

EDITOR

P.K. SEN
CO-EDITOR

N. L. BORDIA

M.D. DESHMUKH

CONTENTS

| | | | | | | |
|--|-----|-----|-----|-----|-----|----|
| Editorial : B.C.G. Vaccination | ... | ... | ... | ... | ... | 1 |
| B.C.G. Vaccination Amongst School children Without Prior Tuberculin Testing — <i>B. K. Sikand and S. P. Parma</i> | ... | ... | ... | ... | ... | 3 |
| Assessment of B.C.G. Produced Immunity— <i>Shrinivas and G.K. Tiagi</i> | ... | ... | ... | ... | ... | 11 |
| A Study of Mycobacteria Including Atypical Acid Fast Bacilli | ... | ... | ... | ... | ... | 16 |
| Sever Hypersensitivity Reactions to Antitubercular Drugs and Their Management— <i>Lt. Col. J. C. Chatterji</i> | ... | ... | ... | ... | ... | 19 |
| Gastric Function studies in Pulmonary Tuberculosis— <i>Mrs. S. Kuldeep and K. S. Grewal</i> | ... | ... | ... | ... | ... | 26 |

NEWS and NOTES * Abstracts

The Indian Journal of Tuberculosis

Vol. XII
No. 1

New Delhi, December 1964

B.C. G. VACCINATION

In the wake of dying controversies on this Vaccination several other organisational and technical problems are becoming prominent. Many millions of vaccinations have proved that it is safe and its complications are rare and never serious. Many good studies have also shown that it confers considerable protection, 60 to 80 percent, to the vaccinated: that such protection is obtainable under any nutritional and environmental conditions of the community or the country; that the duration of protection is quite long; that the chances of endogenous re-infection are very rare and disease developing in later life in the vaccinated is generally milder. In areas with large number of mild tuberculin reactors, possibly due to non-specific infections conferring some amount of immunity, the value of B. C. G. vaccination is likely to be less. Studies, however, proved that even in such areas the range of protection is about the same.

These qualities, along with its cheapness and, above all, its possibility for quick coverage of the vulnerable group, make it most important preventive measure for the countries where infection and disease rates are high and financial and technical resources are poor.

It must, however, be realised that to make any dent on the incidence of tuberculosis, the vulnerable group must be vaccinated very quickly and that the programme must continue for many years for the new-borns till the infection and the disease rates come down very low. Plans and programmes must, therefore, be designed in this light and in relation to the epidemiology and resources of a country. It was right, for many reasons, that India undertook this task through special teams. Of an estimated population of about 250 million upto the age of 25 years, uninfected population is likely to be about 100 millions. Till the end of 1963 about 75 millions of such population were vaccinated which means that about 75% of the vulnerable group has already been covered. It would not be right to have a separate service for all times. The task must be taken over eventually by the normal services like School Health, Maternal and Child Health etc. The writer thinks that the time is ripe now for a gradual change, integrating it first with tuberculosis services and thereafter indoctrinating and training other services with the idea of total integration with general Health Services later.

Ind. J Tub, Vol. XII,
No. 1

The type of vaccine and the method of vaccination are important procedural considerations. Freeze-dried vaccine given intra-dermally should be of greater advantage in countries like ours.

For effective, quick, and convenient coverage of the most vulnerable groups, several considerations are necessary. Due to high rate of tuberculin reactors even in the younger age-group, it becomes a necessity to vaccinate the children as early as possible. Doubts prevailed for a long time about the effectiveness of newborn vaccination. Recent studies seem to allay such fear. New-born vaccination in large maternity hospitals should, therefore, be adopted in the regular programme, as increasing number of babies are being born at the hospitals. Along with this, the school-going group should be the most important focal point. Intended introduction of compulsory primary school education will have to be taken into account in this context.

Dual vaccination at the same time of small-pox and B. C. G. may improve the tempo and coverage. There is no essential contra-indication, but, for various reasons, the writer thinks that such a procedure will not be justified at this stage. Similarly, B. C. G. vaccination without pre-tuberculin testing or direct vaccination will lessen the cost and prevent a large number of fall-outs. The recent B. C. G. Conference held in Ahmedabad agreed on this procedure upto the age of 20 years.

One should realise that no method has yet been evolved to estimate the degree of immunity against tuberculosis in an individual. The value of B. C. G. vaccination can, therefore, only be estimated indirectly. In such an evaluation many factors like the material used, manner of vaccination and efficiency of the services come in question. Besides, changing epidemiology also demands modifications in the service. It is, therefore, imperative that continuous assessment through service-cum-research projects must be associated with this immensely useful but complex mass programme.

BCG VACCINATION AMONGST SCHOOL CHILDREN WITHOUT PRIOR TUBERCULIN TESTING

B. K. SIKAND AND S. P. PAMRA
(*New Delhi Tuberculosis Centre*)

BCG Vaccination can make an effective contribution to reduction of tuberculosis problem in a community only if the susceptible population is covered quickly. One of the main impediments in the way of quick coverage is pre-vaccination tuberculin test. As two visits are required to complete the test and 8 to 15% usually default at second visit (Barua 1964), the output of a vaccination team is reduced by more than half. Pre-tuberculin testing was advocated (and is still advocated for all except the new borns) mainly to prevent unduly severe local reaction and the possible risk of focal and general reaction following vaccination of an infected individual. Apart from scientific accuracy, the aim of pre-testing is to protect the fair name of B.C.G.

Few systematic studies have been carried out to assess the actual risks of direct vaccination and the fears seem to be based more on surmises or casual observations, present study was started in February, 1964 to assess systematically the local, focal and general reactions of BCG vaccination in Mantoux Positive school children.

Plan of Study

Two boys' primary schools situated in one of the most congested localities of the old city of Delhi were selected. The children, by and large, were from the lowest economic group of the population. All children were Mantoux tested with 1 TU RT XXIII with Tween 80, and 72 hours later the Mantoux test was read, and the left deltoid region was inspected for any scar of previous vaccination. All children were then vaccinated intradermally with 0.1 ml of liquid vaccine (0.75 mg. per ml) from Madras. To facilitate follow up, children without previous scar and with a Mantoux reaction of less than 10 mm i.e. those who would have been vaccinated in a conventional BCG programme, were vaccinated in the left deltoid region, and all the others on the right.

A miniature (70 mm) x-ray of the chest was taken of all those children who were

vaccinated on the right arm i.e. those who had Mantoux reaction of 10 mm or more and/or those who had scar of previous vaccination. The x-ray examination was repeated 7 days after vaccination and also at the termination of the study. Children with abnormal x-ray at the 1st or 2nd examination were x-rayed repeatedly at weekly intervals till abnormal lesions cleared or the case was diagnosed as primary disease.

Local BCG lesions were inspected on 7th, 14th, 21st, 28th and 42nd days and axillae were palpated for glands. The original plan was to carry out the terminal examination 90 days after vaccination but owing to a few days' delay at the start, summer vacation set in 77 days after the BCG vaccination and the study had to be terminated at that point. Change of school or leaving Delhi after the annual examination terminated the follow up of some students on the 42nd and some on 63rd day.

Attendance registers of the schools were regularly inspected for any extraordinary rise in absentee rate or illness of more than 3 or 4 days of any child which could be attributed to general reaction of BCG vaccination. Co-operation from the school staff was excellent and no refusals were encountered at any stage.

Material

There were in all 950 students who completed the Mantoux test and the BCG vaccination 3 days later (Table 1). The 175 children who were absent from Mantoux testing (but were vaccinated) and 112 who were absent for BCG are not included in the analysis.

