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CHANGING CHARACTER OF PULMONARY TUBERCULOSIS

Studies made by Prof. Cummins and others showed that tuberculosis on entry in a virgin community takes heavy toll in disease and deaths. In the initial phase the lesions are predominantly exudative and clinical manifestations are very acute. With gradual tuberculation the hard-immunity increases and the disease assumes a chronic form. It may, therefore, be true that the longer a community is in association with wide spread tuberculosis the more chronic cases are detected in it. At a later phase the incidence of tuberculosis also falls. That this may be true is suggested by the fact that in U. S. A. tuberculosis among the Negroes, who have shorter association with tuberculosis, shows acuter forms of the disease than that in the white inhabitants under similar environments and standard of living. This natural course of events may certainly be modified by many factors. Improvement of the standard of living, sanitation, and education, and introduction of extensive anti-tuberculous measures may cause a quicker decline of the incidence of the disease and may even change the character of the disease, but, by and large, the natural curve of the incidence is likely to be retained.

Information with regard to the position of India in such a curve, in the raising or falling limb, is important for planning anti-tuberculous measures. Such an information can only be obtained from proper and accurate practice of notification of the disease and deaths over a few decades. In the absence of such a practice this information may be obtained to some extent by studying the changes in the character of the disease over a few decades.

A comparative study of the character of the disease in the urban and rural cases of the same period and of progressively different periods may also prove very helpful in determining the position of tuberculation and resistance status of these two groups. If acuter disease is more frequent in the rural cases, then very heavy toll is expected in this group in the near future as our rapid industrialisation and fast developing conveyance system will carry infection into a

susceptible soil. This study will, therefore, be very gainful in ascertaining where and how the stress in our anti-tuberculosis campaign should be laid.

It is not unlikely that deliberate tuberculinisation of a community, as is done by mass B. C. G. vaccination, and extensive use of anti-tuberculous drugs which can change the character of the bacilli may have important effect on the evolution and character of the disease in the Community. Studies on the changing character of the disease may, therefore, throw important light on the two most important measures in our program.

On these and many other counts Dr. B. K. Sikand's study reported in this issue of the Journal seems important. To draw any picture of the country with regard to resistance status or of the effect of some measures such studies should be made in different areas on a common program and using common schedules. The schedule should be simple, clear in terminology and generally workable under present conditions of the clinics.

—P. K. Sen.

Changes in the Clinical Manifestations of Pulmonary Tuberculosis during the last ten years

By

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INTRODUCTION

Clinicians from all parts of our country have a feeling that the tuberculosis patient of today is considerably different from that of a decade or so earlier. The object of this paper is to substantiate this impression, if possible objectively, from our own material. There is a dearth of literature on this subject, and most of the references available deal with epidemiological aspects rather than the clinical manifestations of pulmonary tuberculosis (1, 2).

Retrospective studies of this type are subject to serious limitations ; this one even more so because of the changes in diagnostic criteria, improvements in diagnostic aids, availability and cost of materials, especially x-ray films, and the interchange of population that has taken place in Delhi during the last ten years. That in spite of all these limitations, it was considered worthwhile to undertake such a study is an indication of the importance that attaches to this topic, and the interest it arouses among Tuberculosis workers.

MATERIAL

Patients first reporting for treatment at the New Delhi Tuberculosis Centre during the years 1945 and 1946 on the one hand and 1955 on the other, were considered suitable for this comparison. Although this clinic was started in 1941, skiagrams were not available for majority of the patients from 1941-1944 owing to our limited resources and scarcity of x-ray films due to war conditions. Patients for 2 years *i.e.*, 1945 and 1946 were included to make their numbers sufficiently large and approximately equal to those in 1955. Since 1956 a good deal of diagnostic work is being done on 70 mm films, and comparison of data obtained from those as opposed to standard 12 x 15 films taken earlier would have been open to question.

Patients having had any treatment previously, non-residents of Delhi and those discovered through Mass Survey, were excluded.

For comparing the manifestations of disease in these two sets of patients, the common denominators were (i) the available skiagrams as indicative of the extent and nature of the disease (ii) sputum results. Clinical observations and fluoroscopic findings are so subjective that their value for exact comparison would be necessarily limited. In fact, authentic classification of subjective symptoms from the O.P.D of a clinic is not at all possible. Therefore from the analysis given below, it is not possible to deduce how acutely the patients were ill in 1945-46 as compared to 1955. This information may be available in respect of indoor

patients in sanatoria and hospitals, but even so, is of very little value because now-a-days a patient is hardly ever admitted in sanatoria in this country without some treatment outside. The treatment so changes the picture of toxæmic symptoms that any differences noticed are likely to be more apparent than real. Such are the serious limitations-of a study of this sort.

All available skiagrams of patients who first attended the clinic during 1945-46 and 1955 were reviewed. It was found that a certain proportion of films were not available for a variety of reasons, specially during 1945-46 :—

(1) Patients getting admission into sanatoria or hospitals took away their skiagrams which were seldom returned.

(2) The high cost of x-ray films, their scarcity, and our limited funds have already been mentioned as reasons for not taking skiagrams and nearly 55 % of the patients in 1945-46 and 20% in 1955 fall in this category. (3) Skiagrams were usually not taken for advanced bilateral cases in 1945-46 because in those pre-chemotherapy days nothing much could be done to help them. They were dismissed after a preliminary screening—a permanent x-ray record being considered a costly luxury. Fewer cases were considered so hopeless in 1955 due to availability of antimicrobials.

The proportion of films available and reasons for non-availability in the two series are shown in tables 1 (a) and 1 (b). It is unlikely that non-availability of films would detract from the representative character of the available skiagrams, except in advanced bilateral cases.

Table 1(a): *Number of skiagrams available and reasons for non availability of skiagrams during 1945-46.*

Extent of Disease	A	B	C	D	Total films
I	120	78	—	246	444 (24.5%)
II	129	60	—	296	485 (26.8%)
III	136	100	181	465	882 (48.7%)
Total	385 (21.3%)	238 (13.1%)	181 (10.0%)	1007 (55.6%)	1811 (100.0%)

Total I(b): Number of skiagrams available and reasons for non-availability of skiagrams during 1955*

Extent of Disease	A	B	C	D**	Total films
I	154	30	—	51	253 (15.8%)
II	223	53	—	72	346 (23.2%)
III	559	129	43	187	918 (61.2%)
Total	936 (62.4%)	212 (14.1%)	43 (2.9%)	310 (20.6%)	1501 (100.0%)

*A— Skiagram available

B— Skiagram taken away by patient

C— Skiagram not taken (Advanced Bialateral Disease)

D— Skiagram not taken (Other reasons)

**Includes cases whose record was not traceable

In order to dilute individual differences of reading and to get an average reading, all available skiagrams in both series were read by a set of 4 readers ; each reader reading 1/4th of the total films by randomization. A record was made in respect of the following :—

- (1) extent of disease, i.e., number of zones involved ; unilateral or bilateral
- (2) extent of cavitation
- (3) nature of disease, as far as it could be judged radiologically.

For purposes of this paper, entries under “Nature of Disease” were made in the following code :—

1. *Miliary Disease*

Bilateral uniformly distributed, acute, miliary lesions.

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

2. *Haematogenous Disease*

Disseminated bilateral symmetrically distributed lesions predominantly in both upper zones. The individual lesions may not be uniform in size and shape. It includes chronic Miliary and also Haematogenous disseminations of the primary type of disease usually seen in children and young adults.

3. *Pneumonic Disease*

Acute consolidation of at least one lobe of a lung.

4. *Broncho-pneumonic Disease*

Acute disseminated exudative patches predominantly seen in the bases of both lungs. A fresh soft-wall cavity may be present in any of the zones. Localised bronchogenic or post-haemoptoic spreads are not included under this heading.

5. *Localised, Predominantly Exudative Disease*

Cases showing bronchogenic and post-haemoptoic spreads even in both lungs are included under this heading provided the spread is localised in the usual sense of the word. Evidence of marked fibrosis (see below) should be absent.

6. *Localised Fibrotic Disease*

All cases showing incontrovertible evidence of fibrosis, kinked trachea, pulling of the mediastinum and heart, pulling up of the hilum, narrowing of inter-spaces etc.

RESULTS

(A) Radiological Data

The exclusion of all cases with advanced bilateral disease from the earlier series introduces an inadvertent 'selection'. In order to reduce this bias as far as possible, cases with involvement of 1-4 zones only have been compared, in tables 2, 3, 4 & 6.

It is easily seen from tables 2, 3 & 4 that the two series are remarkably similar with respect to extent of disease (as judged by number of zones involved), extent of cavitation and the type of disease. This is contrary to expectations.

Table 2: *Extent of Disease among patients in the two series*

Series	Number of Zones and Sides involved						Total (1 to 4 Zones)
	1	2 (unilateral)	2 (bilateral)	3 (unilateral)	3 (bilateral)	4	
1945-46	83 (23.4%)	61 (17.2%)	54 (15.2%)	29 (8.2%)	68 (19.2%)	60 (16.9%)	355 (100.0%)
1955	205 (24.3%)	131 (15.5%)	128 (15.1%)	28 (3.3%)	200 (23.7%)	153 (18.1%)	845 (100.0%)

Table 3: *Extent of Cavitation among Patients in the two series*

Number of Zones and Sides Involved	Series	Total Cases	Extent of Cavitation		
			Nil	Unilateral	Bilateral
1.	1945-46	83 100.0%	54 65.1%	29 34.9%	—
	1955	205 100.0%	149 72.7%	56 27.3%	—
2. (Unilateral)	1945-46	61 100.0%	24 19.3%	37 60.7%	—
	1955	131 100.0%	47 35.9%	84 64.1%	—
2. (bilateral)	1945-46	54 100.0%	37 68.5%	15 27.8%	2 3.7%
	1955	128 100.0%	86 67.2%	38 29.7%	4 3.1%
3. (Unilateral)	1945-46	29 100.0%	5 17.2%	24 82.8%	—
	1955	28 100.0%	1 3.6%	27 96.4%	—
3. (bilateral)	1945-46	68 100.0%	17 25.0%	48 70.6%	3 4.4%
	1955	200 100.0%	49 24.5%	123 61.5%	28 14.0%
4.	1945-46	60 100.0%	11 18.3%	38 63.3%	11 18.3%
	1955	153 100.0%	34 22.2%	76 49.7%	43 28.1%
Total (1 to 4) (Zones)	1945-46	355 100.0%	148 41.7%	191 53.8%	16 4.5%
	1955	458 100.0%	366 43.3%	404 47.8%	75 8.9%

Table 4; Nature of Ike Disease among Patients in the two series.

Number of Zones & sides involved	Series	Total Cases	* Nature of Disease					
			1	2	3	4	5	6
1	1945-46	83 100.0%	—	—	6.0%	—	73 88.0%	5 6.0%
	1955	205 100.0%	—	—	4 1.9%	—	166 81.0%	35 17.1%
2 (unilateral)	1945-46	61 100.0%	—	—	6 9.8%	—	55 90.2%	—
	1955	131 100.0%	—	0.8%	8 6.1%	—	120 21.6%	2 1.5%
2 (bilateral)	1945-46	54 100.0%	—	4 7.4%	1 1.9%	—	48 88.9%	1 1.9%
	1955	128 100.0%	—	4 3.1%	0.8%	—	113 88.3%	10 7.8%
3 (unilateral)	1945-46	29 100.0%	—	1 3.4%	1 3.4%	—	27 93.1%	—
	1955	28 100.0%	—	—	—	—	27 96.4%	1 3.6%
3 (bilateral)	1945-46	68 100.0%	—	6 8.8%	—	—	61 89.7%	1 1.5%
	1955	200 100.0%	—	6 3.0%	—	0.5%	188 94.0%	5 2.5%
4	1945-46	60 100.0%	—	2 3.3%	—	—	57 95.0%	1 1.7%
	1955	153 100.0%	—	9 5.9%	1 0.7%	2 1.3%	140 91.4%	0.7%
Total (1 to 4 zones)	1945-46	355 100.0%	—	13 3.7%	13 3.7%	—	321 90.4%	8 2.3%
	1955	845 100.0%	—	20 2.4%	14 1.7%	3 0.4%	754 89.1%	54 6.4%

*For explanation of the six categories, see text

Column (6) of table 4 might give an impression that under 1 zone more cases with fibrotic type of disease were seen in 1955, but this difference is only apparent. Actually most of these cases were inactive and were discovered during contact examination whereas in 1945-46 skiagrams were usually not taken for such cases.

