher proportion proved to be non-reactors to BCG as compared to Tuberculin, the difference being statistically significant ( $P < 0.01$ ). In the previous study the proportion of non-reactors to BCG and 1 TU Tuberculin,

**TABLE VI**  
*Non-reactivity among cases detected (20 years of age)*

	Total Cases	Non-reactors	
		No.	%
B.C.G.	35	9	25.71
Tuberculin	35	3	8.50

among the cases detected radiologically was no different, but non-reactors proportion was higher (21.7%) for BCG than for 5 TU Tuberculin (8.7%), the difference being statistically significant ( $P < 0.01$ ).

Of the cases detected, 4 were bacillary and these reacted to both BCG and Tuberculin. In the previous study also it was observed that the 4 bacillary cases in the 1 TU group and 6 bacillary cases in the 5 TU group reacted to both BCG and Tuberculin.

### Discussion

Accelerated exaggerated reaction to BCG Vaccination of naturally infected persons is made use of as a diagnostic test (Ayer et al, 1973); Chandra, K, et al, 1977; and Shrivastava et al, 1977). Erythema, Induration, nodule formation, pustule, ulcer and scar are noticed as in the case of BCG vaccination of uninfected persons. The reaction starts within hours after vaccination and an ulcer 6 to 12 mm in size occurs within a week. However, the vaccination induration is more difficult to read than the tuberculin test mainly because the surrounding oedema is more extensive. The test was also evaluated in several studies (Egsmose, T. 1964; Gothi et al, 1974; Krishnaswami, K.V. et al, 1979).

Boonsong Sunakern and Azuma (WHO/TB/Tech. Inform/66-67) compared the BCG and Tuberculin test reactions at 72 hours and found the correlation not bad. Using a 9/10 mm criterion for the tuberculin reaction and 11/12 mm criterion for the BCG reaction the proportion of positives were 33.7% by tuberculin and 36.2% by BCG; of all examinees 8% would be Mantoux negative—BCG positive while 5.5% would be Mantoux positive and BCG Negative.

In our previous study, comparing the reaction size with 1 TU and 5 TU PPD RT 23 with Tween 80, 19% of tuberculin non-reactors with 5 TU on the 5th day and 23% of non-reactors with 1 TU were reactors to BCG test. Among BCG non-reactors 18% and 20% were tuberculin reactors in the two groups with 5 TU and 1 TU respectively.

In the present study, the relative sensitivity and specificity were 78.4% and 73.4% with 10 TU, with a reaction size of 10 mm and more, the best level to separate the infected and uninfected. Furthermore among the cases in the less than 20 year olds, while the non-reactors to BCG were more, the number was significantly low with 10 TU PPD RT 23 with Tween 80.

### Conclusion

The present study confirms that the reaction of BCG approximates closely to that obtained with a higher strength of 10 TU PPD RT 23 with Tween 80. In the previous study it was seen that the reaction of BCG approximates more closely with 5 TU PPD RT 23 with Tween 80 than with 1 TU PPD RT 23 with Tween 80. The approximation with 10 TU in the present study is found closer.

Besides being not a specific test, individual dose of BCG cannot be standardised as compared to PPD. The size of local reaction to BCG Vaccination, its complications and immunological response are dose dependent (WHO/TB/Tech. Guide/77-8). The results of our study show that BCG test cannot be considered as superior by any means to the standard time honoured tuberculin test with PPD.

### Acknowledgements

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## CASE REPORTS

### CHROMOPHOBIC MYCOBACTERIAL MENINGITIS

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**Summary** : Two cases of clinically diagnosed tubercular meningitis, from the C.S.F of which Mycobacteria were cultured are reported- These isolates could be stained only by the modified method and not by the standard Ziehl-Neelsen technique. These chromophobic mycobactena were identified as belonging to Avium-Intracellulare complex.

#### Introduction

In the clinically diagnosed cases of tubercular meningitis, the percentage actually confirmed by the bacteriological methods varies from author to author (Riley 1953; Koshy, Benjamin and Janaky 1955; Khatua 1961; Suri, Chakravorthy and Sharma 1959; Joishy and Sant 1969; Dalai and Gholkar 1977). Because of the chromophobic nature of some isolates, quite a few cases are likely to be missed and diagnosed as "aseptic meningitis", unless one is aware of the existence of this chromophobic phenotype. In such cases, modified staining methods must be used to demonstrate the etiological agent.

#### Material and Methods

##### Case I :

A one year old girl, whose father was under treatment for pulmonary tuberculosis for the past one year, was admitted in a drowsy condition. She had a history of diarrhoea of two month's duration, controlled by treatment. About a week before admission, she became drowsy and had four to five convulsions. At the time of admission, this marasmic child had her fontanellae full and tense and was responding only to deep sensations. She survived only for 3 days. A postmortem examination was conducted. According to the Pathologist, "the brain was congested and the mesenteric and tracheal nodes showed tuberculosis". The other anatomical findings like the consolidation of lung and caseation of the lymph nodes led them to conclude that it was a case of tuberculosis of lung and lymph nodes.

However, no acid fast bacilli were demon-

strated in any of the tissues. Ante-mortem and postmortem specimens of C.S.F. were sent to the bacteriological laboratory for culture and sensitivity tests.

##### Case II :

An eight year old boy, with a history of chronic ear discharge of five year's duration and recurrent attacks of cyclic vomiting for the past three years, was admitted to rule out any intracranial pathology, urinary tract infection etc. After a barium meal and gastroscopic examination, a tentative diagnosis of "recurrent vomiting secondary to duodenitis with chronic suppurative otitis media" was made. A positive clinical finding was the palpable bilateral post cervical and apical lymph nodes. No biopsy was done. Haematological, biochemical and other parameters were within normal limits. CSF was sent for culture and sensitivity.

#### Investigations and Results

The results of other investigations, apart from CSF, are equivocal and do not contribute much towards diagnosis. These are, therefore not mentioned in this article.

CSF was aseptically collected in both cases. From case one, 2 samples—antemortem (5 ml) and postmortem (10 ml), and 3 ml from Case II were received. All the samples were clear. 2 ml quantity of the CSF from each specimen was spun down at 3,000 r.p.m. for 20 minutes. The deposit was used for preparation of smears and for culture.

The CSF deposits were stained by Gram's method. No organisms were made out. For acid fast staining, the smears were made as

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follows. One loopful of the deposit was placed on slide dried by using a hot air blower. On the same spot another drop of the same deposit was placed and dried as before and this was repeated a third time. This dried smear was then fixed by heat and stained by conventional Ziehl Neelsen method. No acid fast bacilli were seen.

These deposits were cultured individually on paired Lowenstein Jensen media and incubated at 37°C. Growth was observed in all after 15-18 days. Smears from these, when stained by the standard or conventional Ziehl Neelsen method did not reveal any acid fast bacilli. But when stained by the modified Nyka's method (Nyka 1967), the same isolates showed acid fast bacilli.

#### *Nyka's method of staining Chromophobic mycobacteria*

The air dried and flamed films were left overnight in a paraffin oven at 60°C to secure good adhesion of the organisms. The slides were then oxidised in 10% solution of per iodidic acid for 4 to 24 hours according to the intensity of staining desired. They were rinsed first in tap water and then in distilled water. The slides were placed in troughs Jilled with carbol fuchsin prepared as follows: basic fuchsin, 1 c.; absolute alcohol, 10 ml; distilled water 100 ml. phenol 5.6 ml. The troughs were put in the slide drier for 30 minutes at about 70°C. Then the fuchsin was discarded; slides were next rinsed in tap water, and were decolorised in three changes of acid alcohol prepared as follows: alcohol (70%), 100 ml; lactic acid, 2 ml. Finally, they were rinsed in water, dried and examined without counter staining. After this treatment, bacilli appeared homogenously dark red or deep purple (Figures 1 and 2).

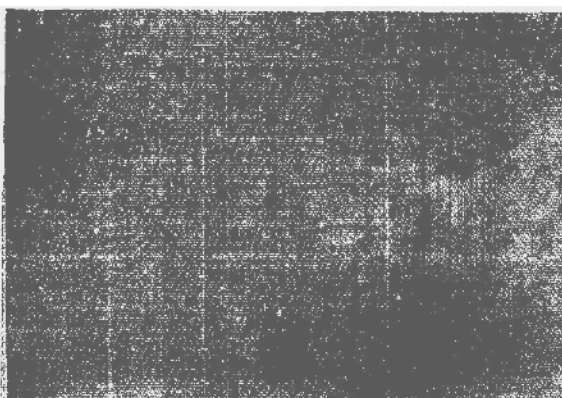


Fig. 1. Micro photo graph showing absence of acid fast bacilli in the growth from Lowenstein Jensen medium stained by conventional Z-N. method (10—100).