Children in the group 'With Scar' had been vaccinated 2 years earlier in a routine vaccination programme. In the absence of individual BCG vaccination cards, it was not possible to find out accurately whether any of the children who did not show a scar were vaccinated or not. Children have been divided into two age groups—6 to 10 years and 11 to 15 years. . Four children 5 to 6

TABLE 1

Total number of children included in the study & their Mantoux reaction

| Mtx. Age | With Scar | | Without Scar | | Total |
|-----------------|--------------|--------------|--------------|--------------|---------------|
| | <10 mm. | > 10mm. | < 10 mm. | > 10mm. | |
| 6-10 year | 148 23.4% | 104 16.4% | 187 29.5% | 194 30.7% | 633 100% |
| 11—15 years | 60 18.9% | 86 27.1% | 63 19.8% | 108 34.2% | 317 100% |
| Total | 208 21.9% | 190 20.0% | 250 26.3% | 302 31.8% | 1 950 100% |
| Mean Induration | 10.6 mm. | | 13.2 mm. | | |

years in age have been included in the 6 to 10 years group. Mantoux reaction of 10 mm or above was considered as evidence of conversion, spontaneous or post-BCG vaccination, and the two groups 'With Scar' and 'Without Scar' further sub divided into those with Mantoux reaction of less than 10 mm (negatives or non-reactors) and those with Mantoux reaction of 10 mm and above (positive or reactors).

It would be seen from Table 1 that slightly larger number of children had a pre-vaccination reaction of 10 mm and above in the higher age group, and this is as expected. The mean induration in the group 'With Scar' was 10.6 mm as against 13.2 mm in those 'Without Scar'.

The number of children available for study of the BCG reaction at each stage up to 42 days was more than 90% of the actual number (Table 2). Thereafter, 286 children could not be followed beyond 42 days. However, this is not likely to have influenced the final results as Table 3 shows that the degree of reaction at 42 days amongst the 286 who could not be followed later was more or less the same as amongst the 616 who were available upto 63/77 days. It may therefore be reasonably assumed that the

former 286 would probably have behaved the same way as the later 616, if their follow up had not ceased for reasons unconnected with the study.

Table 4 shows the extent of pustular reaction 7 days after BCG in relation to age. The percentage was apparently higher in the 11 to 15 years group as compared to 6 to 10 years in all groups, but none of these differences are statistically significant ($P > .05$). Similarly the reaction at subsequent stages did not show any significant difference in the two age groups which have therefore been combined in the analysis that follows.

Local Reaction

Post-vaccination reaction that is likely to frighten the children and the parents is pustule formation including ulceration. Table 5 & Figure 1 show the percentage of children showing pustular reaction at various periods of the study. It would be seen that whereas the reactors, whether With or Without Scar, show a maximum pustular reaction after 7 days, the reaction builds up gradually amongst the non-reactors reaching the maximum at 28 days. At 42 days, the pustular reaction was present in about one third of

BCG VACCINATION AMONGST SCHOOL CHILDREN

TABLE 2

Number of children available for reading of BCG reaction

| | | With Scar | | Without Scar | |
|-------------------|----------------|-----------|--------|--------------|--------|
| | | < 10mm | >10mm. | < 10 mm. | >10mm. |
| Total | | 208 | 190 | 250 | 302 |
| Number read after | No. 7 days | 198 | 170 | 232 | 283 |
| | % | 95.4 | 94.2 | 92.8 | 93.7 |
| | No. 28 days | 188 | 177 | 244 | 284 |
| | % | 90.4 | 93.2 | 97.6 | 94.0 |
| | No. 42 days | 202 | 181 | 242 | 277 |
| | % | 97.1 | 95.3 | 96.8 | 91.7 |
| | No. 63/77 days | 145 | 130 | 162 | 198 |
| | % | 69.7 | 68.4 | 64.8 | 65.6 |

TABLE 3

42 days' reaction after BCG in those completing follow up compared to those whose follow up ceased at 42 days

| | Follow up ceased at 42 days | | 63/77 days' result available | |
|---------|-----------------------------|------|------------------------------|------|
| | No. | % | No. | % |
| Total | 286 | 100 | 616* | 100 |
| Scar | 27 | 9.4 | 62 | 10.1 |
| Ulcer | 45 | 15.7 | 98 | 15.9 |
| Pustule | 54 | 18.8 | 106 | 17.2 |
| Scab | 160 | 56.1 | 250 | 56.8 |

*19 children absent for 42 days' reading but present for 63/77 days' reading are excluded.

TABLE 4
7 days local reaction to BCG according to age and Mantoux Reaction

| | With Scar | | | | Without Scar | | | |
|---------------------------------|--------------|------------|---------------|------------|--------------|-------------|---------------|-------------|
| | 6 to 10 yrs. | | 11 to 15 yrs. | | 6 to 10 yrs. | | 11 to 15 yrs. | |
| | Mx. < 10 | Mx. >10 | Mx. <10 | Mx. >10 | Mx. <10 | Mx. > 10 | Mx. <10 | Mx. >10 |
| Total No. | 148 | 104 | 60 | £6 | 187 | 194 | 63 | 108 |
| Number read No. % | 139 93.9 | 97 93.3 | 59 98.3 | 82 95.3 | 1799 5.7 | 180 92.2 | 53 84.1 | 103 95.4 |
| Induration | 99 | 39 | 40 | 24 | 167 | 41 | 44 | 22 |
| Pustular Reaction | 40 | 58 | 19 | 58 | 12* | 139* | 9 | 81 |
| Percentage of pustular reaction | 28.8 | 598 | 32.0 | 7.0 | 70.0 | 76.6 | 17.0 | 78.6 |

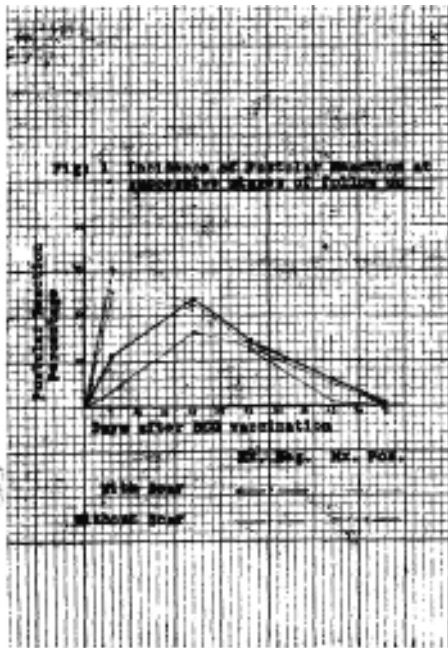
*Includes one ulcer

TABLE 5
Extent of pustular reaction at varying periods after BCG

| Mantoux | With Scar | | | | Without Scar | | | |
|---------|-------------|-------------------|-------------|-------------------|--------------|-------------------|-------------|-------------------|
| | <10mm. | | ≥10 mm. | | < 0mm. | | ≥ 0mm. | |
| | Number read | Pustular reaction | Number read | Pustular reaction | Number read | Pustular reaction | Number read | Pustular reaction |
| 7 days | 198 | 59 29.2% | 179 | 116 64.3% | 232 | 219.1% | 283 | 220 77.7% |
| 28 days | 188 | 112 59.5% | 177 | 97 54.7% | 24 | 102 41.8% | 284 | 160 56.3% |
| 42 days | 202 | 74 36.6% | 181 | 59 32.6% | 22 | 68 32.2% | 277 | 102 36.8% |
| 63 days | 15 | 0 0.0% | 29 | 1 3.4% | 13 | 0 0.0%* | 36 | 0 0.0%* |
| 77 days | 130 | 0 0.0% | 101 | 0 0.0% | 149 | 0 0.0% | 162 | 2 102% |

*Based on small numbers.