It would be worthwhile comparing at this stage the cases involving 5 & 6 zones (including advanced bilateral cases whose skiagrams were not taken for reasons already mentioned). It is surprising that even here (table 5) the proportion of these cases to the total cases is nearly the same in both the periods :—

TABLE 5

Series	Total Pulmonary Tuberculosis Cases	Cases involving 5 or 6 zones (including Advanced Bilateral Cases)
1945-46	1811	211 (11.7%)
1955	1501	164 (10.9%)

(B) Sputum Status

The initial bacillary status of the patients in the two series is shown in table 6 (p. 98). Although the proportion of sputum positive cases appears to be almost equal in both series, yet it is not without some significance. In 1945-46 culture facilities were hardly available, but in 1955, every specimen of sputum negative by direct smear, was put up for culture apart from the customary direct smear examination and further, laryngeal swab cultures were done if no sputum was available. These finer methods of examination, now available, have led to an increased number of positives. As a common denominator between 1945-46 and 1955, the proportion of positives in 1945-46 may be compared with the proportion of 'Direct smear positives' in 1955.

This proportion, it can be seen, has significantly fallen during the ten-year period, even though the disease in all radiological aspects is similar. Possible significance of this change is discussed later.

DISCUSSION

The remarkably uniform breakdown of radiological manifestations in the two series of patients certainly fails to provide any basis for the otherwise strong subjective impression that the patients at the time of reporting sick for the first time, are much less acutely ill now-a-days than they used to be a decade or so earlier. Therefore one cannot but make a guess to explain this lack of parallelism between extent of disease and severity of symptoms.

It could be said that perhaps the patients prior to first visit may have had a short course of treatment which modified toxaemic symptoms without materially changing the radiological picture. However patients who had had any treatment previously have been excluded from this analysis and the majority of those included were, it is felt, so guileless and poor that they could not have held back deliberately the fact of previous treatment to any appreciable extent.

Table 6: Bacillary Status of Patients in the two series

Number of Zones and Sides Involved	Total Cases	Total cases whose bacteriological results are available	Sp-D.S. Pos.	Sp-Cul. or L. S. Cul. Pos.	Total Positive	Total Negative
1	2	3	4	5	6	7
1 1945-46	83	70 100.0	22 31.4%	— —	22 31.4%	48 68.6%
1955	205	195 100.0	35 17.9%	21 10.8%	56 28.7%	139 71.3%
2u 1945-46	61	51 100.0	36 70.6%	— —	36 70.6%	15 29.4%
1955	131	126 100.0	71 56.3%	11 8.8%	82 65.1%	440 34.9%
2b 1945-46	54	47 100.0	19 40.4%	— —	19 40.4%	28 59.6%
1955	128	121 100.0	34 28.2%	15 12.4%	49 40.5%	72 59.5%
3u 1945-46	29	25 100.0	23 92.0%	— —	23 92.0%	2 8.0%
1955	28	27 100.0	19 70.4%	4 14.8%	23 85.2%	4 14.8%
3b 1945-46	68	61 100.0	48 78.7%	— —	48 78.7%	13 21.3%
1955	200	193 100.0	115 59.6%	28 14.5%	143 74.1%	50 25.9%
4 1945-46	60	53 100.0	46 86.8%	— —	46 86.8%	7 13.2%
1955	153	146 100.0	112 76.7%	16 11.0%	128 87.7%	18 18.3%
1945-46	355	307 100.0	194 63.2%	— —	194 63.2%	113 36.8%
Total (zones) 1955	845	808 100.0	386 47.8%	95 11.8%	481 59.5%	327 40.5%

It could also be argued that milder symptoms could, to some extent, be due to patients reporting for diagnosis earlier because of greater health consciousness, increased treatment facilities, and a greater sense of optimism engendered by improved prognosis under antimicrobial therapy. What brings a patient for examination is a complex of the severity and the duration of symptoms, and a feeling of fear and responsibility which may not be directly related to the extent of disease. Intensive early diagnosis campaigns in the Western countries clearly showed that where symptoms have appeared the chances of finding early cases is not more than 20%. Thus milder symptoms need not be accompanied by the change in the extent of the disease. What then could be the explanation for the subjective impression of milder symptoms?

It is a common observation that size of the lesion is not the sole criterion of the degree of symptoms. Patients with extensive disease but minor symptoms are as common as acutely ill patients with minimal or moderately advanced disease. Symptoms depend upon the tempo of tissue changes in the lesion rather than its size.

Degree to which constitutional symptoms will occur in tuberculosis is dependent upon the inter-play of hypersensitivity, resistance, number of bacilli and their virulence ; and depending largely upon the degree to which each factor is present, symptoms may be severe or may be absent (Rich 1951). These factors are, by and large, inter-related and inter-dependent. Virulence governs the proliferation of bacilli (Smithburn 1937) and the larger the number of bacilli, the greater the hypersensitiveness and the tissue destruction. On the other hand, even virulent bacilli do not proliferate well in a resistant host (Griffith 1922). Could milder symptoms noticed now-a-days be, therefore, due to some inter-play of altered virulence of bacilli and host resistance ?

Virulence of bacilli was assumed to "be constant but Griffith (1922), Jensen et al (1936), Stewart (1951) and Middlebrook (1956) have proved that bacilli isolated from different individuals are not quite so uniform in virulence as they were believed to be. Frimodt-Moller (1956) & Balbir Singh (1957) working on sputa of patients in Madanapalle and Delhi have also isolated some attenuated strains. Further, these variations in virulence can not only be introduced deliberately by appropriate methods in vitro (as in B.C.G.), but may also occur spontaneously in vivo (Griffith 1922), without any relation to antimicrobials.

That different nationalities and people of same nationality over a period of time possess varying resistance to tubercle bacilli is also an accepted fact. Selective mortality in situations where environmental conditions either improve or remain stationary is generally accepted as the basis of such a resistance (McDogall 1949, Cobbet 1925).

As for our environmental conditions, people now-a-days do seem to have more money, but whether this has also led to a proportionate increase in the 'real wages' and improved nutrition and housing is not clear ; overcrowding in some of the areas from which these cases have been drawn has certainly increased since 1945.

It may be impossible to prove, yet it is not inconceivable that either altered resistance or virulence of the bacilli or both could have so changed that the host can deal with bacilli more effectively and completely, thereby reducing the tempo of tissue changes without, so far, affecting appreciably the extent of involvement of the tissues, as seen radiologically.

What is the significance of the lowered rate of sputum positivity in the 1955 series ? The rate of sputum positivity also, like severity of symptoms, depends upon the tissue changes, and there is an apparent co-relation between the lower positivity rate of sputum and subjective impression of milder symptoms in the 1955 patients.

At this stage it may be permissible to draw attention to a few other observations which though not directly related to the clinical manifestations of pulmonary tuberculosis, tend to substantiate the above hypothesis.

(a) Many a patient in 1945-46 presented with tubercular enteritis and laryngitis which materially interfered with nutrition thus causing wasting and cachexia. These complications are getting conspicuously rare during the last 5 years

or so. It could be that this phenomenon is due to the diminution of bacillary content of the sputum cutting down canalicular spread of the bacilli to the intestinal tract and the larynx.

(b) Tumorous, suppurating glands in the neck are also now-a-days a rare sight. Although the incidence of tubercular adenitis in relation to total tuberculosis discovered amongst our patients remains very nearly the same yet the glands now dealt with are usually small, and the diagnosis is very often arrived at by biopsy.

These observations would tend to make the above hypothesis at least plausible and may be, further planned studies conducted at several places during the next decade or so may provide an answer to this fascinating problem.

SUMMARY

The available skiagrams of 1945-46 patients on one hand and 1955 patients on the other have been compared regarding the nature and extent of disease and cavitation to find out if these bear out the common subjective impression that the tuberculosis patient of today is considerably different from that of a decade or so earlier. The initial bacillary status of the sputum in patients of both periods has also been compared. Difficulties in direct comparison of the degree of constitutional symptoms then and now have been mentioned.

Lack of co-relation between the subjective impression of the acuity of disease and its nature and extent as seen radiologically, possible explanations there of, and the significance of lowered rate of sputum positivity in 1955 patients are discussed.

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The Present Position of Freeze-Dried BCG Vaccine

By

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I reviewed in 1952 the literature on freeze-dried BCG vaccine in order to help evaluate the relative merits of fresh liquid and dried vaccines on the basis of the results of vaccination. More BCG production centres have since taken to the preparation of dried BCG vaccine for either experimental use or for vaccination. In India, the scene of activity of the mass vaccination campaign has shifted from urban and semi-urban to rural areas in remote parts of the country, thereby accentuating the practical problems in the transport of fresh liquid BCG vaccine and its use in the field. There has therefore been in recent years a renewed interest in dried BCG vaccine in this country, as also in some other countries.

I have had the opportunity to make a personal study of the problems connected with the preparation of freeze-dried BCG vaccine in the Tice Laboratory, Chicago and in the University of Montreal, besides some other centres in Europe. In view of its great topical interest I propose to make a critical evaluation of the present status of freeze-dried BCG vaccine.

I have to point out at the outset that there are some practical difficulties in the production of freeze-dried vaccine of uniform potency. On account of the natural tendency for BCG to clumping, it is difficult to prepare vaccinal suspensions containing only single cells. Hence the fresh vaccinal suspension prepared by grinding the BCG culture with steel balls is a variable mixture of living bacilli of all ages, damaged and dead bacilli. Further, a large proportion of the bacilli dies when subjected to the conditions of freeze-drying. Consequently the viable counts of the vaccines vary considerably from batch to batch despite all attempts to standardize the techniques.

The chief factors that influence the survival of BCG after freeze-drying and storage are the age of the culture, the concentration of the vaccinal suspension, the nature of the suspending medium, the temperature of freezing, the duration and temperature of drying, the amount of residual moisture in the final product and the conditions of storage.

Special mention has to be made of the suspending medium which is regarded as the most important single factor in the whole process of freeze-drying and survival rate. It is generally agreed that the suspending medium should contain a carbohydrate in adequate concentration and also a protective colloid. The carbohydrate and the colloid seem to exert their beneficial effects in many ways. They protect the bacilli during freezing, drying and storage. They facilitate the homogenous suspension of the vaccine upon reconstitution. They give bulk to the product which after drying retains the shape and size of the ice-block in the form of a spongy mass that serves as a visual index of the absence of thawing. They have a binding effect so that there is no fear of the dried product being blown out by the inrush of air when the ampoule sealed under vacuum is opened.

It is interesting to note that in spite of the vital importance of the protective colloid, only three vaccines, Russian, Polish and British, contain it. Table 1 shows some of the different suspending media in current use.