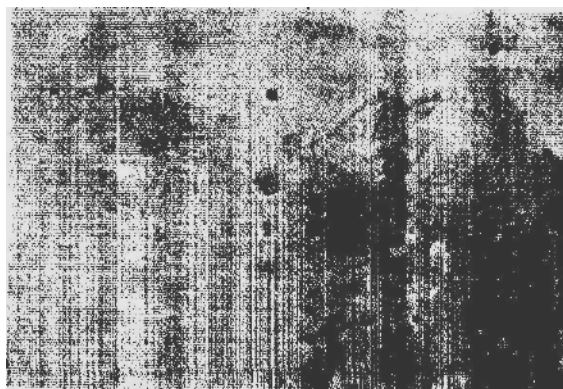


Fig. 2. Microphotograph showing AFB when growth from the same was stained by Nyka's method (10—100).

These isolates were identified as belonging to Avium-intracellulare complex. Method followed was that described by Allen and Baker (1968) and Barksdale and Kim (1977).

#### Discussion

The acid fastness is not peculiar to only Mycobacteria but is also seen in the staining of certain spores, like that of bacillus cereus and fungal spores, embryophores of Taenia and even Corynebacteria (Barksdale and Kim 1977). This property is attributed to the stable complexes formed with certain arylmethane dyes and the biological products responsible in each case varies. Again, this capacity for acid fastness can be removed from various acid fast bacteria e.g. Mycobacteria by treatment with alkaline methanol (loc. cit).

The non-acid fastness i.e. chromophobic property in Mycobacteria may depend on the stage of growth, as often seen in a large proportion of rapidly growing population or it may be a chromophobic phenotype (loc. cit). This probably explains why in so many clinically suspected cases of Mycobacterial infection, the acid fast bacteria cannot be demonstrated.

Two such cases have been reported. In one, a clinical diagnosis of tubercular meningitis was made ante-mortem and confirmed by anatomical findings at post-mortem. In the other, the diagnosis was missed. In both cases, the etiologic agent was isolated and identified from the CSF. The organisms were not demonstrated histopathologically.

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## HYPERSENSITIVITY TO MULTIPLE DRUGS IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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**Summary** ; Eight cases of pulmonary tuberculosis developed hypersensitivity reactions to various anti-tubercular drugs. The offending drug has been established on the basis of disappearance of clinical symptoms on withdrawal of the particular drug and on the basis of "light switch phenomenon" i.e. reappearance of symptoms on challenge with the drug again.

Hypersensitivity reactions are often seen during the long course of treatment of tuberculosis. The incidence of allergy, as reported by Govind Raj and Grant (1968), has varied from 1 % to almost 24%. It is felt that incidence of such reactions is now higher than before. It is uncommon to record allergic reactions to more than one anti-tubercular drugs while a fair number of those who have such reactions to more than one drug, are allergic, commonly to Thiacetazone (TH), Streptomycin (SM) and P.A.S. (Smith and Zirk 1961; Govind Raj and Grant 1968).

Eight cases are presented in whom variety of allergic reactions have been recorded during the course of their treatment of pulmonary tuberculosis have been analysed. Cases No. 1 and 3 being illustrative have been described in detail as under :

### *Case No. 1:*

S.L., a young boy of 15 years, was admitted on 17.7.71 as a case of extensive bilateral pulmonary tuberculosis with very poor general condition. His sputum was positive for A.F.B. and skiagram chest showed extensive bilateral disease.

He was put on SM (0.75 gm), INK (300 mg) and TH (150 mg) daily. There was no history of antitubercular treatment earlier and also no history of drug allergy in the patient and among his family members.

On 17.8.71 patient started having itching and mild rashes all over the body. All the drugs were immediately stopped and anti-histaminics were administered. The symptom disappeared within two days. Then a test dose of TH and INH was given on 28.8.71 which caused reappearance of itching and rashes as before. TH was stopped immediately thinking it to be the commonest causative agent and INH was continued. SM was not tried again as the patient refused to take injections. Ethambutol (600 mg) was added on 6.9.71 and patient was sent home on 21.9.71 to continue treatment at home.

Patient was re-admitted on 24.5.72 with poor general condition, as he discontinued treatment at home. His sputum was positive for AFB. He was put on INH (300 mg) Ethambutol (600 mg) and Pyrazinamide (PZA 1.5 gm) daily which caused improvement in his general condition and he was discharged from the hospital on 18.4.73 to continue the same drugs at home.

Again for the third time, he was admitted on 6.9.73 with generalised pruritis and skin rashes. All the drugs were stopped and with anti-histaminics alone his symptoms improved within ten days. Since his sputum was positive for AFB and skiagram chest showed no radiological improvement, he was again put on INH 300 mg (first day) Ethambutol 600 mg (second day) and PZA 1.5 gm (third day); on the third day, he developed itching and rashes again, hence PZA was discontinued.

He showed little improvement with INH and Ethambutol. Since he could not afford to continue Ethambutol at home, he was discharged from the hospital on INH alone as a desperate case and he never came back thereafter.

### *Case No. 3:*

A.S., 35 years, Hindu male was re-admitted on 13.8.76 as an old case of pulmonary tuberculosis with the complaints of severe itching, breathlessness and maculo-papular rashes all over the body for 2-3 days. He was taking Ethambutol (800 mg daily) and Ethionamide (500 mg daily) for about 3 months and his sputum was positive for A.F.B.

On his first admission in May 1976, he had revealed that for the previous 3 years he had been treated at various places in the district with primary drugs (SM, INH, PAS and TH). The patient was now put on second line drugs (Ethambutol and Ethionamide). He had shown improvement and was discharged after a month's stay in the hospital to continue the same at home.

He had no history of allergic symptoms to

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TABLE I

Cases	Names	Anti-T.B. Drugs administered	Drugs causing hyper-sensitivity reactions	Hyper-sensitivity reactions encountered
No. 1	S.L.	S.M., INH, TH Ethambutol, PZA	TH & PZA	Itching and mild rashes
No. 2	S.P.	SM, INH, TH, PAS	TH, SM, PAS	S.J. Syndrome, giddiness
No. 3	A.S.	SM, INH, PAS, TH, Ethambutol Pyrazinamide (PZA) & Cycloserine	Ethambutol, PZA & Cycloserine	Severe itching, maculo-papular rash, breathlessness, palpitation & uneasiness
No. 4	S.R.	SM, INH, TH & PAS	SM & TH	Severe itching, skin rash and giddiness
No. 5	Rawat	SM, INH, TH	TH & SM	S.J. Syndrome
No. 6	B.L.	SM, INH, TH, Ethambutol & Ethionamide	SM & TH	S.J. Syndrome
No. 7	K.R.	SM, INH, PAS, TH, Ethambutol, Ethionamide and PZA	INH, SM, PZA	S.J. Syndrome
No. 8	K.K.	SM, INH, TH, Ethionamide	SM & TH	Generalised itching

any drug earlier and there was no history of allergy in any of his family members. All the drugs were stopped and he was put on anti-histaminics (Injection Avil 25 mg, twice a day and Prednisolone 10 mg, every six hours) for 5 days. All his symptoms disappeared gradually.

On 28.8.76 he was orally given a test dose of Ethambutol (100 mg) which caused itching within an hour of administration, so much so that he had to be given anti-histaminics and so this was finally stopped. When he became symptomless, he was put on INH 300 mg. (first day), PZA 1.5 gm. (second day) and Cycloserine 500 mg. (third day). Patient started having palpitation and uneasiness on the third day. Thorough cardiac check up was done immediately which did not reveal any abnormality hence Cycloserine was discontinued and the patient felt better. Next day, Ethionamide 500 mg was added which he tolerated well. He was then discharged from the hospital on 30.9.76 to continue INH, PZA and Ethionamide at home.

On 8.2.77 (third admission), he was readmitted with complaints of severe itching, fever and dyspnoea. He also had mild rashes

all over the body. Again all the drugs were stopped and he was put on anti-histaminics and cortisone with which his symptoms disappeared within seven days. As a test dose, half tablet of PZA (250 mg) was given on 16.2.77 and after half an hour patient started having generalised itching all over the body, hence antihistaminic was given and the drug was dropped. Thereafter, treatment was continued with only INH 400 mg and Ethionamide 500 mg. daily which suited him and patient was then discharged to continue the same at home.

### Discussion

It is not always easy to prove that a particular drug is causing hypersensitivity reaction. The sequence of events after administration and abatement of reaction following its withdrawal, provides adequate evidence. A second reaction following challenge with all the previously used drugs one by one eliciting 'Light switch phenomenon' provides more convincing proof. (Bianchine, et al., 1968).