the children in all sub-groups and only 3 children (2 amongst reactors 'Without Scar' and one amongst reactors 'With Scar') showed pustular reaction 63/77 days after BCG vaccination. In this material, even the Koch's phenomenon (pustular reaction at 7 days) took a long time to heal. Fig-1

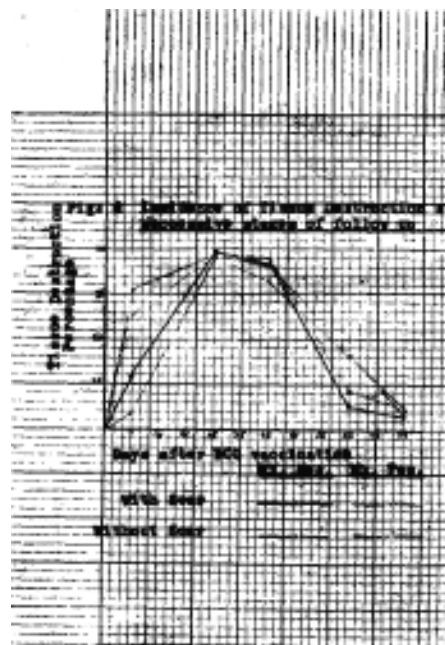


Maximum pustular reaction (77.7%) in reactors 'Without Scar' 7 days after vaccination was significantly higher than in the reactors 'With Scar' (64.3%). Among the non-reactors, those 'With Scar' showed a higher percentage of pustular reaction at 7 and 28 days (29.8% and 59.5% respectively) than non-reactors Without Scar, (9.1% and 41.8% respectively). This difference, which is statistically significant ($P < .05$), is not unexpected as post-vaccination allergy is known to be weaker than the allergy following infection with virulent bacilli. However some of those who show a reaction of less than 10 mm amongst those 'With Scar' may not be non-reactors but only weak reactors—i.e. midway between non-reactors Without Scar and reactors With or Without Scar.

Table 6 and Figure 2 show the extent of tissue destruction (pustule + ulcer + scab) in

the four sub-groups. It shows that practically every child showed evidence of tissue destruction at 28 days and thereafter the lesions started healing with almost identical speed. At the end of the study, 7.7% to 12.8% children were left with scabs in the various groups, but it is likely that if it were possible to continue the study upto 90 days, all these scabs would have fallen off, leading to complete healing. The difference in the speed of pustular reaction noted amongst the reactors and the non-reactors in the first 7 days is also present in the tissue destruction.

Fig-2



Unusually severe local reaction was seen only in 4 children. In one child there was an ulcer at the site of the Mantoux test, but the reaction at the site of vaccination was not unusually severe. The other 3 children showed severe BCG reaction. One child developed a 3 cm ulcer at the site of BCG vaccination (right shoulder) 4 weeks after vaccination; one child developed a gland in the right axilla 6 weeks after BCG and the third child developed a 2.5 cm abscess, 1 cm below the BCG scar (right shoulder) and a gland in the right axilla 6 weeks after vac-

TABLE 6

Extent of tissue destruction (ulcer + pustule + scab) at varying periods after BCG

| Mantoux | With Scar | | | | Without Scar | | | |
|---------|-------------|--------------------|-------------|--------------------|--------------|--------------------|-------------|--------------------|
| | <10 mm. | | ≥10mm. | | < 10mm. | | ≥ 10mm. | |
| | Number read | Tissue destruction | Number read | Tissue destruction | Number read | Tissue destruction | Number read | Tissue destruction |
| 7 days | 198 | 59 29.2% | 179 | 116 64.3% | 232 | 21 9.1% | 283 | 220 77.7% |
| 28 days | 188 | 187 99.5% | 177 | 174 98.3% | 244 | 237 97.1% | 284 | 281 98.9% |
| 42 days | 202 | 186 92.1% | 181 | 166 91.7% | 242 | 202 83.5% | 277 | 259 93.5% |
| 63 days | 15 | 2 13.3% | 29 | 12 41.4% | 13 | 0 0.0% | 36 | 8 22.2% |
| 77 days | 130 | 10 7.7% | 101 | 8 8.9% | 149 | 19 12.8% | 162 | 17 10.5% |

nation. In all cases, however, the glands subsided and the lesions healed leaving a scar at 63/77 days after INK dressing of the BCG ulcer and instillation of streptomycin solution in the abscess cavity. It is worthwhile pointing out here that 2 of the 3 children who had severe BCG reaction were absent from Mantoux test and the 3rd had a Mantoux reaction of 20 mm and all the 3 children had scars of previous vaccination.

General Reaction

Attempt was made to assess the general reaction from any increase in the usual absentee rate of the school or from sickness of any child for more than 3 to 4 days. The teachers were also requested to bring to our notice any child who had any physical complaint during the period of study. No increase in the usual absentee rate was noticed at any time during the period of study. One child was admitted in a general hospital a few days after BCG vaccination, and was

diagnosed to be suffering from epilepsy. Two children complaining of head-ache were found to have astigmatism. No other illnesses were noted.

Focal Reaction

Four children were found showing evidence of primary disease on their first X-ray. Three of them had no scar of previous vaccination and the Mantoux reaction in all four was above 25 mm. The BCG lesion in these children however ended in a scar without any complications in 42 days in three of them and in 77 days in the fourth. Their subsequent X-rays, 7 and 14 days after BCG vaccination, did not show any exacerbation or reaction around the focus. Treatment of these children was started after 14 days' observation and assessment.

Besides these four children, the first X-ray of five more showed abnormal shadows. In four there was a small soft exudative patch in the left upper zone and in one at the right

base. One of them had a definite scar of previous vaccination and three of them had a Mantoux reaction above 20 mm and two between 10 and 20 mm. The X-ray shadows cleared without treatment in one week in two of them, in 2 weeks in one and in 25 days in the remaining two. They had no constitutional symptoms. The BCG lesion healed satisfactorily in three of them who were followed beyond 42 days.

Besides these, four children showed an abnormal shadow in the X-ray taken 7 days after BCG vaccination, their first X-ray having been negative. Two had a small soft exudative patch in the right upper zone, one at the right base and one at the left upper zone. The shadows resembled those seen in the preceding group. Two children had a scar of previous vaccination, three had a Mantoux reaction above 10 mm and the fourth was absent on the day of Mantoux testing. These lesions also cleared completely within 7 days without any treatment. It is thus plausible to infer that these lesions were probably due to non-specific pneumonitis, more or less of the type that the five children showed before vaccination, and had nothing to do with BCG. The BCG lesion healed satisfactorily in two of them followed till the end, and the remaining two showed a scab 5 to 6 mm on the 42nd day.

Comments

De Assis (1949), Oppers 1952 (quoted by Heaf 1955) and Foley et al (1954), had reported that they did not come across any deleterious effects of direct BCG vaccination of children which included reactors also. The vaccination however in all these three studies was oral and the follow up also was not systematic. Gordon et al (1959), made a systematic study of the local reaction following vaccination of 140 Mantoux positive children in Africa between the ages 5 and 16 years and came to the conclusion that the procedure is "more irritating than dangerous". Gothi et al (1964) studied the local and focal reactions of BCG vaccination of reactors in all age groups, and came to a similar conclusion. Our study too has shown that the risks of vaccination of reactors are more imaginary than real. Apart from, an early onset and a slightly higher peak of

pustular reaction in reactors, all children behaved much the same way. All children 28 days after vaccination showed evidence of local tissue damage and healing thereafter in all groups was parallel. Gothi et al (1964) on the other hand, reported a maximum of 11.9% and 42.9% showing tissue destruction 19 days after vaccination among non-reactors and reactors respectively. By the 29th day the tissue destruction was seen only in 9.8% and 23.7% in the two groups. There is a marked variation in the frequency and pattern of tissue destruction in these two studies. Whether this difference is due to observer's error or difference in this definition of tissue destruction or some other factor, is not clear. It is however worth pointing out that three months after vaccination almost all persons in the study of Gothi and his associates too, showed a scar, (Gothi, 1964) which must have been preceded by tissue destruction at some stage or other.