TABLE 1.
Showing some of the suspending media in current use

Origin of vaccine	Suspending medium	Reference
Bergen (Norway) Chicago (U.S.A.)	Hornibrook's menstruum 15 per cent lactose plus buffered salts, asparagine and glycerine	Hesselberg & Hopen (1956) Rosenthal (1952)
London (England)	8.3 per cent dextran with 7.5 per cent glucose	Ungar <i>et al</i> (1956)
Melbourne (Australia)	Hornibrook's menstruum	North & Newman (1951)
Montreal (Canada)	15 per cent lactose	Frappier <i>et al</i> (1951)
Moscow (U.S.S.R.)	10 per cent saccharose with 1 per cent gelatin	Kurylowicz (1955) van Deinse & Senechal (1950)
Paris (France)	50 per cent glucose	Yanagisawa (1951)
Tokyo (Japan)	1 per cent saccharose	Kurviowicz (1955)
Warsaw (Poland)	10 per cent saccharose with 1 per cent, gelatin	

The importance of the survival rate in dried BCG vaccine lies in the fact that tuberculin allergy after BCG vaccination is regarded as the only index of the potency of the vaccine and as measure of the success of vaccination. The larger the number of living bacilli in the vaccine, the higher is its allergenic potency. In this connection, the role of the unknown number of dead BCG in the production of allergy is ignored for all practical purposes.

The effect of freeze-drying is therefore to greatly reduce the number of living bacilli in the dried vaccine and to increase the proportion of dead ones to a corresponding degree. The average percentage of viability reported by different workers has shown wide variations. Leshchinskaya (1946) and van Deinse and Senechal (1950) have reported a 100 per cent survival after freeze-drying with 50 per cent glucose as the adjuvant. Other workers have generally obtained much lower survival rates. Thus a survival rate of 17.02 per cent was reported by Birkhaug (1951) and 40 to 60 per cent by Frappier (1955). Kumabe (1956) cited Yakuwa that most of the products made in Japan showed survivals below 35 per cent. Obayashi *et al* (1956) reported average survival rates of 26.5 and 31.6 per cent in two experiments involving 38 and 22 batches of dried vaccine respectively. Rosenthal (1957) does not use the colony count method for determination of the viability of vaccine. He uses liquid medium, the weakest dilution of vaccine causing growth in Youman's liquid medium indicating the viability of the vaccine. The number of viable units before lyophilization per millilitre of standard vaccine (50 mg./ml., Hopkins tube method) was 6.2×10^{-8} ; immediately after lyophilization it was 2.1×10^{-8} . That is a survival rate of 34 per cent.

It is not surprising that such wide variations are present between the average viable counts of vaccines of different origins, because the techniques of preparation of the vaccinal suspension and freeze-drying are by no means uniform.

Efforts to minimize the loss of viability are made by providing conditions as favourable for survival of BCG as possible during freeze-drying and storage. The ampoules are generally sealed in vacuum as survivals are low in an atmosphere of air or oxygen. Rosenthal (1952) reported that storage in an atmosphere of pure, dry nitrogen was satisfactory provided the vaccine was stored below 5° C. The dried vaccines

prepared in Canada, Poland, Britain, Japan and Australia are sealed *in vacuo* while the French vaccine is sealed in an atmosphere of air and the U.S. vaccine in an atmosphere of nitrogen.

The dried BCG-vaccines prepared at the present day require storage at low temperature below 5° C. As regards the duration of storage, most observers have found that after the initial fall in viability in the early period of preservation, the vaccine becomes more or less stable with only a small loss of viability up to one year. Therefore most of the vaccines prepared in the different centres are used up to six months. The French vaccine is permitted to be used up to eight months, while the Russian and Japanese vaccines are used up to one year.

It has been observed that the stability of the vaccine is related to its moisture content. It is generally agreed that the moisture content of freeze-dried biologicals must not exceed one per cent. The regulations of the National Institute of Health of U.S.A. specify a maximum water content of one per cent for freeze-dried products. The Canadian and U.S. vaccines contain approximately one per cent each, the British vaccine 0.8 to 1.4 per cent, the Polish vaccine 2 per cent and the Japanese vaccine 1 to 3 per cent. Obayashi (1955) reported that while a moisture content of over 4 per cent was harmful to the preservation of the vaccine prepared in Japan, no difference in viability was found among vaccines with a moisture content of 1 to 3 per cent.

It may be of interest to know whether any other changes take place in the dried vaccine besides a reduction in the number of viable units. Flosdorf (1949) noted that *in vitro* dried cultures required a longer period of incubation to obtain satisfactory growth of the first culture generation. Proom and Hemmons (1949) also observed that dried cultures had an usually long phase when subcultivated. This may well be due to the small numbers of living bacteria in the dried stock cultures rather than due to any lowered vitality of the organisms brought about by freeze-drying.

Rosenthal (1952) noted that BCG from the dried vaccine took longer to develop visible growth in Youman's medium, six weeks instead of three weeks for the BCG in the fresh vaccine. He believes that BCG after drying assumes a partial state of dormancy as evidenced by the prolonged lag phase in growth and tuberculin conversion.

Ebina *et al* (1954) showed by culture of lymph glands, liver, spleen and lungs that more colonies were grown from the organs of animals injected with wet BCG vaccine than those injected with dried vaccine. They concluded that the BCG in the wet vaccine grew vigorously immediately after injection while that in the dried vaccine grew after a delay.

Levy (1955) showed by quantitative assessment in animals that BCG in the wet vaccine reached the peak of multiplication in four weeks while that in the lyophilized vaccine took six weeks. It is possible that the BCG in the fresh vaccine is more invasive and multiplies *in vivo* more vigorously producing outright an intense antigenic stimulus.

The dried vaccines from no two laboratories are comparable for the reasons given by Pierce, Dubos and Schaefer (1956). These authors found that the interpretation of comparative tests carried out on preparations of lyophilized vaccines were rendered difficult by the fact that individual samples, even of the same origin, often differed in the number of viable organisms that they contained. Furthermore, the differences in the techniques employed for the production and preservation of the vaccine affected the physiological state of the surviving organisms and consequently their behaviour *in vivo*.

van Deirse and Senechal (1950) reported that the allergy caused by the dried vaccine always lagged behind that due to the fresh vaccine. They therefore suggested that the retesting with tuberculin may be done four months after vaccination. The delay in the development of allergy has been noted by Birkhaug (1951) and several other observers. Rosenthal (1952) reported that the tuberculin conversion with dried vaccine in animals and man compared favourably with fresh vaccine. The most striking difference was in the delay in universal conversion in newborn babies, which was 58 days for the dried and 28 days for the fresh vaccine. Rosenthal (1954) later reported that as a result of changes in the BCG strain and method of freeze-drying the conversion rate and the time taken for conversion were almost similar for fresh and freeze-dried vaccines, when the vaccinations were made by the multiple puncture method devised by him (1950).

Heaf (1954) found, however, that the lyophilized vaccine was inferior to the fresh liquid preparation because of the low conversion rate, the slower development of tuberculin sensitivity and its shorter duration. He stated that "the freeze-dried vaccine continues to be used because of its longer life, which reduces administrative problems considerably, particularly in remote underdeveloped countries". It is only fair to state that his experience of freeze-dried BCG vaccine seems to be limited to the use of the French lyophilized product.

No discussion of the present status of freeze-dried BCG vaccine can be complete without a reference to the large-scale production and use of dried vaccine for mass vaccination in Japan, where the use of lyophilized vaccine was made compulsory by law in 1949. All persons under the age of 30 years are tested with tuberculin once a year and the negative reactors are vaccinated with 0.04 mg. BCG., which is the same dose as that of the fresh vaccine administered before the promulgation of the law. It may be of interest to note that the criterion for a positive tuberculin reaction is an area of erythema measuring at least 10 mm. in diameter.

Yanagisawa (1951) reported that the wet vaccine in a dose of 0.02-0.05 mg. showed 90% positive conversion within 2-3 months, but the tuberculin positive rate dropped down to 50 to 60 per cent by the end of one year. As the legally established dose of the dried vaccine is 0.04 mg. even at the present day, it would seem that a considerable proportion of the primarily vaccinated individuals are revaccinated every year in Japan. This is confirmed by a report by Ebina *et al* (1954) that they experience Koch phenomenon in many cases after revaccination, though it is slight. These authors attribute it to the use of 0.05 mg. O.T. for the pre- and post-vaccination tests in Japan and state that it cannot be avoided as long as the allergy is measured with that dose of tuberculin.

BCG research workers in Japan appear to be aware of the possibility of bettering the results of vaccination by improving the method of vaccine production and increasing the dose of vaccine. There seem to be some practical difficulties in implementing their observations. Firstly, as Ebina *et al* (1954) pointed out, "the people in Japan are worried about complications such as ulcers and abscesses that the dose of dried vaccine to be injected legally is not multiplied and the same dose as that of the wet vaccine is still applied". Secondly, any change in the dose of the vaccine can presumably be effected only through the process of law.

An analysis of the studies on freeze-dried vaccine in Japan shows that the problem of variability of viable units in the fresh vaccinal suspensions and the dried vaccines prepared from them does not appear to have been solved. For example, the variations in the viable counts of the suspensions and the freeze-dried vaccines and the average loss of viability due to freeze-drying reported by Obayashi (1956) are shown in Table 2. It will be seen that in the first experiment there is on an average a ten-fold variation between the highest and the lowest viability in the original vaccinal

suspensions and a fourteen-fold variation between the highest and lowest survivals in the dried vaccine immediately after drying. The average loss of viability due to freeze-drying was 73.7 per cent.

TABLE 2.
Showing loss of viability due to freeze-drying (Obayashi et al 1956)

Experiment I				Lot No.	Experiment II		
Lot No.	Incubation period of Sauton Cultures (days)	Viable units in 10 ⁻⁹ mg bacilli			Incubation period of Sauton Cultures (days)	Viable units in 10 ⁻⁹ mg bacilli	
		In original suspension	Immediately after drying			In original suspension	Immediately after drying
397-B	11		5.2	568-R	10		38.2
397-C	11	16.0	5.4	568-C	10	91.4	31.0
397-E	11		5.4	568-D	10		45.0
399-D	12		3.0	569-A	10		28.2
399-E	12	30.4	4.4	569-B	10		29.6
399-F	12		7.0	569-C	10	50.0	30.8
400-A	11		35.4	569-D	10		38.0
400-E	11	39.5	35.0				
400-F	11		33.6	570-B	10		19.8
401-D	10	73.0	19.4	570-D	10	49.7	49.4
401-E	10		11.6	571-D	10	84.2	25.2
402-C	11	57.0	8.4	572-A	10	89.8	32.0
402-D	11		23.2	574-C	9	31.2	25.6
403-C	9	65.8	37.0	575-A	8	79.8	35.0
403-E	9		30.5	575-B	8		20.2
406-A	10		41.2				
406-C	10	172.0	17.4	576-B	9	100.6	27.4
406-E	10		16.0	576-C	9		31.4
409-A	12	42.4	1.8	577-A	8	82.8	12.4
409-C	12		4.2	577-B	8		26.2
412-A	12	105.4	15.8	579-A	9	118.6	19.4
412-C	12		18.4				
415-C	11	30.2	5.2	580-A	10	150.6	8.8
415-E	11		3.8	581-A	9	97.0	21.0
417-A	11	64.2	14.6	582-C	10	128.2	23.8
417-A	11		34.6				
418-A	8+12		22.6				
418-C	8+12		15.6				
418-E	8+12	63.2	23.2				
418-M	8+12		14.8				
419-D	9	50.4	9.2				
419-M	9		14.2				
420-A	11		5.4				
420-D	11	46.6	11.0				
420-M	11		5.4				
422-A	11		17.0				
422-D	11	50.2	20.8				
422-M	11		9.0				
	Average	60.4	15.9	Average		88.8	28.1

In the second experiment, there is a five-fold difference between the maximum and minimum viable counts of the original vaccinal suspensions and a six-fold variation between the highest and lowest survivals in the dried vaccines immediately after drying, the average loss of viability due to freeze-drying being 68.4 per cent. Thus while there is no appreciable difference between the average loss of viability of the two groups of vaccine, the differences between the survival rates of the individual lots of dried vaccine are considerable.