It is not very unusual to have reactions to more than one anti-tubercular drug but multiple

reactions of such diversity, in a single individual are of rare occurrence. One patient who developed reaction to SM, TH, PAS, INH and Cycloserine was reported by Govind Raj (1968). In his case SM produced ataxia and partial deafness, TH caused agranulocytosis, fever and rashes and cycloserine accounted for marked confusion. With prednisolone and desensitization to PAS and INH, chemotherapy could be carried out. Mittal, et al, (1976) have reported 3 cases, the first produced hyper-sensitivity reactions to SM, PAS TH and Ethionamide; second to SM, INH, PAS, TH, PZA Cycloserine and Ethionamide and third to SM, PAS, TH, PZA and Ethionamide. Mathur et al (1979) have recently reported two cases showing hypersensitivity reactions to SM, PAS TH in the first case and to Ethionamide and PZA in addition to SM, PAS and TH in the second case.

In most of our cases, generalized itching, skin rashes and S.J. Syndrome in its typical form which are of common occurrence with the administration of TH, and SM have been encountered. There was evidence of skin rash and generalised pruritus being produced by Ethambutol in only one case (Case No. 3) and PZA in three cases (Case Nos. 1, 3 and 7). Ethambutol is known to produce rashes rarely as described by Andred Growth (1978) and PZA can also occasionally cause hypersensitivity reactions such as fever, rash and other cutaneous reactions as reported in a controlled trial conducted by Hong Kong Chest Service and the British Medical Research Council, 1977.

Palpitation and uneasiness have been attributed to cycloserine (case No. 3) which has not been documented in the literature. Hence in this case thorough cardiac check up including E.C.G. was performed which did not reveal any abnormality.

It may also be pointed out that similar hypersensitivity reactions like itching and cutaneous lesions were also produced by Procaine penicillin and Liver Extract (in case No. 6) and by Procaine penicillin alone, (in case No. 8). Hence it must be kept in mind before attributing these reactions to anti-TB drugs if the former too are being used simultaneously with the latter.

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## TUBERCULOMA OF THE LARYNX IN MILIARY TUBERCULOSIS

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**Summary** - Laryngeal tuberculosis may be a presenting feature in miliary tuberculosis. The case presented with a growth-like laryngeal lesion having no other symptoms, and radiological examination showed miliary mottling in the chest. Laryngeal lesion was also proved to be tuberculous on histological examination. Both the lesions disappeared within three months of starting anti-tuberculous chemotherapy. Relevant literature concerning this unusual presentation is discussed briefly.

An extensive ulcerative lesion of the larynx as the presenting feature of miliary tuberculosis is very unusual, with only a few cases having been reported (Morrison, 1948; Myerson, 1944 and Rohwedder, 1974). Bid! (1968) described some unusual features including growth-like lesion of laryngeal tuberculosis, but these were not associated with miliary tuberculosis. A case of growth-like tuberculous laryngeal lesion with miliary tuberculosis is presented.

### Case Report

A 50-year old man was admitted to the E.N.T. unit of P.B.M. Hospital, Bikaner, with complaint of hoarseness of voice for last six months. He had been feeling breathless on walking and even with slight work. Shortly before admission, he noticed loss of weight and appetite, associated with cough, scanty sputum but "no haemoptysis. Cough was attributed to smoking.

On examination, he was afebrile with no evidence of anaemia. Enlarged lymph nodes were felt in the anterior triangle of left side of the neck which were non-tender, scattered and soft in consistency. Examination of the larynx revealed an extensive proliferative irregular growth affecting the left vocal cord, false cord, aryepiglottic fold and arytenoid. The contralateral side of the larynx was normal. The epiglottis was somewhat oedematous. The examination of the ear, nose and throat revealed nothing abnormal. A clinical diagnosis of laryngeal carcinoma was made.

Routine blood and urine investigations were normal except E.S.R. (50 mm 1st hour: Westergren). V.D.R.L. was non-reactive. Skiagram of the soft tissue of the larynx (lateral view) showed an evidence of growth involving the laryngeal structures (Fig. 1). X-ray chest revealed miliary mottling throughout lung fields. The smear examination from the laryngeal lesion was negative for A.F.B. as was the estimation of the sputum. Fundus examination was nor-

mal. Biopsy of the laryngeal lesion showed evidence of tuberculosis.



Fig. 1. X-ray of the soft tissue neck (Lateral view) showing soft tissue mass causing laryngeal structures.

He was treated with Streptomycin 1 gm, intramuscularly, and Isoniazid 300 mg in daily doses. After 3 months of the prescribed treatment, the laryngeal lesion healed and the miliary mottling disappeared. He was advised to continue anti-tuberculous therapy from the tuberculosis and chest diseases unit.

### Discussion

With the introduction of modern chemotherapeutic agents, the incidence of upper respiratory tract tuberculosis has diminished dramatically, but its unusual presentation has become relatively more common (Bull, 1966; Nedwick, 1970 and Rohwedder, 1974). Mukherjee (1977) discussed the salient features of laryngeal tuberculosis and he reported a case of growth-like lesion (tuberculoma) of the larynx. The present case also revealed characteristic features of a growth, clinically and radiologically, but on biopsy he was diagnosed as tuberculous. Morse (1974) presumed a similar-looking laryngeal lesion to be tuberculous in

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basis of its association with pulmonary tuberculosis. But when the laryngeal lesion was found to be increased inspite of anti-tubercular therapy, biopsy was done and the histological examination proved it to be a Carcinoma. Jackson and Jackson (1945) reported an association of tuberculosis and carcinoma in a solitary laryngeal lesion. Thus biopsy from the lesion is essential for final diagnosis.

Tuberculous involvement of the larynx is usually secondary to pulmonary tuberculosis either as a direct inoculation or rarely as a result of haematogenous spread. In the present case six month's history of laryngeal symptoms leading to the diagnosis of miliary tuberculosis may seem to indicate the primary nature of the laryngeal lesion. In fact, a primary complex in the larynx has not been described, so the laryngeal lesion in the present case seems to be post-primary. There are two possibilities for such lesions. Firstly, it might be possible that the patient had primary complex in childhood and now developed a post-primary lesion in the larynx. Secondly, there may be an unrecognised primary focus somewhere which gave rise to secondary spread in the larynx and the lungs.

We, however, feel that the laryngeal lesion was of re-infection type and developed six months preceding the symptoms of miliary tuberculosis. Such a sequence seems to be rare, but possible (Mcandrew et al, 1976; and Soni & Chatterji, 1979).

This case is a warning that a growth-like lesion in the upper respiratory tract could be tuberculous in origin and, therefore, efforts should be made to locate an active or inactive lesion elsewhere in the body. Further, the lesion in the upper respiratory tract may be present

even in the absence of a recognisable lung lesion or may even precede the latter.

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## PYRAZINAMIDE INDUCED ARIBRALGU WFTH HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

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**Summary** : A case of Empyeme with hypertrophic pulmonary osteo arthropathy is described, who in addition developed arthralgia. probably due to Pyrazinamide.

A twenty years old male patient was admitted with pain, swelling and restriction of movement of all the joints except shoulder, hip, costo-vertebral and costo-chondral which was gradually progressive since six months.

Patient gave history of having developed pulmonary tuberculosis 3 years back for which he had taken Streptomycin 4. Isonex -f PAS treatment for 6 months. Two years back, he developed tuberculous empyema which was treated with Isoniazid, Pyrazinamide and Ethambutol for 2 years; intercostal drainage tube was put to drain out the empyema.

On clinical examination there were findings of thickened pleura of right hemithorax with pus draining from the intercostal drainage tube. Examination of bones and joints, showed the distal ends of Radius, Ulna, (Wrist) Humerus (Elbow), Femur (Knee), Tibia and Fibula (Ankle) were thickened on palpation and were tender. The knee joints were swollen, tender and there was restriction of movement, left more than right. Free fluid was present in the left knee joint and was demonstrated by positive patellar tap. All the other joints showed mild swelling, tenderness and restriction of movement more in the distal joints like inter-phalangeal meta-carpo-phalangeal wrist and ankle. There was 4th degree clubbing.

### Investigations

1. Sputum was negative for A.F.B. by direct microscopy & culture.
2. Blood sugar was. within normal limits.
3. Serum uric acid was high i.e. 8.4 mgs% (before starting Allopurinol)
4. Chest X-ray showed thickened pleura on right side & fibrotic lesion right-upperzone.
5. X-ray of feet, hands and knee showed marked tufting of the terminal phalanges, marked sub-periosteal new bone formation.
6. Culture swab of pus from discharging sinus showed strepto-cocci, staphylococci & Proteus mirabilis organisms.