Unusually severe local and glandular reaction i.e. the so-called 'complications' were more frequent in the African study but negligible in the Bangalore and the present study. This difference may be racial in character.

It thus seems reasonable to conclude that direct vaccination of reactors is innocuous. Since tuberculin test is a poor separator of infected from uninfected, some reactors, anyhow, are vaccinated even if the vaccination is preceded by a tuberculin test. Considering the numbers covered in mass vaccination programmes, not only in this country but the world over (which has crossed the 150 million mark), the number of reactors unnecessarily vaccinated must be large. It is significant that no deleterious effects have been reported in literature. Omission of pre-testing by reducing one visit and eliminating additional absenteeism at the 2nd visit, and reducing work-load of the technicians will more than double the present coverage of vaccination programmes without any unusual inconvenience or danger to the reactors and without lowering the acceptability of the programme, in general.

One consequence of such a procedure would be that a small percentage of children with silent primary disease would also be vaccinated. Fear of exacerbation of covert

disease is one of the main arguments adduced against direct vaccination. There were four such children in this material and they did not suffer any exacerbation or develop fresh focus following BCG and therefore the presence of covert disease also need not come in the way of direct vaccination. That BCG has no deleterious effect on overt disease was proved by Heaf (1955), and corroborated by Gothi et al (1964) recently.

One more aspect of direct vaccination has to be considered. Sikand (1961) and Frimodt-Moller (1962) have reported disappearance of scars amongst children who were known to have been definitely vaccinated some years earlier. That being so, some children vaccinated without pre-testing could be those who may have been vaccinated earlier but had lost their scars. To assess the effects of re-vaccination, children with previous scars were deliberately included in the study. All three children who had an excessive local and glandular reaction had a previous scar. However the number is too small to be significant and apart from the inconvenience of local reaction, there was no deleterious effect, focal or general, among the re-vaccinated children. Re vaccination therefore cannot be said to be harmful in any way.

Two other features arising from this study are worth pointing out, though they have no direct bearing on its objects.

1. Nearly 50% children with a scar of vaccination two years earlier reacted with less than 10 mm to the Mantoux test and 37% reacted with even less than 5 mm. Whether this waning of allergy is likely to be associated with corresponding reduction in the protective value of BCG and whether such children should be re-vaccinated is a different matter and requires investigation.

2. Five children before vaccination, and four one week after the vaccination, showed parenchymal infiltrative lesions which cleared within a few days without any treatment. Had these children not been followed subsequently, the lesions could have been ascribed to focal reaction following BCG vaccination. Their time sequence and behaviour however would show that they had nothing to do with TB or BCG. Even otherwise, such non-specific areas of pneumonitis are often seen in clinical practice

and have to be kept in mind while labelling lung lesions in x-ray studies to determine prevalence and incidence of tuberculosis.

In conclusion it may be said that direct vaccination of children below the age of 15 does not expose the children to any harm or unusually severe reaction even if they are Mantoux positive or have covert primary disease. Intensive follow up for 11 weeks has failed to show any evidence of general toxic reaction or focal exacerbation or development of a fresh parenchymal lesion following BCG. The study would tend to show that it is safe to vaccinate primary school children without pre-tuberculin testing. Children with scars of previous vaccination may, for the present, be excluded, not because re-vaccination is harmful but because it may be redundant. Further, as direct vaccination will for sometime be on trial, it is desirable to carry it out in the right deltoid region, to distinguish these children from those vaccinated on the left shoulder in the conventional way.

Acknowledgement

The authors are grateful to the Education Department of the Delhi Municipal Corporation and the Headmasters and staff of the Primary School, Pahari Imli & Primary School, Matia Mahal for the facilities to carry out this study and unstinted co-operation all through. The painstaking work of BCG Technician Mrs. Kumar and Mr. Ram Saroop is highly appreciated and acknowledged.

REFERENCES

1. Barua; B.N.M ; Personal Communication, 1964.
2. De Assis, A.; Diseases of Chest; 1949. 16, 266.
3. Foley, H., & Parrot L.; Bulletin Hygiene, London; 1954, 29, 602.
4. Frimodt-Moller, J.; Proceedings of 18th Tuberculosis & Chest Workers Conference, 1962.
5. Gordon, C.G.I., and Shelley, J.H.; 1959, 40, 425.
6. Gothi, G.D., et al; Proceedings of 19th Tuberculosis & Chest Workers Conference, 1964.
7. Gothi, G.D.; Personal Communication; 1964.
8. Heaf, F.R.G.; Lancet; 1955, i, 515.
9. Sikand, B.K.- W.H.O. Document SEA/TB/34. 1961.

ASSESSMENT OF BCG PRODUCED IMMUNITY

(An experimental study)

SHRINIWAS* AND G.K. TIAGI
(G.S.V.M. Medical College, Kanpur)

Since the Premier Congres International du B. C. G , Paris (1948) there seems to be considerable unanimity amongst various workers regarding the value of BCG Vaccination as a means to increase resistance against tuberculosis both in human beings and in experimental animals, Edward & Palmer (1953) have advised mass BCG Vaccination programme to fight tuberculosis on the basis of its known utility. Based on controlled research in U. K. by giving BCG Vaccination to 56,700 school children aged between 14 and 15½ years and following them for a period of 9 years, the M. R. C. report (1959) has also expressed the view that vaccination increases resistance against tuberculosis. Results of further investigations are awaited.

However, the assessment of BCG produced immunity both in laboratory animals and in human subjects is a matter of great controversy. In laboratory, the size of vaccinal lesion has been used to estimate the potency of vaccine by Jensen (1946), Van-Deinse (1948), Ranganathan (1951), and Berger (1953). On the other hand, Palmer et al (1955) have reported that although the size of vaccinal lesion may reflect the dose of vaccine injected, it is of dubious value as an index of the immunising potency of the vaccine.

Tuberculin skin sensitivity test as a means to determine development of immunity to tuberculosis is a highly controversial subject. However, it has been accepted as a means to determine the success of BCG—produced immunity by Jensen (1932) on the basis of extensive experimental work. Development of skin sensitivity to tuberculin after BCG vaccination has been used to determine its success by Edward & Palmer (1953). Wallgren (1953) expressing the view of many workers has stated that if there is hypersensitivity as disclosed by an adequate positive tuberculin test there is present at the same time specific immunity.

Rich (1951) in a comprehensive review of the subject on the basis of experimental

work has asserted that hyper sensitivity can exert local and systemic deleterious effect. It has been demonstrated unequivocally by many investigators both in tuberculosis and in other infections and under wide variety of conditions that hypersensitivity is not essential for successful operation of acquired resistance.

There is, however, a group of workers like Dubos (1949), Fenner (1951), Giovanardi (1953) and Ohara et al (1954) who believe that the relation of tuberculin allergy- to immunity is one of the most obscure aspects of pathogenesis of tuberculosis.

The present study has been carried out with the aim of assessing the relative value of vaccinal lesions and development of tuberculin allergy in detecting BCG produced immunity in experimental animals.

Material and Methods

A total of 48 guinea-pigs were studied; different strains were obtained from various control breeding centres so as to include wide range of biological variations. At the start of the experiment the animals weighed between 200 to 300 Gms. and aged 6 to 8 weeks. Males were separated from the females to avoid pregnancy and its modifying effect on the results. Animals were fed on the standard diet.