Recently some trials with a British freeze-dried vaccine have been reported. Lorber et al (1956) reported a preliminary trial using dried vaccine in a dose of 0.4×10^6 viable units for the vaccination of 276 newborn infants. Compared with the Danish liquid vaccine, the British dried vaccine produced smaller vaccination lesions, less involvement of lymph nodes, a slightly lower rate of conversion, 94 per cent after 12

weeks, and a delay in conversion. They concluded that vaccines of that strength were unsuitable for the vaccination of contacts because the number of viable units present in the vaccine just fell short of the number required to produce the desirable 100 per cent conversion within a short period. The annual testing of the infants showed that out of 126 infants tested 81 or 64 per cent gave a positive reaction, which is a reversion rate of 30 per cent after one year.

Lorber and others (1957) reported the results of further trials for which material from three batches of dried vaccine was used. The first vaccine (batch 50) injected in a dose of 0.014×10^{-6} viable units gave a conversion rate of 56.5 per cent which rose to 67 per cent after one year. It was considered too weak for general use.

The second vaccine (batch 77) administered in a dose of 2.3×10^{-6} yielded a conversion rate of 86.8 per cent which rose to 92 per cent after one year. It caused too large vaccination lesions with frequent ulceration and significant glandular involvement. Ten per cent of the infants had glandular enlargement exceeding 5 mm. and up to 30 mm. with suppuration in four cases. The vaccine was considered too strong for general use.

The third vaccine (batch 93a) injected in a dose of 1.1×10^{-6} viable units was compared with the Danish Liquid vaccine given in a dose of 2.3×10^{-6} viable units. The tuberculin conversion between the 6th and 11th weeks with 10 T.U. O.T. was 43.8 per cent for the British dried vaccine and 48.9 per cent for the Danish fresh vaccine. It was concluded from this trial that a freeze-dried vaccine with a viable count of approximately $10 \times 10^{-6}/\text{ml}$. was suitable for contacts and mass vaccination. The results of the annual follow-up testing of these groups are not yet available.

Lorber and Menneer (1958) used vaccine of the same batch (93a) for the vaccination of 174 children below 14 years of age. On retesting, 98.9 per cent of those tested with 10 TU. BCG tuberculin gave a positive reaction. Tuberculin conversion, it was reported, was demonstrable as early as the tenth day after vaccination in all the 23 children tested. They re-affirmed that a vaccine of that strength was suitable for the vaccination of contacts and other groups, including the newborn. The annual follow-up tests have not yet been done for this group.

Discussion: I have indicated some of the chief factors that tend to make freeze-dried vaccine an inconstant product in so far as the viable units contained in it are concerned. Neither the variations in the viable counts of the original vaccinal suspensions nor those in the freeze-dried vaccines would have mattered if it were possible to obtain single-cell suspensions of BCG after reconstituting the dried vaccines with the appropriate diluent. Unfortunately the interpretation of the results of the viability tests is rendered difficult because of the tendency for BCG to remain in aggregates, though small. The viable count is therefore not a true index of the total number of viable bacilli contained in the vaccine. It is probably this lack of uniformity of dried vaccine, even of the same origin, that is responsible for the sceptical attitude of Dubos (1955), Aronson (1955) and others on the future of freeze-dried BCG vaccine.

Some of the claims of the survival rates of freeze-dried vaccine after storage are somewhat misleading and call for clarification. There seems to be no uniformity among BCG research workers in the method of expressing the number of living elements in the dried vaccine after storage. Some observers express it as a percentage of the number of viable units found in the vaccine immediately after drying, while others express it as a percentage of the number of viable units in the original vaccinal suspension before it was dried. For instance, in two experiments reported by Obayashi *et al* (1956) the authors reported survivals as high as 67.3 and 76.2 per cent after six months, 64.2 per cent after 11 months, 56.0 and 57.6 per cent after 17 months, etc. in terms of

the number of viable writs present in the vaccines immediately after drying, which is reckoned as 100%.

Birkhaug (1951), on the other hand, reported the viability of a dried vaccine as 17.02 per cent two days after drying and that after 12 months as 13.82 per cent in terms of the viability of the fresh vaccine. If the survival rate had been represented as a percentage of the viable count obtained two days after drying, the unrealistic survival rate of 81.25 per cent would have been obtained.

I submit that as the dried vaccine is intended as a substitute for the wet vaccine, the comparison at all stages during storage should be between the dried vaccine and the original suspension and not between the same dried vaccine of different ages. Otherwise the publication of the viable counts of the original suspensions becomes meaningless.

Although the studies with the use of isotopes by Strom (1955), Sternberg and Frappier (1955) and Pasquier (1955) have thrown considerable light on the relation of tuberculin sensitivity to immunity against tuberculosis, the optimum level of tuberculin sensitivity to be obtained by BCG vaccination is still undetermined. In the absence of such a knowledge, one cannot be certain about the dose of BCG for vaccination. In these circumstances, the method and dose of tuberculin employed for the assessment of BCG vaccination are largely empirical and governed by practical considerations. The selected dose of tuberculin and method of test are such that do not cause unpleasant reactions. At the same time the test should not be too sensitive. It is important, however, that the same method and dose of tuberculin should be used after vaccination as those employed before vaccination. This does not, of course, apply to newborn babies vaccinated within a few days after birth.

In Japan, the minimum requirement of viable BCG required to guarantee satisfactory antigenicity has been established as 120,000 viable units per dose, but most of the vaccines prepared at the present time in Japan exceed 400,000 viable units per dose (Obayashi, 1955).

The significance of the dead BCG in the vaccine is generally overlooked in the standardization of the vaccine. Because of the direct relation of the number of living bacilli to the degree of tuberculin sensitivity the emphasis has always been on the number of viable bacilli. It has to be remembered that the liquid vaccine is composed of a predominant proportion of dead BCG and a small proportion of living ones. Krohn (1953) found that only 10.2 per cent of the intact, acid-fast particles in the wet vaccine were viable on culture. The effect of freeze-drying is to reduce it further. It is well known that even dead BCG can induce the development of allergy, though not to the same level as living BCG.

In this connection, the field studies by Meyer and Palmer (1952) on the significance of dead bacilli in BCG vaccine are of great interest. They showed that there are distinct differences between the allergy— and lesion-producing capacity of killed and fresh BCG. "Because of the different properties of living and dead bacilli, vaccines containing different proportions of the two are not of the same composition, they are *qualitatively* different".

The exact nature of the interaction, if any, between the dead and living BCG *in vivo* is not known. It has been shown, however, that the living and dead, intact bacilli contain a sensitizing antigen that is different from the non-sensitizing antigen *viz.* tuberculo-proteins that are released into the culture medium or into the body of the animal after disintegration of the bacilli. Theoretically speaking, it is possible for the

dead bacilli to play a dual role inside the body, sensitizing when intact, and desensitizing after dissolution. Therefore the influence of the dead BCG in the vaccine may not altogether be negligible.

Is it possible that the unexpected results of vaccination with some lots of dried vaccine are explainable with reference to the ratio of the dead bacilli to the living ones in the vaccine? If so, the conventional method of assessing the potency of the vaccine in terms of viable units contained in it would be inadequate. The total number of organisms in the vaccine should also be known. Experience may perhaps show whether there is an optimum ratio of living to dead BCG for successful vaccination.

It has been suggested by several workers that the results of vaccination with dried vaccine could be improved, if necessary, by increasing the dose of the vaccine. It is forgotten that by increasing the dose of the dried vaccine, one increases also the dose of dead BCG, which is present in freeze-dried vaccines in a higher ratio than that found in the original suspension. For instance, if the ratio of dead to living units in the fresh suspension is 9 to 1, and there is a 60 per cent loss of viability on freeze-drying, the ratio is altered to 24 to 1. Briggs (1955) used the French lyophilized vaccine for intracutaneous injection in doses as high 0.4 mg. and 0.6 mg. He found that while the increased doses produced significantly higher percentages of "successful vaccinations", they also increased the number of persons showing stronger local reactions. He was unable to confirm that the allergy conferred on those who showed the larger local reactions was any more permanent than that conferred on those with smaller local reactions.

The tuberculin reactions of the trials with the British freeze-dried vaccine are summarized in table 3. Five groups of infants and children were vaccinated with five batches of dried vaccine and one with the Danish fresh vaccine for comparison. The results of the annual follow-up tests are available only for the first three groups. Three batches of dried vaccine (batch 42, 48 and 50) were rejected as too weak, and the fourth batch (batch 77) as too strong, for general use. This leaves only one batch of dried vaccine (batch 93 a) which was used for the vaccination of 158 newborn infants and 174 children below 14 years of age. Prior to vaccination the latter group was tested by tuberculin Jelly test or Mantoux test with 10 T.U. O.T. or BCG tuberculin.

TABLE 3.

Percentages of Tuberculin conversion in the clinical trials with British freeze-dried vaccine.

Trial number	I	II	III	IV		V
Vaccine batch No.	42 and 48	50	77	93a	Danish liquid vaccine	93a
Dose of vaccine (viable units)	400,000	14,000	2,300,000	1,100,000	2,600,000	1,100,000
O.T. 10 T.U.	94	56.5	86.8	43.8	48.9	—
O.T. 100 T.U.	—	—	—	100	100	—
BCG Tuberculin 10 T.U.	—	—	—	98.6	99.4	8.86
	Annual follow-up tests				Not done yet	
O.T. 10 T.U.	64	67	92			
O.T. 100 T.U.	—	—	100		"	
BCG Tuberculin 10 T.U.	—	100	98		"	

Of the 158 infants, 73 were tested by Mantoux 10 T.U. O.T. and only 32 or 43.8 per cent were found positive after 6 to 11 weeks. But a 100 per cent of the infants tested with 100 T.U. O.T. and 99.4 per cent of those tested with 10 T.U. BCG tuberculin were shown to be reactors. Of the 174 children below 14 years, 172 were shown to be reactors, 142 by 10 T.U. BCG tuberculin and the rest by "other tests" which included Jelly test with BCG tuberculin or O.T. or Mantoux with 100 T.U. O.T. The results of the annual follow-up tests are not available for the infants and children vaccinated with vaccine batch 93a.

It will be seen from table 3 that the same method and dose of tuberculin have not been employed for retesting all the groups and therefore the results are not strictly comparable. Geddes (1957) states that cutaneous allergy after successful vaccination should attain induration of 6 mm to 10 T.U. tuberculin. The results with Mantoux 10 T.U. O.T. available for four batches of dried vaccine will be seen to be erratic. For instance, vaccine of batches 42 and 48 (rejected as too weak) has given the highest conversion (94 per cent), which is higher than that of batch 77 which was rejected as too strong for general use. Vaccine of batch 93a whose strength is recommended for general use by the authors has given the lowest conversion rate of all the batches including batch 50. In this connection one is surprised to find that the fresh Danish vaccine used for comparison has also given an unexpectedly low tuberculin conversion. It may be recalled that in the Medical Research Council trials of anti-tuberculosis vaccines (1956), the Danish vaccine yielded a conversion rate of 86 per cent, with 3 T.U. O.T. The results of the annual following-up study are awaited with interest.