7. Pus was also sent for A. F. B. culture which turned out to be Negative.

Alk PO4 are	18.3KAU	(N 3—B KAU) (N
Acid PO4 are	1.6 KAU	1—3 KAU) (N9-11
Calcium	10.6Mg%	MG%) (N2-
Phosphates	2.7 Mg%	8.4 MG% 4.5MG%) (2-4
Uric Acid	8.4 MG%	1.0MG% MG%) (N. 7-
Creatinine	1.0MG%	1.5MG%)

Patient was treated with Rifampicin, Isoniazid and Cycloserine. For secondary infection he was put on Ampicillm 2 gm. daily. He was also put on anti-goutic agent Allopurinol 300 mgm. per day in divided doses. After the treatment there was no restriction of movement, no tenderness and the fluid in the knee joint had reduced, but the thickening remained the same. Subsequent X-Rays of the limbs showed persistence of sub-periosteal new bone formation. The serum uric acid level came down to normal after treatment. Since the tenderness was relieved with Allopurinol it may have been due to Pyrazinamide Hyperuricaemia. Clubbing of 4th degree, restriction of movement and sub-periosteal bone formation support the diagnosis of Hypertrophic Osteoarthropathy.

### Discussion

Secondary Hypertrophic Osteoarthropathy refers to the association of manifestations of Hypertrophic Osteoarthropathy and an internal disorder. Clubbing is a regular feature. When the internal disorder is in the lungs, the designation Hypertrophic Pulmonary Osteoarthropathy is used (Fishman, 1980).

The syndrome of secondary Hypertrophic Osteoarthropathy includes:

- (1) Bilateral subperiosteal new bone formation involving the distal diaphysis of long bones (Baldwin, 1959, Camp & Scartan, 1948, Fishman 1980).
- (2) Clubbed Digits.
- (3) Increased thickness of upper and lower extremities specially in the distal 1/3 of the leg, where the Osteoarthropathy evokes painful swelling that is warm and non-pitting (Fishman, 1980).

(4) Articular signs & symptoms including arthralgia, stiffness, joint swelling and effusion. The diagnosis is suggested by the symmetrical localization of pain to the distal bones, particularly if the fingers are clubbed.

Confirmation rests on the radiographic demonstration of subperiosteal formation of new bone. (Baldwin, 1959, Camp & Scanton, 1948, Keats, 1954). Radionuclide scanning with <sup>99</sup>mTc phosphate sometimes will suggest the diagnosis. (Rosenthal, 1976).

Secondary Hypertrophic Osteoarthropathy is often confused with Rheumatoid Arthritis. Besides R A the differential diagnosis includes Syphilis, Thyroid Achropachy and Pachydermo-periostosis (Fishman, 1980).

Hypertrophic Osteoarthropathy that is localized solely to lower extremities sometimes accompanies the clubbing and cyanosis caused by Right to Left Shunt by patient Ductus arteriosus. It occasionally develops when an abdominal aortic prosthesis becomes infected. (King, 1972) The most common disorder that underlines secondary Hypertrophic Osteoarthropathy is Bronchogenic Carcinoma (Fishman, 1980).

Malignant chest tumors account for 90% of Typical Hypertrophic Pulmonary Osteoarthropathy. Majority of these are metastatic (Carlotta, Fogelde & Bantan, 1958; Charles, 1960; Youcoub, 1965). Pulmonary tuberculosis is rarely, if ever, associated with Hypertrophic Osteoarthropathy (Skorneck & Ginsburg, 1958).

Clinically there was no evidence of thyrotoxicosis, Syphilis, congenital or acquired, (V.D. R.L. was negative) no skin changes of dermo-periosteitis and there was no evidence of primary pulmonary/pleural malignancy or naso-pharyngeal carcinoma. Hence we feel that this is a case of Hypertrophic Pulmonary Osteoarthro-

pathy due to long-standing empyema. In conclusion we would like to say that long standing pulmonary/pleural infection has resulted in Hypertrophic Osteoarthropathy and this had no relationship to arthralgia which, probably, was due to Pyrazinamide and disappeared when Pyrazinamide was withdrawn and Allopurinol was administered.

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# INTRACTABLE VOMITING FOLLOWING STREPTOMYCIN

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**Summary :** A case of intractable vomiting due to streptomycin administration is reported.

## Introduction

Vertigo, tinnitus, ataxia and loss of balance are common ototoxic effects of streptomycin. Vomiting induced by streptomycin is a rare phenomenon but has been described by Biswas, S.K.. (1965). A case is reported where vomiting was intractable.

## History

A.R., 30 years, male was admitted with the complaints of pyrexia, cough with expectoration, pain in chest and anorexia for the last 4 months. He also complained of inability to walk, vertigo of five days, duration and intractable vomiting for a day prior to admission in the hospital. The vomiting was projectile in nature consisting of gastric contents tinged with the bile eight to ten times per day.

There was no history of pain in abdomen and food poisoning. Past history was not contributory. Drug history revealed that the patient was treated with streptomycin, isonex and ethambutol by a general medical practitioner for a period of 5 days prior to his admission in hospital.

## Examination

On general physical examination, he was looking ill and found to be of normal build. There was no lymphadenopathy, cyanosis or dyspnoea. Pulse 82/mt; B.P. 100/70 mm of Hg, Resp. 20/mt. Examination of respiratory system revealed findings suggestive of tuberculosis lesions in upper zones of both lungs. Other systems showed no abnormality.

## Investigations

1. Laboratory investigations revealed haemoglobin 70 per cent, total red blood cells count 3.29 million/c.m.m., total leukocytes count 11800/c mm, with polymorphs 83 per cent, lymphocytes 12 per cent, monocytes 5 per cent. There were no eosinophils, basophils and immature cells. F.S.R. was 48 mm 1st hour (by Wintrob's Method).

2. Sputum examination revealed acid fast bacilli and gram positive organisms with pus cells and occasional epithelial cells.
3. Complete C.S.F. examination and Urine analysis revealed no abnormality.
4. Liver function test, barium meal and ophthalmic examination done later, revealed normal findings.
5. Blood Chemistry :- Fasting Blood Sugar 74 mg. percent, Blood Urea 26 mg per cent, Serum Calcium 11.6 mg per cent, Serum Amylase 180 units, S.G.O.T. 13, I.U., S.G.P.T. 14 I.U.
6. X-ray Chest P.A. view showed evidence of bilateral pulmonary tuberculosis involving both upper zones.

## Management

At the time of admission patient was put on injection streptomycin, Tablet Isonex, Marzine, Antacid with oral fluids for a period of three days but without any improvement. On fourth day all oral drugs and fluids were stopped and Injection streptomycin and antiemetics were administered parenterally. This too could not give any relief. All anti-tubercular drugs were omitted from the regime and only parenteral fluids and antiemetics were administered. This resulted in the cessation of vomiting.

After three days of complete amelioration of vomiting, Isonex was added in a dose of 100 mg and increased gradually to 300 mg per day. There was no untoward effect.

On the tenth day of subjective improvement Injection streptomycin 0.25 gm. I.M. was given with Isonex and patient complained of mild uneasiness. Next day the dose of streptomycin was raised to 0.5 gm and patient developed nausea and vomiting. Considering streptomycin as an offending agent the regime was modified and the patient was put on Ethambutol 800 mg and Isonex 300 mg per day. Patient tolerated

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## INTRACTABLE VOMITING FOLLOWING STREPTOMYCIN

Ethambutol and Isonex very well and there was no nausea and vomiting.

### Discussion

The patient was on anti-tubercular drugs viz. streptomycin, Isonex and Ethambutol for a period of 5 days and then developed nausea, vomiting, vertigo and inability to walk independently. All the probable causes of vomiting were excluded by clinical examination and laboratory investigations. Amelioration and recurrence of vomiting coincided with discontinuation and read ministration respectively of streptomycin and this confirmed the above contention. The patient was kept on adequate parenteral fluids and antiemetics which resulted in improvement.

Some of the drugs like P.A.S., Thiacetazone and Ethionamide and known to cause nausea and vomiting but none of these was used in this case. Purohitetal 1976 claimed that streptomycin toxicity (vestibular) could be relieved by giving I.V. fluids alongwith diuretics but different procedure has to be followed for vomiting due to Streptomycin.

A number of investigations like barium

meal study, C.S.F. examination, could be avoided in such cases, provided the possibility of intractable vomiting induced by streptomycin administration is kept in view.