Development of animals was assessed by keeping a check on their weight. All animals were numbered by a special dye evolved by us which keeps for more than a week and the dye mark was repeated periodically to keep it permanent. Hair was removed from the site of injection by close cutting by a pair of sharp scissors; other methods were not found superior to this.

Mantoux (Tuberculin) test was carried out by injecting 0.1 ml. of 1: 100 old tuberculin (T) (Wellcome)-representing 100 T. U. intradermally in the skin. Reaction was measured as maximum transverse diameter of induration and not erythema after 48 hours. After some practice it was possible to differentiate between induration and erythema.

Tuberculin test was carried out on all the

*Now in the College of Medical Sciences, Banaras Hindu University.

animals at the beginning of the experiment. Only negative reactors to tuberculin were taken for the study. They were then divided into two groups of 24 guinea-pigs. One group was labelled as group-V and was vaccinated, the other group acted as control which was labelled group-C and was not vaccinated.

Vaccination was made by injecting 0.1 ml. of BCG vaccine (Guindy) intradermally. Maximum transverse diameter of induration and ulceration after vaccination were recorded at the interval of 10 days for one month from the date of vaccination.

Mantoux test was again carried out on all the animals after 10 weeks of vaccination and results were recorded.

All the animals were then challenged with 0.1 mgm. of virulent human tubercle bacilli (H-37 Rv strain) by injecting suspension of the bacilli intraperitoneally. Two groups were kept separate to avoid possibility of cross infection within the cages after challenge infection from less protected to presumably more protected vaccinated animals.

Detailed autopsy and histopathological examinations were carried out to establish the cause of death and to study the course of disease.

Results

The vaccination of group-V animals was followed by induration, (nodule) which was measured on the 10th day as given below (Table 1). It was followed by ulceration

TABLE I
Distribution of size of vaccinal lesion on 10th day of vaccination

| Maximum trans diameter. of induration in m. m. | Number of animals | | |
|---|-------------------|------|--------|
| | Total No. | Male | Female |
| 8 | 6 | 3 | 3 |
| 7 | 6 | 1 | 5 |
| 6 | 7 | 6 | 1 |
| 5 | 3 | 2 | 1 |
| Total | 22 | 12 | 10 |

Trans.=Trans verse

which in all cases healed up within 4 weeks of vaccination.

Mantoux test 10 weeks after vaccination showed that all the animals of group-V developed induration measuring 4 to 8 mm. as given below (Table 2). two animals in group-C showed an induration of 1 mm. and 8 animals showed only erythema measuring 2-3 mm. Both induration and erythema in group-C animals could be accounted for by secondary infection after Mantoux test.

TABLE 2
Tuberculin reaction of vaccinated animals after 10 weeks

| Maximum trans, diameter of induration in mm. | Number of animals | | |
|---|-------------------|------|--------|
| | Total No. | Male | Female |
| 8 | 5 | 2 | 3 |
| 7 | 10 | 5 | 5 |
| 6 | 4 | 3 | 1 |
| 5 | 2 | 2 | |
| 4 | 1 | - | 1 |
| Total No. | 22 | 12 | 10 |

Trans.=Transverse

Complete observations could only be done on 42 (22 vaccinated group-V animals and 20 unvaccinated group-C animals) out of a total of 48 guinea pig, as 6 animals died during the course of experiment.

Challenge infection with virulent human tubercle bacilli produced progressive tuberculosis in all the animals. On 10th day of the experiment 2 animals of the group-C and 1 of group-V died. All the animals of group-C which were not vaccinated died between 27 and 30 days, with an average survival time of 28.2 days. The animals which died on 10th day of challenge infection were not taken into consideration while calculating average survival time. In group-V (vaccinated animals), 11 animals showing post vaccination tuberculin allergy of 4-6 m.m. died between 34th to 46th day of challenge infection, with an average survival time of 42

days. 10 vaccinated animals of group-V which showed vaccinal lesions and also tuberculin allergy of more than 7 mm. survived a period ranging from 12 weeks to 78 weeks with an average survival time of 179.1 days. Table 3 gives size of tuberculin allergy with corresponding minimum, maximum and average survival time in days.

TABLE 3

Survival period of unvaccinated and vaccinated animals in relation to size of Tuberculin allergy

| Group of animals | Size of Tuberculin allergy in mm. | Minimum survival time in days | Max. survival time in days | Average survival time in days |
|------------------|-----------------------------------|-------------------------------|----------------------------|-------------------------------|
| Group-C | — | 27 | 30 | 28.2 |
| Group-V | 5 | 34 | 35 | 34.5 |
| | 6 | 38 | 40 | 39.0 |
| | 7 | 39 | 545 | 132.4 |
| | 8 | 84 | 290 | 132.0 |

Max.=Maximum

The average survival time of group-V animals was 101.9 days as compared to 28.2 days of group-C animals.

Autopsy and histopathological studies established tuberculosis as the cause of death in all animals which died up to 6 months from the date of challenge infection. Healed tuberculosis was observed in the animals which died after this period. The death in these cases was due to secondary infection. The course of tuberculosis was delayed in group-V (vaccinated) animals as compared with those of group-C (control) animals.

Discussion

Edward & Palmer (1953) have advocated that adequate development of tuberculin skin sensitivity should be taken as criterion for development of immunity expected after BCG vaccination. In human studies size of

vaccinal lesions have rarely been used for the purpose of assessing the post BCG vaccination immunity. In experimental studies, in addition to vaccinal lesion and development of tuberculin allergy, survival time after challenge infection and course of disease could be studied and could be directly correlated with the degree of development of immunity.

The size of vaccinal lesion in the present study was directly proportional to the degree of development of tuberculin allergy and survival time. In laboratory, size of vaccinal lesions has been used to estimate the potency of vaccine by various laboratory workers like Ranganathan (1951) and Berger (1953). However, Palmer *et al* (1955) have reported that the size of vaccinal lesion may indicate the dose of vaccine injected but it is of no value as an index of immunizing power of the vaccine.

In the present study, BCG vaccine (Guindy) from one single batch was used on the same day to immunize all the animals under study. Hence the proportion of the dead to the living organisms in the vaccine must have been the same. Therefore, it is felt that if necessary precautions are taken regarding the viability of the organisms, the size of vaccinal lesions can be used to indicate the immunizing power of the vaccine. While carrying out mass BCG vaccination programme in this country the vaccinating team after vaccinating the person just forgets about them till assessment team does periodical sample survey by tuberculin testing. In such circumstances when reasonable precautions have been taken for the use and storage of vaccine, development of vaccinal lesions, as in case of small pox vaccination, may be studied at a proper time for indication of development of immunity expected from it.

Tuberculin test after vaccination produced induration of 1 m.m. in only 2 guineapigs of group-C while in all vaccinated guineapigs in group-V induration ranging between 4 to 8 m.m. was seen, (Table 2), thus indicating that development of tuberculin allergy in vaccinated guineapigs was due to BCG vaccination and was not a coincidence. The course of disease was more rapid in group-C animals than in group V-animals.

All the control animals of group C died within 30 days of challenge infection.

Animals in group-V showing various degrees of tuberculin allergy after vaccination showed proportionate increase in survival time (Table 3). Those showing Tuberculin reaction of 5 mm. showed only slight increase in survival time, their average survival time being 34.5 days as compared with those of control animals having average of 28.2 days and maximum survival time of 30 days. The average survival time in animals showing tuberculin allergy of 6 mm. was 39.0 days thus showing some increase over those having tuberculin allergy of 5 mm. and survival time of 34.5 days. Animals showing tuberculin allergy of 7 mm. and 8 mm. had average survival time of 132.4 days and 132 days respectively. Thus considering the average survival time there is no difference in these two groups but the maximum survival time in groups of animals showing tuberculin allergy of 7 mm. has been 39 days while in those showing tuberculin allergy of 8 mm. has been 84 days.