As regards the use of BCG tuberculin for the control of BCG vaccination, it must be said that BCG tuberculin is a comparatively new product and we need to know much more about it, for experience of it is negligible compared with the pattern of results that tuberculosis workers throughout the world are familiar with O.T. and P.P.D. BCG tuberculin must therefore be regarded as still in the experimental stage.

Ustvedt (1949) considered it inadvisable to use BCG tuberculin for the control of BCG vaccination. He wrote "through different methods of testing with living or killed BCG, killed virulent tubercle bacilli, vole bacilli or BCG tuberculin, it is possible to ascertain that the BCG vaccination produces some effect also in organisms which give a negative response to the most sensitive tuberculin tests. No evidence has been brought forward, however, to make it probable that positive reactions to these tests are connected with a maximum specific resistance against superinfection obtainable through BCG vaccination. Even if it is theoretically possible that a state of allergy, which can only be detected through tests of this kind, may be connected with some increase in the resistance against superinfection, it cannot in the light of our present knowledge be advisable to regard positive reaction to such tests as sufficient indication of immunity".

Rosenthal (1957) does not recommend the use of BCG tuberculin for the control of BCG vaccination, but considers that O.T. is the tuberculin of choice for the purpose, a view that is strongly endorsed by Aronson (1955).

In view of the small number of infants and children vaccinated with British dried vaccine batch 93a, the low conversion rate and the incompleteness of the trial, the available evidence does not justify any valid conclusions to be drawn on the optimum dose of dried BCG vaccine for general use. The fact that Mantoux test with 10 T.U. BCG tuberculin gave a 100 per cent conversion (or nearly so) in all the groups tested irrespective of the dose of the vaccine administered, should be sufficient to raise doubts regarding the specificity of the test. The results of the tests with BCG tuberculin must therefore be viewed with great caution.

Further controlled studies on a larger scale are needed to establish the optimum dose of dried BCG for the vaccination of infants and others.

In view of the observed fluctuations in the viable counts of dried BCG vaccine from batch to batch and the technical difficulty of preparing vaccines with uniform viable counts, the dose of BCG for vaccination may, for the present, have to be established within a given range of viable units, rather than as a given number of viable units. The extremities of the range may represent the minimum and maximum limits, the former to ensure satisfactory tuberculin conversion and the latter to safeguard against too strong vaccination lesions. For example, the dose may be expressed as 2 to 4 x 10⁻⁷ viable units. This would enable the production centre to release dried vaccines of the appropriate strength and withhold the weak and strong vaccines.

One of the drawbacks of the freeze-dried BCG vaccine as at present prepared is the necessity for storage at refrigerator temperature till it is used. It is unfortunate that the need for the cold storage of BCG vaccine is greatest where the facilities for it are least, as in tropical climates. Intensive studies are being made in Japan to conserve the surviving BCG elements in the dried vaccine without further loss, even without refrigeration. The WHO Tuberculosis Office, Copenhagen and the Japan Anti-tuberculosis Association (1957) have reported the results of a field trial of two batches of dried vaccine prepared with 1 per cent sodium glutamate as the adjuvant. The allergenic potency of the vaccines stored under various conditions was compared with that of a batch of fresh liquid vaccine stored at 2° to 4° C. The results showed both lots of the dry vaccine to be remarkably heat-stable even after 30 days' exposure to tropical temperatures, and no marked loss of antigenic potency was observed. The report is of immense interest and one looks forward to see whether the allergy induced by the heat-exposed vaccine will maintain its level over the years.

In conclusion, there can be no doubt of the future of freeze-dried BCG vaccine. We have gone on too long using the fresh vaccine before the controls of the potency and safety of the vaccine could be completed. That it has been successfully used can be no argument for its continuance. It is therefore inevitable that freeze-dried BCG vaccine must sooner or later replace the fluid preparation.

There is equally no doubt that distinct advances have been made in the preparation of dried BCG vaccine, although some problems still persist. Two of the outstanding problems are to maintain a uniformly high viability and to obtain an uniform dispersion of the bacilli on resuspension. I felt that if the compression and grinding of the BCG mass with Steel balls could be avoided, a great step would have been taken towards making a more uniform vaccine. Therefore Ranganathan (1952) suggested the possibility of developing the method of submerged BCG cultures described by Dubos and Fenner (1950) for large-scale production of vaccine. It is interesting to note that the British freeze-dried vaccine is prepared from submerged BCG cultures. The Tween 80 method of homogenization reported by North (1956) and Obayashi (1956a) is of great interest and calls for further studies.

Whatever the improvements effected in the preparation of the wet vaccine and in the technique of freeze-drying, they will be of no avail if the bacilli in the resuspended vaccine are not uniformly distributed. This, in my opinion, is the most important surviving problem. Studies are in progress in the Madras Laboratory to find, if possible a solution to this problem.

It is, at the same time, desirable to keep the number of dead bacilli in the vaccine as low as possible in order to minimize the lesion-producing capacity of the vaccine. The first essential is therefore to standardize the technique of the preparation of the fresh

vaccinal suspension so as to be able to obtain a product with uniformly high viable count batch after batch. It should then be freeze-dried under strictly standardized conditions. It is relatively more easy to standardize the latter than the former. The design of the freeze-drying plant and its mechanical and electrical efficiency are important factors in the production of a good product.

SUMMARY

1. The factors that influence the survival of B.C.G. after freeze drying and storage, and the measures taken to minimize loss of viable bacilli are mentioned.

2. Attention is drawn to the observed variations in the viability of dried vaccines not only from different sources, but even of the same origin.

3. Further studies are needed to determine the optimum level of allergy to be obtained by B.C.G. vaccination and the appropriate dose of vaccine that will produce it under standardised conditions of tuberculin testing.

4. There can be no doubt of the future of freeze-dried vaccine if the methods of production can be further improved and the laboratory assay of the vaccines well standardized.

I have to express my deep sense of gratitude to the Technical Co-operation Mission of U.S.A. in New Delhi for kindly awarding me a Travelling Fellowship which made the above study possible.

I am indebted to the chiefs of B.C.G. production centres and others, too numerous to mention by name, for affording full facilities for the study and for the full and frank discussion of the problems.

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Anti-Tuberculosis Treatment & Adrenal Cortex

By

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AND

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This paper is a continuation of our earlier work, already reported (1957). The idea is to find out how specific antitubercular therapy modifies the adrenal function.

Methods & Material

The present report deals with a follow up of the thirty cases reported in the previous paper. Each case was followed for a period of 2½ months from the date of admission, unless the patient expired or left earlier. During this period each patient was put on the following therapy regimes:

1. *Bed Rest*—The patient was put on bed rest for a period of a fortnight. During this period no specific chemotherapy or collapse therapy was started.

2. *Chemotherapy*—After the period of bed rest was over the patient was put on chemotherapy. The various regimes followed were:—

- (a) Streptomycin (1 Gm. daily) plus INH (200 Gm./day).
- (b) Streptomycin (1 Gm. daily) plus PAS (8 Gm. day for 5 days a week).
- (c) INH (200 mg./day) plus PAS (8 Gm./day for 5 days a week).

Chemotherapy was given for a period of one month.

3. After the end of one month's chemotherapy, collapse therapy was given when indicated. Only Pneumoperitoneum or Artificial Pneumothorax was given in these cases.

The cases were fully investigated on admission, at the time of change of a therapy regime and at the end of 2½ months period of follow up. The investigations included:—

1. A detailed history with special reference to chest symptoms, symptoms of toxemia, gastrointestinal symptoms and symptoms suggesting involvement of other organs.

2. A thorough clinical examination-general and systemic.

3. Laboratory investigations:

- (i) Routine-including Total and Differential W. B. C. Count, total R.B.C. Count and Hb%, urine and stool examination.

- (ii) Special-including ESR (Westergren), sputum examination for A.F.B. (Gaffky count), Tuberculin Test (using 5 T. U. PPD.) Vital capacity, Radiological investigations, and where indicated, laryngeal examination, C.S.F. examination and Funds examination.
- (iii) Adrenocortical Function Tests :—
- Total 17-Ketosteroids excretion in urine in 24 Hrs. (by Robin & Gibson's method).
 - Thorn's Test (by the rapid technique).
 - Urinary Uric Acid-Creatinine Ratio.

State and activity of the disease was assessed by analysing the (i) degree of systemic effect (the cases being classified into Severe, Moderate, Slight and Absent according to the criteria laid down by the subcommittee of Indian Tuberculosis Association), (ii) weight (iii) ESR (iv) Bacteriological examination of the sputum, (v) quantity of sputum in 24 hrs. (vi) vital capacity and, (vii) serial X-ray examination.

The cases were again classified according to the anatomical extent of the disease into three stages according to the criteria recommended by Indian Tuberculosis Association.

Analysis & Results

1—Bed Rest—

Table No. 1 shows the state and activity of the disease, before and after a fortnight period of bed rest in 29 cases. In one case (case No. 11) it was not thought advisable to withhold chemotherapy and so the case was put on chemotherapy straight away.

TABLE No. 1

	Before bed rest	After bed rest
1. Degree of systemic effect		
Severe.	18 cases (62.1%)	17 cases (58.7%)
Moderate.	10 cases (34.5%)	10 cases (34.5%)
Slight.	1 case (3.4%)	1 case (3.4%)
Absent.	0 case(—)	1 case(3.4%)
2. Weight.		
Range.	70-124 lbs.	70-124 lbs.
Average.	89.7 lbs.	89.8 lbs.
3. ESR.		
Range.	15-140 mm.	15-135 mm.
Average.	70.7 mm.	70.6 mm.
4. Sputum. (Bacteriological)		
T.B. Positive.	28 cases.	28 cases.
T.B.—ve.	1 case.	1 case.
Gaffky count (Average).	G 3.4	G 3.4
5. Sputum-quantity 24 hrs.		
Range.	Slight (½ drachm)— 16 drachms.	½-16 drachms.
Average (% of average normal).	5.9 drachms.	5.5 drachms.
6. Vital capacity (% of average normal).	45.6% (Average)	45.9% (average)
7. Radiological.		
Improvement.	—	case (-)
Slight or no improvement		28 cases (96.6%)
Worse.		1 case (3.4%)

NOTE: Improvement means clearing of exudation and/or reduction in cavity side.

It is evident from Table No. 1 that a fortnight's bed rest causes little change in the state and activity of the disease. There was slight improvement in the amount of sputum, in systemic effect and in vital capacity. Radiologically there was no change in 28 cases, while one became worse.

Adrenocortical Function (Lab. Tests)

TABLE No. 2.

Tests	Before bed rest	After Bed Rest
1. Urinary 17-ketosteroids (mg./24 hrs.). Range. Average.	3.2-11.0 7.37	3.1-10.8 8.14
2. Thorn's Tets (% reduction in eosinophil count after ACTH). Range. Average.	30-64% 38.1%	32-64% 40.9%
3. Uric Acid-Creatinine Ratio. Range. Average.	0.14-0.55 0.314	0.164-54 0.318

Table No. 2 shows that after a fortnight's bed rest there was only slight change towards better in adrenocortical function as shown by laboratory tests.

II Chemotherapy—(Total no. of cases-30.)

1. *State & Activity of the disease*—Table No. 3 shows the state and activity of the disease before and after chemotherapy.

TABLE No. 3.