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*Editor*

## NEWS AND NOTES

### ANNUAL GENERAL MEETING

The Fortysecond Annual General Meeting of the Tuberculosis Association of India was held on Tuesday, the 21st of April, 1981 in the Conference Hall of the Association, 3, Red Cross Road, New Delhi,

Shri S. Ranganathan, ICS (Retd.), President of the Association, presided. Dr. I.D. Bajaj, Director-General of Health Services and Chairman of the Association presented the Report of the Association for the year 1980 and Shri S. Ratnam, the Honorary Treasurer, presented the audited accounts for 1980.

While presenting the Report of the Association, Dr. I.D. Bajaj stressed the importance of voluntary work in dealing with a serious problem like tuberculosis and said that though TB control is primarily the responsibility of the Government, voluntary bodies too had a significant role to play in the planning and shaping of the programme and, above all, in involving the community in implementing it. Reviewing the progress made towards the control of tuberculosis he observed that there had been spectacular and revolutionary advances in the management of tuberculosis as a result of which tuberculosis had become both curable as well as preventable. He appealed to the State Associations to implement the various recommendations of the Technical and Research Committees and of the Secretarie's Conference and to redouble their efforts to involve the community much more than at present in the campaign against tuberculosis. What is of utmost importance today, Dr. I.D. Bajaj said, is that T.B. Associations must step up their activities with a view to become active and equal partners with Government in the implementation of the "National Programme.

Shri S. Ranganathan, President of the Association, while addressing the meeting said that "any money invested in the control of tuberculosis would be worthwhile in the long run in the shape of better health of the community, less man-hours of work lost and therefore increased production". Describing tuberculosis as a 'multifactoral phenomenon' Shri Ranganathan said that the problem was influenced not only by available diagnostic and treatment facilities but also by socio-economic conditions. He regretted that the National TB Control Programme introduced two decades ago had yet to cover as many as seventy districts in the country. Even in the areas where it had been in operation

the results were far below what was expected mainly because what should have been everybody's responsibility had really become no one's responsibility. He felt that unless the National Programme is centrally sponsored with 100% Central subsidy, it will take a long time to cover the entire country,

Shri Ranganathan reiterated the need for a second National Sample Survey to determine the epidemiological status of tuberculosis in the country and expressed the hope that necessary funds will soon be made available by the Government for the purpose. Referring to the controversy regarding the role of BCG in the overall control of tuberculosis, he advocated another study to determine the protective effect of BCG vaccination in children in the vulnerable age group in respect of all manifestations of tuberculosis. He hoped that International assistance will be forthcoming for this trial as this problem concerns the whole world.

The Meeting terminated with a Vote of Thanks proposed by Dr. D. Umapathy Rao,

### TECHNICAL COMMITTEE

A meeting of the Technical Committee of the Association was held on 20th April, 1981 with Dr. G.D. Gothi, Director, New Delhi TB Centre, in the Chair. The meeting was attended by Dr. I.D. Bajaj, Director-General of Health Services and Chairman of the Tuberculosis Association of India, Dr. M.S. Chadha, Vice-Chairman of the Association, members of the Committee and other senior specialists in the tuberculosis field. Some of the important recommendations made by the Committee at this meeting are :-

(1) The second national sample survey on prevalence of tuberculosis in the country should be carried out as early as possible. The survey should be representative of as large a part of the country as possible.

(2) Since tuberculosis is known to be a self-limiting and self-healing disease, a study is essential to determine the host factors involved in the evolution of disease.

(3) Notification of all tuberculous cases, but more particularly direct smear positive cases, should be mandatory throughout the country.

(4) Tuberculosis control programme should be a centrally sponsored scheme with 100%

financial subsidy as it used to be before the 5th five year plan.

(5) The production of anti-tuberculous drugs should be stepped up to the licensed capacity of the manufacturers. No anti-tuberculous drugs should be exported till the entire requirements of the country have been met.

(6) In view of the frequent shortage of 70 mm x-ray films in the country, steps may be taken to produce the films in the country itself like the conventional size x-ray films. Till such time as the country can produce its entire requirements, regular import of 70 mm films in sufficient quantity to meet the country's requirements should be allowed.

(7) A study should be carried out to determine the protective value of BCG in children in respect of *all* manifestations of tuberculosis, including those abacillary manifestations which arise soon after primary infection and which were not studied in the Chingleput trial.

(8) Short refresher courses in tuberculosis should be arranged for general practitioners all over the country in such a way that the courses do not clash with their work. The courses must be free of charge.

(9) Government may be requested to step-up publicity against smoking, ban smoking in public places and advertisements about cigarettes, etc. in addition to prohibitive taxation on tobacco products.

The Committee discussed the programme drawn up by the Local Advisory Committee for observing the Centenary of the Discovery of Tubercle Bacillus in 1982 and the steps to be taken for the effective delivery of tuberculosis services as an integral part of primary health care and resolved that these may be finalised by the Advisory Committee in the light of the views expressed at the Secretaries' Conference.

The Committee, also noted that seven TB centres, namely, at Trivandrum, Nagpur, Bombay, Cuttack, Patna, Lucknow and Jammu have offered to participate in the cooperative short term intermittent chemotherapy trial.

The Committee noted with regret the recent decision of the Medical Council of India to split Tuberculosis and Chest Diseases into two different specialities for purposes of Post-Graduate Medical Courses and resolved that the Tuberculosis Association of India should write to the Medical Council of India protesting against the unilateral decision of the Council in this regard.

## SECRETARIES' CONFERENCE

The 32nd Conference of Secretaries of State TB Associations was held in New Delhi on Tuesday the 21st April, 1981. Dr. M.S. Chadha, Vice-Chairman, Tuberculosis Association of India, presided. The Conference was attended by Dr. I.D. Bajaj, Director-General of Health Services and Chairman of the Association, representatives from Assam, Meghalaya, Bengal, Bihar, Delhi, Gujarat, Kerala, Madhya Pradesh, Maharashtra, Orissa, Tamil Nadu, Tripura and Uttar Pradesh, members of the Technical Committee and other invitees. Dr. Bajaj in his address emphasised the importance of voluntary work in dealing with a serious problem like tuberculosis and said that efforts to control this disease can succeed only if there is full participation of the community in implementing these. The Conference reviewed the activities of State Associations, with special reference to the TB Seal Campaign, considered the steps to be taken to bring about involvement of general practitioners in the implementation of the National Tuberculosis Programme, chalked out a programme for observing the Centenary of the Discovery of Tubercle Bacillus by Robert Koch in 1982 and considered the various steps to be taken for the effective delivery of tuberculosis services as an integral part of primary health care.

## 36TH NATIONAL CONFERENCE -

The 36th National Conference on TB & Chest Diseases will be held in Baroda from 2nd to 5th November, 1981. The main subjects selected for discussion at the conference include (1) Acute respiratory infection in children, (2) Respiratory failure in children, (3) Immunology of TB, (4) operational aspects of case-holding and case-finding, (5) Geriatric TB, and (6) Socio economic aspects of tuberculosis. As usual, the programme will also include papers on 'Chemotherapy' and other assorted aspects. The Registration form and other details about the Conference can be had from the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001.

## ESSAY COMPETITION 1981

The Tuberculosis Association of India will award a cash prize of Rs. 300/- to a final year medical student in India for an original essay on Tuberculosis adjudged best by a special committee of this Association. The subject selected for the 1981 competition is 'Aetio-Pathogenesis of Tuberculosis'. The essay should not exceed 15 double-spaced fullsize typed pages (approximately 3000 words) excluding tables, diagrams

etc. Four copies of the manuscript, forwarded through the Dean or Principal of College/University, should reach the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi by not later than 31st August, 1981.

#### **CHANCHAL SINGH MEMORIAL AWARD 1981**

The Tuberculosis Association of India will award a cash prize of Rs. 500/~ to a TB Worker, preferably below 45 years of age for an original article not exceeding 30 double-spaced full-scape typed pages (approximately 6,000 words excluding charts and diagrams) on a subject relating to Tuberculosis. Paper may be sent in quadruplicate to reach the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi by not later than the 31st August, 1981.

#### **REFRESHER COURSE: THANJAVUR**

The District TB Association, Thanjavur conducted a refresher course in Tuberculosis on the 26th and 27th of April, 1981 for the benefit of doctors in the rural areas of the districts of Thanjavur and Pudukottai. The course was inaugurated by Prof. K.V. Krishnaswami, Prof. of Tuberculosis & Chest Diseases, Madras Medical College and the function was presided over by Dr. G.M. Yahya, Dean, Thanjavur Medical College. Dr. K. Subramaniam, Honorary Secretary, District TB Association and District TB officer, Thanjavur welcomed the gathering. The Scientific sessions opened with a talk on Epidemiology of TB by Prof. K.V. Krishnaswami. This was followed by talks by other specialists on different aspects of TB including the National TB Control Programme, role of voluntary organisations, etc. There was also a Panel discussion on the Role of General Medical Practitioners in the control of TB. The participants, numbering about 80, later visited the District TB Centre, Raja Mirasdar Hospital, Thanjavur and saw the working of the different sections. The valedictory function was presided over by Dr. A. Sukumar, Vice-Principal, Thanjavur Medical College and certificates were distributed to the participants by Dr. V. Rangaswamy, Prof. of TB & Chest Diseases, Stanley Medical College, Madras.