Thus, on the basis of present study we are of the opinion that BCG vaccination gave protection to animals against virulent infection of tuberculosis. The degree of protection was reasonably good as the vaccinated animals could survive for a maximum period of 290 days after challenge infection with a dose which produced progressive tuberculosis and death within 30 days in all the unvaccinated animals of group-C of almost identical weight, age, and living in the same environmental conditions. The average survival time in group-C (unvaccinated control) animals was 28.2 days as compared to 101.9 days in group-V (vaccinated) animals after challenge infection with virulent human tubercule bacilli.

Autopsy and histopathological examinations confirmed that the development of tuberculosis was inversely proportional to the size of vaccinal lesions and degree of tuberculin allergy. The survival time in the present study was directly proportional to the size of vaccinal lesion and degree of development of tuberculin allergy, other variables being the same.

Ind. J. Tub., Vol. XII, No. 1

Wallgren (1953) expressing the view of many workers has stated that "... if there is hypersensitivity as disclosed by adequate positive tuberculin test there is present at the same time specific immunity . . . the immunity lasts in a latent or manifest form as long as there is evident hypersensitivity".

There remains, however, in academic as well as practical circles a cautious group of workers namely, Dubos (1949), Fenner (1951), Giovanardi (1953) and Ohara et al (1954) who believe that the relation of tuberculin allergy to immunity is one of the most obscure aspects of pathogenesis of tuberculosis.

Our findings that the development of immunity after BCG vaccination can be judged by the development of tuberculin allergy is in accordance with Heimbeck (1948), Heaf (1950), Yanagisawa (1951), Frappier et al (1952), International Tuberculosis Campaign (1953), Ranganathan (1952) and Edward and Palmer (1953) who have reported that skin sensitivity to tuberculin after vaccination can safely be taken at present, in absence of any other means to measure immunity, as evidence of development of resistance against tuberculosis.

Summary and Conclusions

On the basis of this study, carried out on 48 tuberculin negative guineapigs to find out the relative values of vaccinal lesions and development of tuberculin allergy, we came to the following conclusions:

1. The size of vaccinal lesions may be purely a local phenomenon but the present study with its limitations, show that the size of vaccinal lesion to a great extent indicates the development of immunity (resistance) against tuberculosis and can be taken as a sign of successful vaccination.
2. The development of tuberculin allergy, in absence of any other means to measure immunity against tuberculosis after BCG vaccination, can safely be taken as evidence of the development of post-vaccinal immunity.

REFERENCES

1. Berger, K. (1953) *Z. Hyg. Infekt Kr.* 136, 1-18. quoted by Palmer et al (1955). *Bull. Wld Hlth Org.*, 12, 13-29.
2. Dubos, R.J. (1949) *Amer. Rev. Tuberc.*, 60, 673.
3. Edwards, L.B., Palmer, C.E. and Magnus, K. (1953) *B.C.G. Vaccination, Studies by the W.H.O. Tuberculosis Research office, Copen-hagan.*
4. Fenner, F. (1951) *Bibl. tuberc. (Basel)* 5, 112- 186.
5. Frappier, A., Guy, R. and Desjardins, R. (1952) *Rev. Tuberc. (Paris)*, 16, 749-762.
6. Giovanardi, A. (1953) unpublished working document WHO/Exp. Vac. TBC/4; Quoted by Palmer et al (1955), *Bull. Wld Hlth Org.* 12, 13- 62.
7. Heaf, F. (1950) *J. roy. Sanit. Inst.* 70, 139-143.
8. Heimbeck, J. (1948) *Premier Congres International du B.C.G., Paris*, 263-265.
9. International Tuberculosis Campaign (1953) *Mass B.C.G. Vaccination Campaign, a practical guide.* Neuilly-Sur-Seine.
10. Jensen, K.A. (1932) *Acta path, microbiol. scand. suppl.* XI, 64. 11. Jensen, K.A. (1946) *Acta tuberc. scand.* 20, 1-45.
11. M.R.C. Second Report (1959) *Brit. Med. J.*, 2, 379-396.
12. Ohara, T., et al (1954) *Jap. J. Tuberc.* 2, 116-127.
13. Palmer, C.E. et al (1955) *Bull. Wld. Hlth. Org.* 12, 13-62.
14. Premier Congres International du B.C.G. Paris (1948) M/s Dyva and J. Jeppesens Bogtrykkori Aktieselskab, Copenhagen.
15. Raoganathan, K.S. (1951) *Lancet* 1, 529.
16. Ranganathan, K.S. (1952) *Tubercule (Lond)* 33, 365-368.
17. Rich, A.R. (1951) *The pathogenesis of tubercu- losis*, Springfield, 111. 2nd ed., 569.
18. Van Deirse, F. (1948) *Amer, Rev. Tuberc.* 58, 571-575.
19. Wallgren, A. (1953) *Acta tuberc. scand.* 28, 182.
20. Yanagisawa, K. (1951) *History of BCG program in Japan with minimum requirements for BCG Vaccine & tuberculin*, Tokyo.

A STUDY OF MYCOBACTERIA INCLUDING ATYPICAL ACID FAST BACILLI

(Cultural and Biochemical Characteristics)

HARMINDER KAUR AND N.L. CHITKARA
(*Medical College, Amritsar.*)

The existence of acid fast bacilli producing pulmonary disease in man, but differing from *Mycobacterium tuberculosis* in cultural, biochemical and other characteristics has been reported sporadically for many years. Tarshis and Frisch (1952), Buhler & Pollak (1953) and Timpe & Runyon (1954) suggested that a group of these organisms potentially pathogenic to man, could be distinguished by their virulence to animals and cultural characteristics. Tarshis and Frisch were able to distinguish three main groups of atypical mycobacteria on the basis of their pathogenicity in mice, pigment production, and consistency of the colonies. They recognized two main types of chromogenicity. In one type the colonies developed colour only on exposure to light (Photo chromogenicity), and in the other type pigment was produced in the dark (Scotochromogenicity). The only comprehensive classification of these atypical or anonymous mycobacteria is that of Runyon (1959). A study of the literature shows that several types of atypical mycobacteria are involved in pulmonary disease. The same type of organisms have been isolated from the sputum and resected lung tissue. Some of these organisms can undoubtedly produce disease, but their true significance is still largely unknown.

It was therefore considered desirable to carry out an investigation on the incidence of disease due to atypical acid fast bacilli in this part of the country. A study of cord formation, catalase and peroxidase tests, the Niacin test, the Neutral red test and the Arylsulphatase test has been made to differentiate the anonymous acid fast bacilli from the Human tubercle bacilli.

Material and Methods

Fifty positive cultures obtained from the sputa of cases of pulmonary tuberculosis were studied. The sputum was concentrated by Petroff's method and cultured on

Lowenstein Jensen Medium. Four bottles of culture media were used for a single case. Two of these were incubated at 37°C after being wrapped in black paper, while the other two were incubated without any wrapping. The morphology of the positive cultures was studied by preparing smears and staining them with the Ziehl Neelsen technique, acid alcohol solution being used for decolourization.

Pigment Production

The positive cultures obtained in the wrapped bottles, were examined for the production of pigment. One of the bottles was exposed to light from a 30 watt lamp placed at a distance of 45 cm, for one hour daily, for a period of 7 days. The colonies were then re-examined for pigment production.

Cord Formation

A small amount of the growth was sub-cultured into Proskauer and Beck liquid medium. These bottles were then incubated at 37°C for 10-15 days or till growth appeared. Smears were prepared, stained by the Ziehl Neelsen technique and examined for cord formation.