	Before Chemotherapy	After Chemotherapy
1. Degree of systemic effect Severe. Moderate. Slight. Absent.	18 cases (60%) 10 cases (33.4%) 1 case (3.3%) 1 case (3.3%)	3 cases (10%) 14 cases (46.7%) 12 cases (40%) 1 case (3.3%)
2. Weight Range. Average.	46-124 lbs. 86.8 lbs.	46-134 lbs. 94.1 lbs.
3. ESR. Range. Average.	15-135 mm. 68.2 mm.	8-110 mm. 42.3 mm.
4. Sputum. T.B. Positive. T.B.—ve. Gaffky count.	29 cases (96.7%) 1 case (3.3%) G3.5	12 cases (40.0%) 18 cases (60.0%) G1.2
5. Sputum-quantity/24 hrs. (drachms). Range. Average.	½-16 5.3	0-12 2.4
6. Vital Capacity (% of average normal).	44.9%	51.2%
7. Radiological. Improvement. Slight or no improvement. Worse.	— —	23 cases (76.7%) 5 cases (16.7%) 2 cases (6.6%)

It is obvious from Table No. 3 that there was marked improvement in the thirty cases after chemotherapy, as assessed clinically, bacteriologically and radiologically.

2. Adrenocortical *Function (Lab. Tests)*.

TABLE No. 4

Test	Before Bed Rest	After Bed Rest
1. Urinary 17-ketosteroids. (mg./24 hrs.) Range. Average.	3.1-10.8 8.08	5.5-12.4 9.04
2. Thorn's Test (% reduction in eosino- phil count after ACTH) Range. Average.	32-64% 40.9%	30-68% 48.4%
3. Uric Acid-Creatinine Ratio. Range. Average.	0.16-0.54 0.3-14	0.16-0.64 0.42

As is clear from Table No. 4, the lab. tests showed improvement in adrenocortical after chemotherapy.

When the various Lab. tests for adrenocortical activity were assessed in relation to various chemotherapeutic regimes, it was noted that the improvement in adrenocortical function noted after chemotherapy was contributed by all the combinations of drugs. The results are shown in Table No. 5.

TABLE No. 5

Chemotherapy Group	No. of cases	Before Chemotherapy			After Chemotherapy		
		17Kts. mg/24hrs.	Thorn's Test	U-C ratio	17 Kts. mg/24hrs.	Thorn's Test	U-C Ratio
S & INH	16	7.77	41.3%	0.31	8.66	48.4%	0.43
S & PAS	9	8.66	41.5%	0.30	9.97	49.3%	0.44
INK & PAS	5	7.86	40.2%	0.35	8.94	44.6%	0.43

III. Collapse Therapy—(Total No. of cases—20)

Collapse measures (A.P. or P.P.) could not be given in 9 out of the total 30 cases due to various reasons. In one case (case no. 18) it was not thought advisable; one case (case no. 2) was waiting for resection; case no. 30 was waiting for thoracoplasty, case no. 3 left against medical advice, two cases died (case Nos. 11 and 20); in three cases (case nos. 10, 15 & 26) collapse therapy was tried without success. Out of the remaining 21 cases in whom collapse measures were given, 6 were given A.P. and 16 were given P.P. This represents the trend in the hospital these days of giving lesser A. P's

1. *State and Activity of the disease* Table No. 6 shows the state and activity of the disease before and after collapse measures.

TABLE No. 6

	Before Collapse Therapy	After Collapse Therapy
1. Degree of systemic effect		
Severe.	0 case (—)	0 case (—)
Moderate.	11 cases (52.8%)	7 cases (33.3%)
Slight	10 cases (47.6%)	9 cases (42.9%)
Absent	0 cases (—)	5 cases (23.8%)
2. Weight		
Range.	78-134 lbs.	80-133 lbs.
Average.	98.6 lbs.	100.5 lbs.
3. ESR.		
Range.	8-70 mm.	8-70 mm.
Average.	41.2 mm.	33.7 mm.
4. Sputum.		
T.B. Positive.	6 cases (28.5%)	5 cases (23.8%)
T.B.—ve.	15 cases (71.5%)	16 cases (76.2%)
Gaffky Count.	G0.5	G0.33
(Average)		
5. Sputum-quantity/24 hrs (drachms)		
Range.	0-8	0-4
Average.	2.2	1.1
6. Vital Capacity.		
(% of average normal)		59.6%
7. Radiological		
Improvement	53.9%	10 cases (47.6%)
Slight or no improvement	—	11 cases (52.4%)
Worse.	—	0 case (—)
	—	

It can be inferred from Table No. 6 that after one month's collapse therapy there was some degree of improvement in the state and activity of the disease.

2. Adrenocortical Function (Lab. Tests)

TABLE No. 7

Test	Before Collapse measures	After Collapse measures
1. Urinary 17-Keto-stroids (mg./24 hrs.)		
Range.	5.5-12.4	5.6-12.4
Average.	9.58	9.88
2. Thorn's Test (% reduction in eosino phil count after ACTH)		
Range.	41-60%	42-62%
Average.	49.8%	51.8%
3. Uric Acid-Creatinine		
Ratio.		
Range.	0.34-0.64	0.40-0.62
Average.	0.46	0.50

Table No. 7 shows that there was slight improvement in adrenocortical function as shown by Lab. tests.

When the various Lab. tests for adrenocortical activity were correlated with the various forms of collapse therapy (A.P. or P.P.), it was noted that both the groups of cases contributed to the improvement in adrenocortical function. The results are shown in Table No. 8

TABLE No. 8

Collapse measures.	No. of cases.	Before Collapse Therapy			After Collapse (average)		
		17-kts.	Thorn's Test.	U-c Ratio.	17-kts.	Thorn's Test.	U-c Ratio.
P.P.	15	9.6	50%	0.46	10.0	52.1%	0.51
A.P.	6	9.3	49%	0.45	9.6	50.5%	0.47

Discussion & Conclusions

In our previous paper we found that an average case of Pulmonary Tuberculosis showed evidence of adrenocortical hypofunction as assessed by laboratory tests. An analysis of our observations in the present report shows that after antitubercular treatment, there is a partial correction of hypocorticalism present on admission. A slight improvement in adrenocortical function was found after bed rest therapy (table No. 2). An improvement in adrenocortical function was also noted after chemotherapy and, again after collapse measures (table Nos. 4 & 7).

Most of the reported work in literature is confined to the effect of INH on adrenocortical function in pulmonary tuberculosis. Thus Schmidt (1954) observed a return of the 17-ketosteroids values to normal in all cases as a result of treatment with INH. De Luca, R and Lomardo G (1954) also came to a similar conclusion. They also observed clinically evident hypercorticalism after INH therapy. Radebach et al (1954) also observed an "overcompensation" of adrenocortical hypofunction in tuberculosis manifesting an "moon-face", striae, mild hypertension, and other toxic manifestations resembling Cushing's Syndrome and overdosage of ACTH.

Our own cases, however, did not show such "Overcompensation". None of our cases showed clinical or laboratory evidence of hypercorticalism after any form of treatment, including various combinations of chemotherapeutic drugs. We did not try various drugs separately due to obvious reasons. However, various combinations of streptomycin, INH and PAS enable us to have an idea of the effect of separate drugs. As improvement in adrenocortical function was noted after all combinations (Table No. 5), it was concluded that the effect is not due to any single drug. Also that it was not due to any particular form of collapse therapy was inferred from the observation that the adrenocortical function improved after each form of collapse therapy (table No. 8). This shows that the change in adrenocortical function after treatment cannot be attributed to any one drug or form of therapy. The explanation must, therefore, be sought in some other mechanism.

A close parallelism was noted between the improvement in activity of the disease process as assessed by degree of systemic effect, weight, ESR, bacteriological examination of the sputum, quantity of sputum, vital capacity and serial radiological examination, on one hand, and the improvement in adrenocortical function on the other hand.

This suggests that there is a relation between resistance and adrenocortical function in tuberculosis, because "the degree of resistance can only be surmised from the manner of progress of lesion under observation" (Rich 1951). As adrenocortical activity alters with alteration in the course of the disease, one is tempted to attribute the improvement in adrenocortical function after treatment to enhanced resistance. Our observations on the correlation between the extent and type of the disease and the adrenocortical function, already reported, lends support to this idea. We found that the adrenocortical functions were best in the productive type of lesion, and we know that this type of lesion is associated with high degree of resistance. Impaired functions were found in acute miliary type of disease, which is supposed to be a manifestation of low resistance.

Goldman et al (1952) observed that 63% of patients who had an impaired adrenocortical function, as determined by Thorn's Test preoperatively developed some sort of post-operative complications after surgical treatment for pulmonary tuberculosis (compared to only 16% of patients with good adrenocortical function

having postoperative complications). Pakkarinen & Turnen (1955) came to a similar conclusion, and advised a routine pre-operative check up of adrenocortical activity in all cases of pulmonary disease going for surgical treatment. This suggests that low adrenocortical activity means a general low resistance of the patient.

“In the human being acquired resistance cannot be measured under controlled conditions as in experimental animals.” (Rich, 1951) In view of our conclusions a laboratory assessment of adrenocortical function may be used as a measure of resistance in pulmonary tuberculosis.

SUMMARY

Function of the adrenal cortex was assessed by laboratory tests before and after various forms of antitubercular treatment in thirty cases of pulmonary tuberculosis. After anti-tubercular therapy a partial correction of the hypocorticalism present on admission was observed. The conclusion has been drawn that adrenocortical activity of a tuberculous patient is closely related to the activity of the disease process. The relation of the adrenal cortex to the resistance in tuberculosis is discussed.

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Extra Pleural Pneumonolysis with or without Plombage in Thoracoplasty Failures

(Review of 21 cases)

By

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The Principles of Pneumonolysis cannot be thought of as a new arrival in the field of treatment of Pulmonary Tuberculosis. History records its use as early as 1891 and its further development lies closely with the progress of Collapse Therapy in general.

The introduction of standard Thoracoplasty was soon followed by the first Extra Pleural Pneumonolysis by Tuffier in 1891. Extra Pleural Pneumonolysis is the term given to the operation in which both the layers of Pleura and the underlying lung are stripped from the thoracic wall and the space thus created is filled with a 'Filling' whether it be air or any other substance. The idea attracted attention and the provision of the needed collapse without resorting to mutilated procedures were welcomed. Then came the problem of finding the suitable material for filling the extra pleural space. A review of literature tells us of the different substances that had been used but only to be discarded for various reasons.

In 1910 Tuffier used fat and later used omentum and fresh lipomas. In 1913 Baer used liquid paraffine and Jessan used wax in 1921, in the same year Archibald used pedicled muscle as pectoral muscle and female breast etc. Other substances used were:- gauze, gelatine, rubber balloons, gum sheeting, bone graft etc. But one by one all of these were given up because of the intolerance of foreign body to host (John Alexander 1933) but paraffine and air were continued for some time.

In recent years a whole-new array of synthetic filling material has been put in the market which increased the interest in Plombage. In 1946 Wilson reported the use of methyle methacrylate spheres as a filling material and since then lucite balls, ping pong balls, spongistan, polystan etc have been widely used.

John Alexander in 1933 recorded the advantage of extraperiosteal plan of separation over the extra pleural. Woods, Buente, Goldman, Adam and others thought that the high complication rate associated with the extrapleural Plombage could be due to the proximity of the Plombage to the diseased area which may interfere with its blood supply so the additional thick vascular layer of muscles and fascia between the Plombage and the diseased lung might solve the problem. So mostly the extra periosteal Plombage Thoracoplasty is done now in place of former extra plueral Plombage. In 1951, Roger Mitchel said that the extraperiosteal Plombage Thoracoplasty might even take the place of standard Thorocaplasty; whether this will happen or it will remain an other incident in the history of the evolution of the surgical therapy of the pulmonary tuberculosis remains to be seen.