#### **ANDHRA PRADESH CONFERENCE**

The Ninth Andhra Pradesh TB and Chest

Diseases Workers' Conference was held on the 14th and 15th March, 1981 at the Andhra Medical College, Visakapatnam under the joint auspices of the TB Association of Andhra Pradesh and the Visakapatnam District TB Association. About 250 delegates attended the Conference which was presided over by Dr. C.C. Mukhopadhyaya, Head of the Department of Tuberculosis, Arogyavaram. The Conference was inaugurated by Shri Auvila Sambasiva Rao, Vice-Chancellor of the Andhra University. Sri C.S. Rao, IAS, District Collector and President of the District TB Association welcomed the delegates. Dr. K. Sambasiva Rao, Principal, Andhra Medical College, Visakapatnam, inaugurated the Scientific Sessions of the Conference which included 2 panel discussions, one on 'National TB Control Programme' and the other on 'Chemotherapy'. In all 30 scientific papers were presented. There were sessions on 'Pulmonary Tuberculosis—Diagnosis and Management', 'Studies on Ventilatory Function and Air-way obstruction', 'Pathology', 'Non-tuberculous Chest Diseases', etc. There were also three orations, namely (1) Dr. P.V. Benjamin Oration on 'Short-term Chemotherapy' by Dr. N.L. Bordia, (2) Dr. Kanwal Chander Memorial Oration on 'Present Status of Immunisation in Tuberculosis' by Dr. G.V.J. Baily and (3) The Wander-TAAP Oration on 'Cardio Vascular System in Pulmonary Tuberculosis' by Dr. S.C. Kapoor. Dr. G.M. Narayanaswamy released the Souvenir brought out on the occasion and Dr. D. Umapathy Rao, Honorary Secretary of the State TB Association announced the various awards and prizes. The Conference concluded with a vote of thanks proposed by Shri D.V. Subba Rao, Honorary Secretary of the District TB Association.

#### **XIITH EASTERN REGIONAL TB CONFERENCE—BANGLADESH**

The XIth Eastern Region TB Conference of the IUAT will be held under the joint auspices of the National Anti-TB Association of Bangladesh, the Government of the People's Republic of Bangladesh and the Eastern Region of the IUAT in Dacca, Bangladesh, from the 9th to 14th November, 1981. For Registration form and other details about the Conference please contact Dr. Sakhawat Hossain, Secretary-General, Conference Secretariat, National Anti-Tuberculosis Association of Bangladesh (NATAB), 24, Banga Bandhu Avenue (1st and 2nd floor), Dacca, (Bangladesh) before the 30th June, 1981.

# The Indian Journal of Tuberculosis

## ABSTRACTS

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### Legionnaires' Disease

*Thomas F. Keys; Mayo Clinic Proceedings; 1980; 55; 129.*

An explosive outbreak of acute respiratory disease occurred among those attending an American Legion convention in a Philadelphia Hotel in the summer of 1976. Of the approximately 3,700 persons attending the convention, 149 cases of Legionnaires' disease were detected. These included 125 delegates, 17 family members, 4 auxiliary members and 3 non-delegates. An hotel employee working as a airconditioner repairman and suspected to be a case of Legionnaires' disease could have been the source. Many previous epidemics of pneumonia of uncertain cause developing in other places, inside and outside of U.S.A. could have been due to this disease.

During the 2-year period 1977 to 1979, 26 patients with Legionnaires' disease were seen at the Mayo Clinic and affiliated hospitals. The patients ranged in age from 17 to 81 years with a median of 51 years. Twelve (46%) were immunologically compromised. Most of the other patients had underlying chronic tobacco bronchitis. Hectic fever, cough and diarrhoea were common symptoms. Chest radiographs showed patchy perihilar infiltrates that often progressed to consolidation. Diagnosis was made by indirect fluorescent antibody testing in 15 patients (58%), but in no case was the test diagnostic during the first week of illness. In seven patients the diagnosis was established by positive direct fluorescent anti-body testing of lung tissue, in two cases by culture of lung tissue, and in one case each by direct fluorescent antibody positivity of sputum or bronchial washing. Of the 26 patients, 3(12%) required hemodialysis for acute renal failure and 5(19%) died. A favourable clinical response to therapy with erythromycin was noted. The differential diagnosis of Legionnaires' disease must include other bacterial pneumonias, as well as mycoplasma, psittacosis, Q fever and viral pneumonia. For critically ill patients, open-lung biopsy may be necessary to provide a rapid diagnosis. Current evidence suggests that erythromycin alone or in combina-

tion with rifampin is the treatment of choice. A 3-week course of therapy is recommended in order to prevent relapse.

S.P.P.

### Hyper sensitivity Pneumonitis and Legionnaires' Disease

*John E. Basich, et al. Amer. Rev. of Resp. Dis.; 1980, 121, 885.*

Four outbreaks of Legionnaires' disease (LD) and numerous instances of hypersensitivity pneumonitis (HP) have been associated with contaminated water in air-conditioning and cooling tower systems. The present study was carried out to determine if anti body to Legionella Pneumophila (LP) could be detected in the serums of persons with HP related to airconditioning and cooling tower systems, thus suggesting a possible relationship between the 2 diseases. Sera from 209 persons with suspected or confirmed HP were examined for antibody to LP by the microagglutination method. The result of only 3 serum tests were positive; these sera were from persons with respiratory symptoms suggestive of HP from air-conditioning and cooling tower systems, but who lacked clinical and laboratory confirmation of the disease. The results of all serum tests from confirmed cases of HP were negative. The results indicate that there probably is no association between the organisms causing LD and those associated with HP.

S.P.P.

### Ultrasound in the diagnosis and management of pleural disease

*DJ. Lipscomb et al; P.r. J. Dis. Chest (1980) 74, 353.*

A-mode ultrasound investigation has been performed in 62 patients, of whom 35 presented problems of diagnosis and management of pleural disease. In seven patients with known pleural effusions in whom aspiration had failed, ultrasound correctly identified fluid at a site different from the aspiration attempts and in all seven cases it was successfully removed. The

remaining 28 patients had the radiographic appearances of localized pleural disease and ultrasound correctly distinguished fluid and solid lesions in 26. Ultrasound was found to be a simple and reliable technique which was particularly valuable in locating fluid for aspiration and in distinguishing between fluid and pleural thickening. The simplicity and 'bedside' availability of ultrasound offered certain practical advantages over radiography.

S.P.P.

#### **Observations on Pleural Fluid Pressures as Fluid is Withdrawn during Thoracentesis**

*Richard W. Light, et al. Airier. Rev. Resp. Dis.; 1980, 121, 799.*

In 52 patients with pleural effusion, pleural pressures were measured initially and serially as pleural fluid was withdrawn. Pleural fluid aspiration was continued until the pleural pressure fell below  $-20$  cmH<sub>2</sub>O, or the patient developed excessive symptoms, or no more fluid could be obtained. The initial pleural pressure ranged from 4-8 to  $-21$  cmH<sub>2</sub>O. The rate of pleural pressure change as fluid was withdrawn was highly variable. In 13 of 52 procedures (25%) thoracentesis was terminated because the pressure fell below  $-20$  cmH<sub>2</sub>O. Negative initial pleural pressures and/or rapid changes in the pressures as fluid was withdrawn were suggestive of malignancy or trapped lung. (Thick fibrous visceral pleura enclosing the lung). The measurement of pleural pressures in patients with pleural effusions may be useful diagnostically. More importantly because large changes in pleural pressures are not readily detectable by the operator, pleural pressures should be monitored when large amounts ( $> 1,000$  ml) of pleural fluid are removed to increase the safety of the procedure.

S.P.P.