Catalase Test

This test was performed by the method described by Dunbar, McAlister and Jefferies 1959. A Positive test was indicated by the evolution of gas bubbles from the colonies within 2-5 minutes.

Peroxidase Test

The presence of peroxidase was indicated by the colonies being turned brown to black within a period of 45 minutes, after performing the catalase test.

Neutral Red Binding Test

(After Dubos and Middlebrook 1948, modified by Ganguli, 1957).

The colonies were examined for pink or red staining. Any degree of colouration was taken as a positive test.

Niacin Test:—

(After Runyon, Selin and Harris 1959).

0.5 to 1 ml of sterile physiological saline was added to the culture on Lowenstein Jensen Medium. After placing these bottles in a slanting position for 5-10 minutes the fluid was transferred into a test tube and equal quantities of 4% alcoholic aniline and 10% aqueous cyanogen bromide were added to it in that order, using a fume hood. The prompt development of a yellow colour throughout the entire solution was taken as a positive niacin test, the intensity of the colour denoting the amount of niacin produced. A control test was performed with a loopful of Lowenstein Jensen Medium alone. In cases showing a negative reaction the extraction time with saline was increased to 30 minutes.

Arylsulphatase Test: —

(After Arora, Dudani and Krishna Murti 1953)

The results were recorded as follows: —

| | |
|--------------------|-------|
| Deep red colour | +++ + |
| Red Colour | +++ |
| Orange Colour | ++ |
| Pale Orange Colour | + |
| Slight Orange tint | + |
| No Change | — |

Results: —

All the cases studied showed a buff coloured growth except 4 strains in which the colonies exhibited dark yellow to orange colour and were thus chromogenic. Apart from this pigmentation the four chromogenic strains showed no distinctive morphological characteristics. Pigment was produced both when these strains were grown in the light and when grown in the dark. None showed pigment production exclusively in the dark or in the light.

Frank cord formation was present in 33 cases, 7 showed a tendency to cord forma-

Cord Formation



(Fig. No. 1)

tion and ten strains showed no cords. The four pigmented strains showed no cord formation.

Natural Red Binding Test

A frankly positive test was obtained with all the strains.

Catalase and Peroxidase Tests

Catalase activity was present in 45 strains and absent in 5 strains. Peroxidase activity was absent in 9 strains. The catalase activity of 3 of the pigmented strains was vigorous and immediate while in the fourth strain it was vigorous but took 1-2 minutes to develop. In this latter strain peroxidase activity was absent.

Niacin Production

This test was positive in 47 cases. A deep yellow colour was obtained in three cases and a light yellow colour in the remaining 44 cases. Three of the chromogenic strains showed a positive test with the development of a light yellow colour and one strain was niacin negative.

Arylsulphatase Test

This test was positive with 45 strains and negative with 5 strains. In 8 cases the reaction was + + +, in 10 cases + + +, in 3

cases + and in 15 cases -f

Discussion

A systematic comparison of the results obtained by the tests carried out was made. (Table 1)

As compared to the buff coloured strains, the pigmented strains showed a greater tendency to be non-cord forming and niacin negative. It was also of significance that all the pigmented strains were strongly catalase positive. No definite correlation existed between the colour of the colonies and the peroxidase and arylsulphatase test.

TABLE I
Relation of Colony Colour to other Characteristics

| | | Yellow to orange. | Buff |
|---------------------|------------------|-------------------|------|
| Total No. | | 4 | 46 |
| Cord formation | Positive | 0 | 33 |
| | Tendency | 0 | 7 |
| Catalase activity | Negative | 4 | 6 |
| | Vigorous | 4 | 27 |
| Peroxidase activity | Weak to Moderate | 0 | 14 |
| | Negative | 0 | 5 |
| | Positive | 3 | 38 |
| Niacin activity | Negative | 1 | 8 |
| | Positive | 3 | 44 |
| Neutral Red test | Negative | 1 | 2 |
| | Positive | 4 | 46 |
| Arylsulphatase test | Negative | 0 | 0 |
| | Positive | 4 | 41 |
| | Negative | 0 | 5 |

Four strains isolated in this series were chromogenic. They produced yellow to orange coloured colonies both when grown in the dark and when grown in light. They thus belong to the scotochromogenic group of Runyon (1959).

As already discussed all of these pigmented strains were non cord forming, vigorously catalase positive, and neutral red and arylsulphatase positive. Three of them also showed a positive peroxidase and niacin test. All of them were isolated from active cases of pulmonary tuberculosis. Although no human strains of tubercle bacilli were obtained from the sputa of these patients in addition to the pigmented strains, it cannot be conclusively said that they were the causative organisms of the disease, as no

importance can be given to a single isolation of chromogenic acid fast bacilli.

Ten strains of this study have been designated as non-photochromogenic. Their precise classification is difficult as no definite criteria have been laid down for their identification. Moreover it is difficult to distinguish them from attenuated strains. These strains were buff coloured, non cord forming or showed a tendency to cord formation, catalase, peroxidase, niacin and neutral red positive. The view of Huppert, Wayne, and Jaurez (1957) supports their inclusion in atypical strains. According to these investigators a non-pigmented, neutral red positive and a non-corded atypical strain of mycobacterium can be distinguished from a weakly corded M. Tuberculosis by the fact that the latter organisms is catalase negative and the former catalase positive.

Thus it was found that out of the 50 strains studied, 14 were atypical, 4 being scotochromogens and the rest non-photochromogens. This gives an incidence of 8% for the chromogenic atypical acid fast bacilli.

Summary

The cultural and biochemical characteristics have been studied in 50 strains of acid-fast bacilli isolated from cases of pulmonary tuberculosis.

Four strains have been classified as scotochromogens. They produced a yellow to orange coloured pigment.

The incidence of chromogenic acid fast bacilli obtained in this series is 8%.

REFERENCES

- Arora, K.L., Dudani, A.T. and Krishna Murti. C.R. (1953) J. Sci. Industr. Res., 12B: 502.
 Buhler, V.B. and Pollak, A. (1953) Am. J. Clin. Path., 23: 363.
 Dubos, R.J. and Middle Brook, G. (1948) Am. Rev. Tuberc., 58: 698.
 Dunbar, P.P., McAlister, E. and Jefferies, M.B. (1959) Am. Rev. Tuberc., 79: 669.
 Ganguli, S. (1957) Ind. J. Med. Res., 45: 173.
 Huppert, M., Wayne, L.G. and Jaurez, W.J. (1957) Am. Rev. Tuberc., 76: 468.
 Mackie and McCartney (1960) Handbook of Bacteriology 10th Ed. Cruickshank, R. Pd. 116, 212 and 547.
 Runyon, E.H. (1959) M. Clin. North. America., 43: 273.
 Runyon, E.H., Selin, M.J. and Harris, H.W. (1959) Am. Rev. Tuberc., 79: 663.
 Tarshish, M.S. and Frisch, A.W. (1952) Am. Rev. Tuberc., 65: 278.
 Timpe, A. and Runyon, E.H. (1954) J. Lab. & Clin. Med., 44: 202.

SEVERE HYPERSENSITIVITY REACTIONS TO ANTITUBERCULAR DRUGS AND THEIR MANAGEMENT

LT. COL. J.C. CHATTERJI (*Military Hospital, Aundh Camp, Poona*)

Introduction

Severe hypersensitivity reactions to standard antitubercular drugs are rare, but they may be fatal. The most common reactions encountered are fever and skin rashes. These usually occur during the first four to six weeks of commencing the therapy. Skin reactions consist of erythema sometimes leading to severe dermatitis (Heaf and Rusby, 1959). Jaundice has been reported due to para-aminosalicylic acid (PAS). Streptomycin and PAS both have been held responsible for eosinophilia and encephalopathy (Crofton, 1960; Heaf and Rusby, 1959). Rarely anaphylactic reactions may occur.