Extra pleural Pneumonolysis has been tried on 21 cases treated in this Sanatorium from 1949 to 1953. Of these, 17 were men and 4 women. The average age is 30 years, the youngest being 19 years and the oldest 52 years.

TABLE I

AGE			
Total cases	= 21	maximum age	= 52 years
Men	= 17	minimum	= 19 years
Women	= 4	average	= 30 years

All these cases had undergone standard Thoracoplasty operations but the result of the Plasty was not completely successful.

In order to assess the results, the cases have been divided into following groups:—

Group I :— Contralateral lung practically free from disease.

Group II :— Contralateral lung having disease but fairly controlled by other measures.

Group III :— Advanced cases (Contralateral lung having active disease) where this procedure has been tried as a desperate measure.

Each of these groups have been further subdivided into:—

A = Sputum not converted but with or without cavity being visible on X-ray after thoracoplasty.

B = Sputum converted but cavity visible on X-ray after thoracoplasty. -

The time interval between the Thoracoplasty and the Pneumonolysis is indicated in the following tables :—

TABLE No. II.

		No. of Cases	Average period	Maximum	Minimum
Group I	A	6	5 months	7 months	3 months
	B	1	5 months	5 months	5 months
Group II	A	6	6 months	18 months	1 month
	B	4	10 months	23 months	5 months
Group III	A	4	4 months	12 months	3 months
	B	—	—	—	—

From table 2 we can assess the results of Thoracoplasty in Group I, seven cases were free of disease in the contralateral lung. Out of them 6 remained positive for A.F.B. and though one was converted negative but still showed cavity on X-ray.

In Group II, ten patients had disease in the contralateral lung which was controlled before operation; out of them 6 remained positive though 4 were converted but cavity persisted.

In Group III, all the 4 cases remained positive with persistent cavitation on the operated side. The time interval between Thoracoplasty and Pneumonolysis is also shown, showing the maximum, minimum and the average period.

The result of the Pneumonolysis is shown in table III.

TABLE III

		No. of cases	Sputum converted negative.	Sputum remained positive.
Group I	A	6	4	2
	B	1	1	—
Group II	A	6	4	2
	B	4	4	—
Group III	A	4	1	3
	B	—	—	—

In Group I, out of 6 cases with positive sputum after Thoracoplasty, 4 were converted after Pneumonolysis, while in Group II, out of the 6 cases with positive sputum 4 were converted negative while 2 remained positive. In Group III, out of the 4 cases only one could be benefitted and converted negative.

Time lag of sputum conversion after the Pneumonolysis.

Maximum = 8 months

Minimum = 1 month

Average = 3 months

Packing material used:

Simple stripping (no pack) = 9 cases

Polystan = 8 cases

Spongistan = 2 cases

Lucite or Ping Pong Ball = 2 cases

Table IV shows the condition in the immediate post—operative period. Duration of fever is 8 to 13 days with average deviation of temperature from 100-101 F. In 3 cases there was marked serum collection and 2 got wound infection.

TABLE IV.

		Stripping only (No pack)	Polystan	Spongistan	Ball Pack
Fever	Average range	99-100 F.	100-101 F.	100 F.	100 F.
	Average duration	7 days	13 days	10 days	8 days.
Serum Collection		—	2	1	—
Wound infection		—	1	1	—
Dyspnoea		—	—	—	—

Complications : Pleural tear..... 2
Broncho--Pleural Fistula.... 1

Results : Quiscent..... 1
much improved..... 9
improved..... 8
stationery..... 3

CASE REPORTS

Case No. I

Shri P. K. Male 52 years, Electrical Engineer from Nagpur was admitted at Lady linlithgow Sanatorium on 9th June, 1951 with the complaints of fever, cough with expectoration and irregular bowels.

Present illness :

Onset 1946 with infiltration and cavitation right upper zone, for which he had A.P. (right) for 2 years. In 1950 he developed cavity left upper zone.

Sputum was positive for A.F.B.

He was operated for Cholelithiasis.

Diabetics for 4 years before admission.

Family History :

Uncle died of T. B. in 1928.

Sister died of T. B. in 1935.

On Admission :

X-ray Chest:

Right lung showed healed opacities upper zone and obliteration of Costo-phrenic angle.

Left lung showed infiltration and cavitation upper zone.

Pathological Investigations :

R.B.C. 4.32 million
 Hb 98%
 W.B.C. 10312
 D.L.C.

Polymorph 52%
 Lymphocyte 42%
 Large mono 4 %
 Eosinophil 2%

B.S.R. 17 mm 1st hour (Wester-green)
 Urine sugar 1.75%
 Blood sugar 260 mgm %
 Sputum positive for A.F.B.

Treatment ;

A. P. left started on 18.6.1951 but had later to be abandoned being contra-selective as one thick adhesion was attached to the subclavian artery which on thoracoscopy could not be cauterised.

5 rib Thoracoplasty on the left side was completed on 7-11-1951. He was on anti-tuberculous drugs before and after Thoracoplasty. Diabetics was treated with Insuline.

After Thoracoplasty, sputum remained positive for A.F.B. So on 27.2.1952 extra Pleural Pneumonolysis was done and the space packed with Spongistan. Sputum got converted negative in June, 1952. The patient was discharged as much improved on 11.7.1952.

CASE No. II

Shri P. R., male, 19 years, student from U.P. was admitted on 11.1.1952.

Onset :

April 1951 with hemoptysis. Sputum was found positive for A.F.B.

Family History :

2 brothers died of T.B.

Before Admission he had the following treatment :—

Streptomycin— 30 grams.
 P.A.S. — 400 grams.
 A. P. left was tried but unsuccessful.
 Left phrenic crush — July 1951.
 P.P. from October 1951 to December 1951.

On Admission :

x-ray chest showed cavity left upper zone.

Pathological Investigations:

R.B.C. 4 million
 Hb 90%
 W.B.C. 8900
 D.L.C.
 Polymorph 54%
 Lymphocyte 37%
 Esinophil 6%
 Large mono 3 %
 B.S.R. 3 mm 1st hour (Wester green)
 Sputum positive for A.F.B.

Treatment ;

6 rib Thoracoplasty left side completed on 17.3.1952. Sputum remained positive for A.F.B. in spite of post-operative Chemotherapy.
 On 8.10.52 extra Pleural stripping alone was done after removing a piece of 7th rib.
 Sputum was converted negative by the end of October 1952. Chemotherapy was given in the post-operative period for two months.
 Patient was discharged as quiescent on 3.2.1953.

CASE No. III.

Shri V., male, 35 years, a clerk from U.P. was admitted on 28.4.1953.

Onset ;

April 1942 with fever and cough. Sputum was negative for A.F.B. He was treated at Bhowali sanatorium (U.P.) and was discharged as clinically cured in November 1942.
 Relapse in August 1948 with cavity right upper zone, sputum was positive for A.F.B. He was treated at New Delhi T.B. Centre with Chemotherapy and P. P. The cavity closed and sputum became negative in 1949.
 Cavity reappeared in 1950. He was again put on Chemotherapy and cavity disappeared in 3 months time.
 Cavity again reappeared in 1953. From 1948 to 1953 all along for 5 years he was on P. P.

On Admission :

X-ray chest showed a cavity with infiltrative lesions in the right upper zone.
 Evidence of P. P. under both the diaphragm.

Pathological Investigations ;

R.B.C. 4.13 million
 Hb 90%
 W.B.C. 9000
 D.L.C.

Polymorph 58 %
 Lymphocyte 40%
 Large mono 2 %
 B.S.R. 40 mm 1st hour (Wester green)
 Sputum positive for A.F.B.

Treatment :

A. P. right — unsuccessful

4 rib Thoracoplasty completed on 10.6.1953. Sputum remained positive inspite of the use of Chemotherapy.

Extra Pleural Pneumonolysis with Polystan Pack was done after removing the 5th rib on 23.9.53 Sputum got converted negative in December 1953. Pack got infected and fistula formed. So on 20.8.1954 the pack was removed and broncho—pleuro—cutaneous fistula was detected. Wound was cleaned. Revision Thoracoplasty was done, Strepto and Pencil in was put in. Fistula got closed later on and the patient was discharged on 25.12.54 as improved.

Discussion

In the cases under review though extra pleural Pneumonolysis with and without pack was tried in Thoracoplasty failure cases; but this is not considered an elective procedure. If facilities for resection were available that could have been an elective and effective procedure. But under the circumstances this was undertaken as the next best procedure available, and 14 cases were converted negative and sent as non-infectious; giving us in this series 66% good results.

Two cases got wound infection and the pack was removed later; In one, Spongistan and the other Polystan was used as pack and the dissection was extra pleural; one of them developed broncho-pleuro-cutaneous fistula which got healed after the removal of the infected pack and revision Thoracoplasty.

It is better to do extra periosteal pneumonolysis then the extra pleural, as in the latter the pack may burrow into the lung parenchyma leading to bronch-pleural fistula.

Summary

21 cases out of which 16 cases remained sputum positive with or without cavity seen in the X-ray after Thoracoplasty are reviewed. In 5 cases though the sputum was converted negative by Thoracoplasty the cavity was still visible on X-ray.

Out of this series 10 cases had a lesion in the contralateral lung which was fairly controlled by other measures. 4 cases were far advanced with active disease on the contralateral lung.

Extra Pleural Pneumonolysis was done in all these cases. In 9 cases only stripping was done and in the other 12 cases, pack was done. Out of the 21 cases, 14 cases were converted negative while 7 cases remained positive. 2 cases got wound infection and one of them developed broncho-pleuro-cutaneous fistula.

Acknowledgement

I am grateful to Dr. T. J. Joseph, Medical Superintendent for his guidance and permission to publish this paper.

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NEWS AND NOTES

Dr. B. K. Sikand has been appointed by the Tuberculosis Association of India as the Chairman of the Standing Technical Committee of the Association and also President of the Fifteenth Tuberculosis Workers' Conference.

XVth Workers' Conference

The Fifteenth Tuberculosis Workers' Conference organised by the Tuberculosis Association of India will be held in Jaipur early in 1959. Papers on the various aspects of Tuberculosis control and treatment will be presented at this conference and there will be panel discussions on Domiciliary Service in Tuberculosis and Surgery.

Dr. Hans Kumar, Honorary Secretary, Rajasthan Tuberculosis Association, K.G.V. Sanatorium, Jaipur is making necessary arrangements for the Conference.

As usual rail travel concession is admissible to those delegates, whose travelling expenses are not met by either the Government, Central or state, or any local body or statutory authority.

The Conference will be presided over by Dr. B. K. Sikand.

Proceedings of the XIVth International TB Conference

Proceedings of the XIVth International Tuberculosis Conference held in New Delhi in January 1957 will be ready very shortly. As only limited number of copies are being printed, orders together with remittance, should be placed in advance to avoid disappointment. The copy is priced at Rs. 45/-. To those who have already reserved copies and paid for it will be sent to them as soon as the publication is out.

New Seal Design

Design for the TB Seal for the Ninth TB Seal Sale Campaign organised by the Tuberculosis Association of India, has now been selected. Out of a large number of designs sent in for the Seals by a number of artists from different parts of India, the one submitted by Shri Purushotam Paul, a Delhi artist was selected. The design depicts a young damsel engaged in handiwork which focusses the usefulness of such occupation for Indian Women. It is expected that the adoption of an Indian woman at work on graphic art will be well received in foreign countries, particularly as thousands of Indian TB Seals are now used on correspondence in foreign countries also.