#### **An account of pleural effusions, pulmonary nodules and cavities attributable to rheumatoid disease by J. Spencer Jones**

*Br. J. Dis. Chest; 12, 39; 1978.*

Nine case histories and references to published reports are used to illustrate the manifestations and management of pleural effusions, lung nodules and lung cavities which may occur in cases of rheumatoid disease. Repeated aspiration of effusions is seldom useful. They are often chronic and symptomless. What is taking place in some turbid and purulent effusions is debatable, since there can be an associated leucocytosis without infection. In the presence

of acute symptoms, such as rigors, careful evaluation of such effusions is required, since there have been fatal examples with rather uncertain bacteriological findings. Lung nodules ordinarily cause a radiographic blemish without symptoms but may predispose to small haemoptyses or may rupture into the pleural cavity to cause a pneumothorax, usually requiring surgical resection of the nodule, whether or not a pleural effusion is present. Some nodules and lung cavities do not have the histology of the typical necrobiotic nodule but it is unlikely that they are fundamentally different. Large cavitated lung lesions which closed on azohipprine treatment are described\* together with similar untreated cavities which became secondarily infected with a fatal outcome. It is suggested that the history of possible rheumatoid disease, even of 'aches and pains' must be sought if this aetiology for pleural effusions, lung nodules and unusual lung cavities is not to be overlooked, with the penalty of diagnostic thoractomy or wrong treatment for the patients.

S.P.P.

#### **Usefulness of serum lysozyme measurement in diagnosis of intrathoracic**

*S.C. Lodha and M.A. Mir, Tubercle; 1908, 61, 81.*

The value of serum lysozyme as a helpful test in distinguishing tuberculous involvement of intrathoracic glands from lymphoma was studied. Nineteen of the 28 patients (all Asian immigrants) with intrathoracic glandular tuberculosis had raised serum lysozyme level as compared with 2 of the 29 patients with lymphoma. While a normal serum lysozyme level is unhelpful, a raised level in an Asian immigrant with hilar or mediastinal lymphadenopathy makes tuberculosis a highly probable diagnosis.

S.P.P.

#### **The Immunological Evaluation. Its Possibilities and Difficulties**

*Max Bloch; Revista Del Institute De Investigaciones Medicas; 1980, 9, 328.*

Studies carried out at the institute of Medical Research of the Hospital Resales over the past decade have led to the hypothesis that there exist in the general population about 2% persons who suffer from a severe immunological deficiency which is hereditary and possibly cellular. Most of the deaths in the community take place in this 2% population. Correlation between immunological deficit and widely

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varying diseases like ankylostomiasis, schistosomiasis, hepatic cirrhosis, typhoid, tuberculosis other infectious diseases, etc. has been observed. The possibility of using skin test to evaluate immunological status of a patient is worked out. The skin test may be as effective as the highly complex lymphocyte migration test in determining the immune status. It may be possible in future to concentrate preventive measures in these immunologically deficient individuals as also to use the test in determining the prognosis of a patient.

S.P.P.

### **Diagnostic potentialities of enzyme-linked immunosorbent assay in tuberculosis using purified tuberculin antigen**

*Aruna Tandon et al., Tubercle; (1980), 61, 87.*

Delayed hypersensitivity tests with tuberculin or purified tuberculin (PPD) have been used for detection of tuberculous infection. The paper describes an enzyme-linked immunosorbent assay (ELISA) for detection of PPD-antibodies in tuberculosis patients. The ELISA test was positive in nearly 80% of cases having bacteriological evidence of tuberculosis. The test could also detect PPD antibodies in 66% of the cases not showing bacteriological evidence of tuberculosis. The potentiality of the test in the immunodiagnosis of tuberculosis, is discussed.

S.P.P.

### **Experimental studies on the use of an immunoadjuvant (B-1,3 Glucan) to prevent relapse after termination of chemotherapy**

*Eiko Kondo et al; Kekkaku Vol. 55, No. 9, 1980, 411.*

Experimentally infected tuberculous mice were treated by intensive chemotherapy with three drug combinations (SM + INH + RFP, EB + INH + RFP or SM + INH + PZA) for 5 months so that viable counts from the spleen and lung were decreased below the undetectable level.

After termination of chemotherapy, the mice of each group were divided into two groups, which subsequently received or did not receive intravenous administration of B-1,3 glucan, 0.5 mg once a week, for 4 weeks and again 4 weeks after one month interval.

During this period and the succeeding 5 months, the mice were subjected to occasional sacrifice at random for cultivation of the two organs to detect the reincrease of latent tubercle

bacilli therein. The results indicated that the regimens with SM+INH+RFP or with EB+INH-j-RFP were highly efficient in eradicating infecting tubercle bacilli in mice, if not perfectly, and the use of B 1,3 glucan as an immunoadjuvant was effective in preventing the reincrease of latent bacilli.

S.P.P.

### **A review on mechanism of Anti-Tumor Action of BCG-Tohru Tokunaga**

*Kekkaku; 1980, 55, 351.*

The effector mechanisms in BCG therapy in tumors are composed of three different steps which arise sequentially after administration of BCG. Mechanism A is an immediate-type inflammation caused by BCG without T-lymphocytes collaboration. Mechanism B is a tuberculin-type inflammation in which the effector cells are macrophages activity by lymphokines released from BCG-sensitized T lymphocytes. The activated macrophages destroy tumor cells non-specifically at the site of activation. Mechanism C is the indication of tumor-specific immunity. This mechanism is, however, difficult in cancer, because of lack of tumor-specific antigen or of reduced ability of immune response. Anti-tumor effect of BCG is weak because the effector cells of mechanisms (A) and (B) cannot be activated at the tumor site. Possible merits of systemic BCG, therefore, may be due to the activation of R.E. system and natural killer cells.

S.P.P.

### **BCG Plus Levamisole following Irradiation of Advanced Squamous Bronchial Carcinoma**

*A. Pines; Br. J. Dis. Chest (1980) 74, 424.*

Patients with squamous carcinoma of the bronchus with locally advanced and inoperable lesions, but without obvious metastases, were irradiated with a dose of at least 4000 rads in an attempt to bring about a cure.

An original series was randomized between controls and patients given BCG at two-weekly intervals. Survival was significantly better for the BCG-treated patients during the first year only. Three are still alive and well, seven to nine years later. All control patients had died by the end of the third year. Metastases were common among control patients but not among the BCG-treated group.

To improve these results levamisole was given in addition in a dose of 2.5 mg/kg body weight

cm two days of the week. Treatment was allocated at random to three groups: control, BCG two-weekly and BCG four-weekly. At the end of the first year 44% of 27 controls, 50% of 16 patients given levamisole and BCG four-weekly and only 4% of 23 patients given levamisole and BCG two-weekly had died. At the end of the second year deaths were 66% among the control group and 22% in the levamisole and two-weekly BCG group, in the third year deaths was 85 % and 74 % respectively. The four-weekly BCG regimen had been discontinued. Skin testing with tuberculin and *Candida* showed some correlation with these results. There were many fewer metastases in the group given BCG two-weekly. BCG two-weekly thus appears to give some prolongation of life, though after two years there is no further benefit.

**S.P.P.**

**Adjuvant Levamisole in the treatment of patients with respectable lung cancer**

*Willen Karel Palmar Cornelius Amery; Annals of Clinical Research; 19SO, Vol. 12, Suppl. 21.*

Nisaitigans have been found on human lung cancer cells and the patients mount an immunity reaction to the tumour. The immunity, however, is relative since it has only a limited capacity to eradicate the tumor. The consensus seems to be that once a cancer becomes clinically detectable, it has crossed the limit where immunological eradication is possible. Levamisole is a thymomimetic drug and restores to normal the defense mechanisms but it does not stimulate it above the normal level. Its effects are primarily focused on T-Lymphocytes and the phagocytes and possibly also other killer cells and fail to occur early after the intake of the drug, tending to appear at a time when the drug is no longer detectable in the blood. However, what is exactly happening when levamisole is given to a patient, is still an enigma. The changes may be, at least partly, mediated by a serum factor. Levamisole is used in congenital immune-deficiencies, chronic infections like tuberculosis, recurrent herpetic lesions, rheumatoid arthritis, etc. Its optimal use is not as a monotherapy but as an adjunct to measures that reduce the antigen load.

Two hundred and eleven patients of cancer lung where resection was done in 1972-1975 in Netherlands are reported. Patients with metastasis, poor lung function, presence of an autoimmune disease or an allergic disorder were excluded. None of the patients was given any other adjuvant treatment e.g. Radio-therapy, Chemotherapy and Corticosteroids. Patients

were randomly allocated to levamisole or a placebo regimen. Levamisole was started three days before the operation. The dose was 50 mg T.D.S (Optimum dosage 2.5 mg/kg per day) for 3 days every fortnight. The patients were instructed not to smoke. 96 patients received levamisole and the remaining 115 were controls.