The prize amount of the Seal design is Rs. 500/-. For the Ninth TB Seal Campaign, the Poster will be of the TB Seal Design.

Ninth Seal Campaign

The Ninth Seal Sale Campaign will commence on October 2, 1958, the birthday anniversary of Mahatma Gandhi and terminate on January 26, 1959, the Republic Day.

A TB Seal costs five Naya Paise only.

The Indian Journal of Tuberculosis

ABSTRACTS

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Tuberculosis Cervical Adenitis:

A review of 81 cases of tuberculous cervical adenitis is presented. Of these, in 54 cases, the glands were excised and in 47 the tonsils were removed.

In 95 % of the cases, the disease was limited to upper deep cervical group of glands. In 97% cases the involvement was unilateral. 44(54%) cases were below the age of 15, of which the maximum incidence, i.e. 25 cases were below the age of 5—9. None of the patients were below the age of 3, when pyogenic cervical adenitis was more common.

37 (46%) were over the age of 15 and 29 (36%) out of these were over 25.

In only 8 cases, the glands were enlarged for less than a month before the patients came for treatment and in only 8, these have been noticed for ten years and over.

4 or (5%) had active Pulmonary Tuberculosis.

17 or (21 %) have a previous history of tuberculosis and in 12 of these the previous lesion was the cervical adenitis.

In 15 of (19%) cases, the causative organism was human tubercle bacillus, in 10 or (12%) there was the family history of tuberculosis and in 5 there was evidence of healed pulmonary foci.

In 47 cases, where tonsillectomy was done. In 30 tonsils were examined, of these 14 or (147 %) showed evidence of tuberculosis in the tonsils.

It has been concluded that tonsils is the most common source of tuberculous cervical adenitis and it is infected by inhalation at the time of primary infection. Some of the tubercle bacilli remain in the tonsils and the remainder pass to the lungs to produce the familiar Ghons' lesion with hilar adenitis, when a tuberculous cervical gland has laid quiescent for many months or years, the commonest reactivating factor has been an acute tonsillitis. In children the bacilli are usually of the Bovine type, while the human type of tubercle bacillus is responsible for all but an occasional case of lymphnode disease.

Of the 50 recorded cases, 31 were positive in a dilution of 1/1,000, and 13 in a dilution of

1/1,000, only 1 was negative. Surgical excision is the treatment of choice chemotherapy is useful as a cover during the operation prior to prevent relapse and to reduce periadenitis before operation.

Surgical treatment also included routine removal of oral and pharyngeal sepsis with particular attention to dental caries and tonsillectomy.

Tonsillectomy should be done before surgical excision of gland, if there is no evidence of gland softening or cold abscess formation and after excision of the gland when softening *a* present.

Calcified gland should not be excised but a partially calcified gland guilty of frequent flare ups, should be excised if the patient is young.

Once surgical treatment is completed the patient is sent home and continues his chemotherapy.

It is preferable to excise glands before a cold abscess forms and skin is involved.

Isoniazid 5 mgm per kg. of body weight with P.A.S. 1.5 gm for each 50 mgm tablet of Isoniazid has been recommended.

In very young children Isoniazid syrup is given and P.A.S. is omitted.

Chemotherapy in conjunction with surgery has been effective, because of the mechanical difficulty in getting the agents into the avascular tissue.

(*Tuberculous Cervical Adenitis* : Wilnot, T. J., James, F.E., Reilly, L. V. *Lancet*, No. 7007, *Satu*, 14, 1957.)

Prednisolone in the Treatment of pulmonary Tuberculosis.

A controlled Trial:

A Preliminary report on 110 cases treated for 6 months with Prednisolone is presented.

The criteria for selection of cases were:—

1. Patients were hospitalized for six months.

2. No surgical treatment was to be done during the trial period.
3. Patients were excluded if:—
 - (a) they had previous collapse therapy or chemotherapy.
 - (b) They had tubercle bacilli resistant to streptomycin, para-aminosalicylic acid or isoniazid.
 - (c) If they were less than 15 years of age.
 - (d) With active extrapulmonary disease.
 - (e) Pregnant or within three months of parturition.
 - (f) Associated conditions such as peptic ulcer, hypertension, cardiac failure etc.

Patients were classified into 3 categories:—

1. Acute Disease; of less than 2 years duration.
2. Chronic : of more than two years.
3. Chronic Disease with acute spread.

Control Group (Chemotherapy only) :

- (a) *Patients aged 40 years or under* :— were given streptosulphate 1 gm daily, Isoniazid 100 gm twice daily.
- (b) *Patients over 40 years* :— streptomycin 1 gm. thrice weekly, P.A.S. 5 gm twice weekly, Isoniazid 100 mgm twice daily.

Prednisolone Group : (*Chemotherapy plus Prednisolone*) :—were given chemotherapy as in control group.

II. Prednisolone 5 mgm four times daily for three months plus A.C.T.H. gel 30 units I. M. on two successive days every fortnight during Prednisolone therapy.

III. Potassium citrate 2 g. twice daily during prednisolone therapy.

Of the 110 cases, a review of 46 in control and 44 in Prednisolone is presented. The rest 20 cases have been excluded.

General condition and weight gain: Subsidence of fever and improvement in appetite and gain in weight was more rapid in the prednisolone group than in the control group.

Following the cessation of prednisolone therapy, there was no fall in the weight suggesting

that there had not been any retention of fluid in the group.

E. S. R. :—There was rapid fall in E.S.R. in the prednisolone group in the first month as compared to leasurly fall in the control group.

Radiological change : The number of cases showing radiological improvement was greater in prednisolone group than in the control group.

Cavity closure and sputum conversion :—

Cavity closure and sputum conversion were slightly hastened by prednisolone, but not to a significant degree.

Toxic Effects:—

No patients receiving prednisolone showed any significant evidence of deterioration, though a temporary rebound phenomenon was observed radiologically in one sixth of cases. No serious side effects were recorded.

The antiinflammatory action of the corticosteroids might be expected to reduce the toxic effects of tuberculosis in acutely ill patients.

It is concluded that pulmonary tuberculosis should not be considered a contraindication, when corticosteroid therapy is required, provided, there is adequate chemotherapy cover.

Thus patients with active pulmonary tuberculosis can be safely treated with prednisolone provided chemotherapy cover is given. Prednisolone causes more rapid remission of toxic symptoms.

(Prednisolone in the treatment of Pulmonary Tuberculosis: A—controlled trial:—A Preliminary report by the research Committee of the Tuberculosis Society of Scotland: B.M.J. Nov. 16, 1957.)

Recent Developments in the Treatment of Tuberculosis in Man.

Basic Chemotherapeutic Regimens: Of these basic chemotherapeutic regimens namely Isoniazid plus aminosalicylic acid, Isoniazid plus streptomycin and streptomycin plus aminosalicylic acid, the combination of 300 mgm of Isoniazid plus 12 gram of aminosalicylic acid was superior to others as judged by the incidence of bacteriological conversion by culture, X-ray improvement and closure of all visible cavities.

Though the results with smaller cavities are much better than when the cavities are larger and multiple.

Cavity Closure after the 8th month in those cases with larger cavities or multiple cavities at the start of treatment was less frequent. Though

closure of all cavities during the first eight months of chemotherapy is an important measure of therapeutic success or failure. With continued expectant treatment beyond this point is likely to lead to disappointment and even loss of ground already gained. Further if the sputum is positive subsequent control with one adjunct surgical measure, additional drugs or both was unusual.

If for any reason surgical treatment is not possible chemotherapy should be prolonged indefinitely.

Thoracic Surgery: Surgical mortality and morbidity taking empyema as index was greatest with the Pneumonectomies and least with the segmental and subsegmental resection.

Factors which have a bearing on both of these are:

- (i) Extent of disease.
- (ii) Presence or absence of Tubercle bacilli in the sputum.
- (iii) Susceptibility or resistance of these micro-organism to drugs.
- (iv) Availability and use of additional drugs for coverage, when resistance to the original drugs in use was already manifest. As for the resection of stable closed necrotic tuberculous pulmonary lesions there was not enough evidence, that relapse was prevented or made less frequent by resection of such kind of lesions.

New Drugs Regimens: Cycloserine: 1 Gm. of cycloserine daily was less effective compared with that of Isoniazid plus aminosalicic acid and further neurotoxicity was more.

Hence the use of this drug has been reserved for those when less toxic chemotherapeutic resources are lacking or the urgency of therapeutic problems outweighs the risk of toxicity.

Simultaneous administration of phenobarbital and Diphenylhydantoin (Dilantin) sodium has been found to reduce neurotoxic manifestations.

Isoniazid plus cycloserine: 300 mgm. of Isoniazid and 500 mgm of cycloserine daily was as effective as Isoniazid plus aminosalicic acid and the toxic reactions were less as the dose of cycloserine is less.

Isoniazid plus pyrazinamide: With daily dose of 3 Gm. of Pyrazinamide with Isoniazid plus aminosalicic acid but the toxic effects on the liver were quite alarming—There was Hypericemia in patients treated with Pyrazinamide. This was as a result of the disturbances of renal function characterized by increased tubercular reabsorption of

urates, decreased urinary excretion of urine acid and consequent accumulation of metabolites in the blood.

Strepto-Varicin: This antimicrobial is active against human tubercle bacilli (H, 37 R.V.) in Vitro.

In the vivo the experimentally infected animate survive the infection for a longer period whereas the untreated controls die. Nevertheless when later sacrificed than treated animals harbor large number of viable tubercle bacilli, which are fully virulent and lethal for other animals and are still susceptible to the action of strepto varicin in vitro.

The drug is not very toxic but has low therapeutic efficacy.

Isoniazid Metabolism: Due to acetylation the Isoniazid is converted into biologically inactive agent. For this higher doses of Isoniazid or its combination with para aminosalicic acid has been recommended.

But it has been found that frequency of Isoniazid resistant variant was similar regardless of the dose and of the degree to which it was inactivated.

Adrenal Steroid Therapy: The use of glucocorticoid in tuberculous meningitis or in overwhelming toxemia and prostration or in advanced pulmonary tuberculosis when toxemia is marked or the initial response to chemotherapy is inapparent or inadequate has been recommended.

This has limitations:

(1) Organism must be susceptible to an effective standard combination of chemotherapeutic agents when used.

(2) The dose of steroids and chemotherapeutic agents should be adequate.

Prednisone in dose of 60 mgm. daily is recommended.

(3) Presence of tuberculosis does not protect the patient against ordinary complications of steroid therapy and these must be watched.

(4) Steroids should be discontinued gradually as soon as response of patient will permit.

The use of adrenal steroid therapy in tuberculosis patient should be considered as an emergency measure.

Ambulation versus bed rest: Results of study in 2 groups with liberal ambulation and bed rest as adjunct to effective chemotherapy did not show much difference between the two.

Air Borne Transmission of Tuberculosis: Ambient air drawn from side rooms in which tuberculous patient with highly positive sputum are housed can, cause tuberculous infection in guinea pigs exposed to this air under experimental conditions.

A typical Mycobacteria: Such as photochromogens can cause pulmonary disease resembling tuberculosis in human beings. Scotochromo-

gen and nonchromogens are saprophytes.

Treatment of experimental infections suggest that Isoniazid thiocarbanilide and streptomycin is more effective than aminosalicylic acid, amithiozone and cycloserine.

(Recent developments in the treatment of Tuberculosis in Man. Raleigh, W. James and Steel, D. John; Joun., Amer Med. Assoc. Feb. 22, 1958.)