During the first two years there were 34 recurrences in the levamisole group and 43 in controls, the difference being not significant. A trend towards increased survival is seen in the levamisole group ( $p < 0.10$  after 1 and 21 months) because of decreased hematogenous dissemination following surgery. The beneficial effect of levamisole was regardless of the histological tumor type. Most marked benefit was seen in the patients with the more advanced tumors. Lymph node status did not affect, the survival within the first two post-operative years. Mantoux reaction had a clear relationship with survival in the control patients.

The only untoward reactions noted were mild gastro-intestinal complaints, nervousness, sleep disorders, drug fever, skin rash etc. No case of agranulocytosis was observed.

**S.P.P.**

**Surgical Treatment of Carcinoma of the lung- Report of 340 cases**

*Chinese Medical Journal-92(11): 744-747, 1979.*

A series of 340 cases of Carcinoma of the lung from 1961 to 1976 have been reviewed. Of these, 271 or 79.7% were resected. The tumor size was greater than 5 cm. in diameter in 35.6% of the resected specimens. Lymph-node metastases were present in 36.1 %. Operative mortality was 1.5%. 44.6% patients survived for a period of five years and 31.9% survived for 10 years. The five years survival was 25% amongst those with metastases and 55.6% amongst those without metastases, a difference which is highly significant statistically.

**S.P.P.**

**The Prognosis of Lung Cancer Originating as an infiltrate**

*William Weiss et al. Amer. Rev. Resp. Dis.; 1980, 121, 805.*

In a periodic screening study of 6,027 old men (age 45 years & above) 121 developed lung cancer during 10 years of observation. The overall 5-year survival rate was 8 %, but when the 121 men were subdivided according to the initial

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radiographic appearance of cancer, a group of 23 with ill-defined peripheral lesions that were labeled "Infiltrates" had the best prognosis over the first 5-years- of follow-up. This advantage tended to disappear thereafter. The men whose tumors originated as infiltrates also had the highest reaction rate and were detected most frequently infiltrates within 7-5 months of negative film. The infiltrates tended to be, smaller than the well defined peripheral tumors that were designated round lesions. In 8 of 13 instance with radiographic follow-up the infiltrates assumed the appearance of round lesions of Irregular masses. These observations suggested that the infiltrate is often a biologically earlier lesion than other radiographic forms of lung cancer.

S.P.P.

Amoxycillin versus ampicillin in treatment of exacerbations of Chronic Bronchitis

*A.D. Mackay, Br. J. Dis. Chest* (1980) 74, 379.

To compare the efficacy and unwanted effects of amoxycillin and ampicillin in the treatment of acute exacerbations of chronic bronchitis, 199 patients were recruited from 28 centres into a double-blind comparison of four regimens: ampicillin 250 mg or 500 mg, amoxycillin 250 mg or 300 mg, each given orally three times daily for seven days. In these doses, amoxycillin and ampicillin were equally effective and there was no apparent advantage in using the higher dose of either drug in preference to the lower dose. Unwanted effects were few. Only in five patients did diarrhoea; lead to withdrawal of therapy and there was no significant difference between the two drugs in this respect. Rashes occurred in four patients, all on ampicillin.

S.P.P.

Cryptogenic Fibrosing Alveolitis and Lung Cancer

*M. Turner-Warwick et al. Thorax*—1980, 35, 496-499.

Lung cancer was diagnosed in 20 (9.8%) of 205 patients with cryptogenic fibrosing alveolitis (C.F.A.) or 12.9%, of the 155 patients in this series who died. An excess relative risk of lung cancer of 14.1 % was found in patients with C.F.A. compared to the general population of comparable age and sex.

The relative risk for male smokers was (observed/expected)  $15/1.06 = 14.2$  and for female smokers (observed/expected)  $2/0.3=6.7$ . Only one male and one female non-smoker had lung cancer. The distribution of histological types was not obviously different from that found in

lung cancer without pulmonary fibrosis. Finger clubbing was present in 19(95%) compared with 116/185 (63%) of those so far not developing cancer. Cancer was not found especially in those with lung survival from the onset of symptoms of C.F.A. or with greater initial radiographic change.

H.B.D.

Adjuvant Immunotherapy with B.C.G. in Squamous Cell Bronchial Carcinoma

*Jansen, TH The and N.G.M. Orie; Thorax; 35, 781-787, 1980.*

Fifty four patients with evidence of primary squamous cell bronchial carcinoma (SCC) and three patients with adenocarcinoma (AC) had pulmonary resection. After resection 20 S.C.C. patients were randomly give B.C.G. immunostimulation by scarification (BCG-A). An additional group of 14 SCC patients and three AC patients received initially intra-pleural B.C.G. treatment and subsequently scarification (BCG-B). A control group of 20 SCC patients received no adjuvant treatment. Patients were followed from three to 51 months. Immune reactivity was monitored *in vivo* with PPD skin tests in 33 treated and in 18 untreated patients.

In both the B.C.G. treated SCC groups recurrence rates decreased statistically during follow up.) (BCG-A: 6 to 51 months.  $P < 0.001$ , BCG-B 6-9 months  $P < 0.01$  and 9 to 24 months  $P < 0.001$ ). However no difference could be demonstrated between systemic and combined systemic and intra-pleural treatment. The three B.C.G. treated AC patients all relapsed within nine months of follow up. A pronounced increase in skin reactivity to PPD was seen six months after surgery in the B.C.G. treated patients (BCG-A,  $P < 0.001$ . BCG-B,  $P < 0.001$ ), whereas the control patients remained antigenic after surgery. This improved immune reactivity went parallel with a more favourable outcome of the individual patients (BCG-A,  $P < 0.02$  BCG-B  $P < 0.05$ ). It is concluded that adjuvant B.C.G. immunotherapy used in strictly selected patients with minimal residual cell bronchial carcinoma improves the prognosis.

H.B.D.

Increased non-specific Bronchial Reactivity in Cigarette Smokers with Normal Lung Function

*John W. Gerrard et al Am. Rev. Res. Dis.. 1980, 122.*

Seventeen life time non-smoking male teachers and seventeen smoking male teachers with

normal lung function were compared. The smokers showed a significantly greater prevalence of cough ( $P < 0.01$ ), sputum production ( $P < 0.05$ ) and **wheezing** ( $P < 0.01$ ) but not dyspnoea. The geometric mean provocation concentration histamine required to reduce the SG by 35% (PC) was significantly lower in the smokers (1.84 mg/ml) than in the non-smokers (4.83 mg/ml)  $P < 0.005$ . Increased non-specific bronchial reactivity may be a factor contributing to the development of airway obstruction in smokers.

H.B.D.

#### **Aminophyllin Salbutamol and Combined Intravenous Infusions in Acute Severe Asthma**

U.K. *Evans et al.*. *Brit. J. Dis. Chest* 1980, 74, 385.

Twenty one patients with acute severe asthma were allocated at random to receive intravenous infusions for 24 hours of either aminophyllin or salbutamol or a combination of the two drugs as follows:

1. Aminophyllin 0.285 mgm/Kg/min followed by 0.014 mgrn/ Kg/min (20 mgm/min followed by 1 mgm/min for a 70 Kg. subject).
2. Salbutamol 0.2R5 ug/Kg/min for 15 min followed by 0.057 ug/Kg. min (20 ug/min followed by 4 ug/kg/min for a 70 Kg subject).
3. Combined regimen of the above infusions.

In addition each patient received intravenous hydrocortisone (4g) and potassium chloride (4g)

in 2 liters of 5% dextrose infused over 24 hours and 35% oxygen.

**Peak** expiratory flow rates showed a significant improvement after 15 minutes **treatment** with aminophyllin and the combined **infusion** and it was not seen until 60 minutes with salbutamol infusion. No synergistic bronchodilator effect was seen with the combined infusion. The results show that intravenous aminophyllin is superior to intravenous salbutamol in the initial treatment of acute asthma and the combination when given intravenously is not better than aminophylline above.

H.B.D.

#### **The Prevalence and Incidence of Asthma and Asthma-Like Symptoms in a General Population Sample**

*Russel R, Dodge and Benjamin Burrows.*, *Am. Rev. Rest. Dis.*, 1980, 122.

A longitudinal epidemiological study showed that point prevalence of asthma was 6.6.% with the highest rate occurring in children. Rates were also high in older subjects in most of whom chronic bronchitis/or emphysema had been concomitantly diagnosed. The point prevalence of wheezing exceeded 3%. New asthma developed in 1.4% of the subjects followed over a period of 4 years. New attacks of shortness of breath with wheeze occurred in 10.3% of subjects. The frequency of asthma was greatest in young children, least in late adolescence and increased in early adult life. The incidence was 1.5 times greater in young boys than in young girls but was much greater in women older than 40 years of age.

H.B.D.