When hypersensitivity reactions occur, all antitubercular drugs have to be stopped as any one of the drugs may be responsible. There is no difficulty in testing for hypersensitivity in mild cases and desensitizing them. There is, however, real difficulty in dealing with the severely hypersensitive cases. In this paper it is proposed to deal with them.

Material and Methods

During 1961 and 1962, 6 cases of severe hypersensitivity reactions were encountered in Military Hospital, Aundh, out of a total of 710 patients of pulmonary tuberculosis. These cases, together with one admitted towards the end of 1960, are discussed here.

Case 1. PD aged 30 years was suffering from pulmonary tuberculosis involving left upper zone with a moderately large cavity. There were few opacities in right lower zone also. Antitubercular chemotherapy with Streptomycin, isoniazid (INH) and PAS was started on August 20, 1960. On October 10, during the eighth week of treatment, he complained of itching and developed macular eruptions on the body which progressed to severe exfoliative dermatitis in spite of stoppage of antitubercular chemotherapy. The patient became severely ill but recovered. Test dose of 5 mg INH after all the skin lesions had cleared up completely produced severe itching. With PAS, he also complained of discomfort in upper abdomen. He was desensitized to PAS and then to streptomycin both in second attempt with smaller

doses. With streptomycin, he complained of warmth and burning sensation all over the body, had watering from the eyes and nose, and papular rashes on the body. Desensitization to INH was carried out after this. Streptomycin had to be withdrawn because of toxic reactions and PAS and INH were continued. Off and on he developed itching and papular eruptions, sometimes severe, and drugs had to be stopped. Desensitizing procedures had to be repeated. Lesions, however, regressed well. Sputum became negative on culture after July 1961. The patient left the hospital on February 28, 1962.

Case 2. PKM aged 49 years was admitted in March 1961 in another hospital with pulmonary tuberculosis involving right upper and mid zones with multiple small cavities. He was started on treatment with Streptomycin, INH and PAS on March 19, 1961. He began running temperature on April 24, that is, five weeks after antitubercular chemotherapy was started. Temperature sometimes went up high with chill and rigor and came down with perspiration. He was administered 600 mg amodiaquine orally. Half an hour later he complained of severe burning sensation of abdomen and difficulty in breathing. He vomited and became cyanosed. He also developed a rash all over the body. He recovered with treatment. Antitubercular chemotherapy was stopped and he was transferred to this hospital on May 12. On arrival here the medical officer attributed the above reaction to amodiaquine and the patient was given 1 G. of Streptomycin, 100 mg INH and 5 G. PAS. About two and half hours later the patient felt burning sensation all over the abdomen and difficulty in breathing as before. Two hours later his temperature rose to 102°F and blood pressure fell to 80/40 mm Hg. He recovered with treatment. Very small dose of PAS increasing by similar doses were given to him with no reaction. Similarly INH was given but after two weeks he again had fever, anorexia and headache. Test doses showed hypersensitivity to PAS and desensitization failed, even when given with 10 mg of prednisolone.

Ind. J. Tub., Vol. XII, No. 1

Pulmonary lesions showed progression during this period. In November 1961, however, he was desensitized under 20 mg. prednisolone daily. During this period he was given INH 200 mg. daily. Prednisolone dose was reduced soon to 10 mg. daily and continued for a total of about three months. INH 200 mg daily and PAS 10 G. daily were continued. Serial radiographs showed good regression of lesions with disappearance of cavitation as seen in plain films and tomograms. Sputum became negative on culture after February 1962 and remained so till he left the hospital on July 14, 1962.

Case 3. BP aged 41 years was admitted on July 3, 1961 with far advanced pulmonary tuberculosis. On August 5, in the fourth week after commencement of streptomycin, INH and PAS the patient developed maculopapular rashes all over the body which progressed to severe exfoliative dermatitis. After recovery from the dermatitis, test doses showed hypersensitivity to streptomycin and PAS. Desensitization was not successful and the lung lesions were progressing. Two days after commencement of treatment with 40 mg. prednisolone and 200

mg INH daily with a view to desensitization under cover of steroid the patient developed pneumothorax and further complications and expired.

Case 4. KPS aged 38 years was admitted on January 2, 1962 with pulmonary tuberculosis. Right lower zone showed opacities with cavitation (Plate 1). Streptomycin, INH and PAS were administered with effect from the same date. He was transferred to this hospital on February 9. Two days later, in the fifth week of treatment, he complained of rash and itching all over the body and fever. The disease progressed in spite of stoppage of antitubercular chemotherapy and he had very severe dermatitis with widespread erythema, vesicular eruptions over the whole body, eczematous eruptions and swelling of the face. He was extremely ill. He was put on prednisolone 60 mg daily together with INH 200 mg. daily and oxy-tetracycline 2 G. daily in four divided doses. The patient responded very well to the treatment and the dose of prednisolone was reduced gradually to 10 mg. daily and withdrawn after six weeks. But he was put back on the same two weeks later and

Case 4

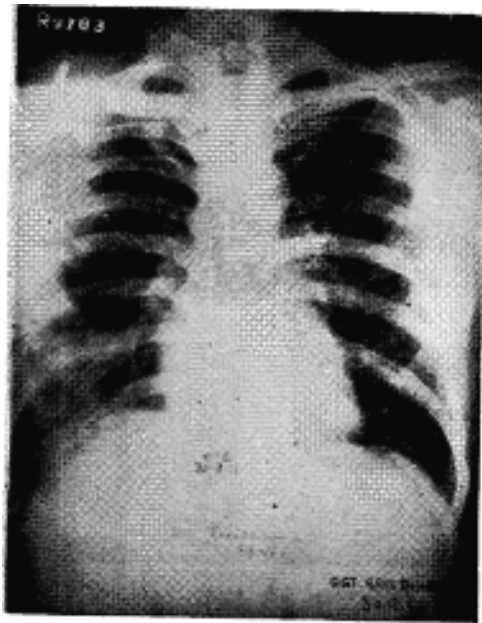


PLATE 1 (Film dated 30-12-61)

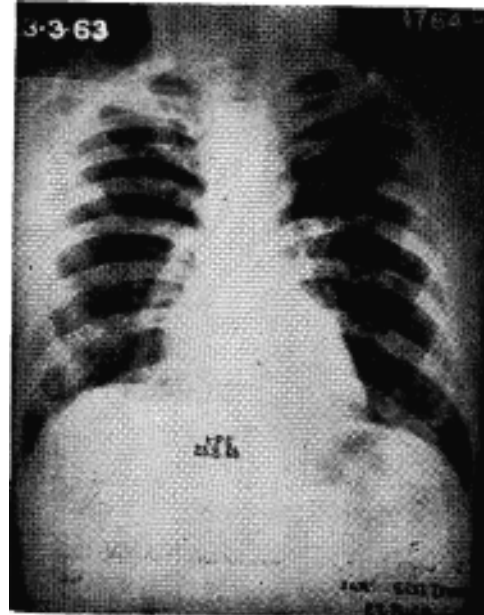


PLATE 2 (Film dated 23-3-62)

streptomycin was given in desensitizing doses till 1 G. daily dose was reached. He was continued on streptomycin and INH and the steroid was withdrawn after two months, Pulmonary disease regressed very well (Plate 2). Sputum became negative after May 1962 and remained so thereafter. Residual lesions were stabilised in plain X-ray and tomograms did not show any significant lesion. He left the hospital on March 23, 1963.

Case 5. CB aged 24 years was similar to Case 4 and was treated as above. He was admitted to this hospital on March 30, 1962 with extensive bilateral pulmonary tuberculosis with multiple cavitations in left upper and mid zones. Reactions similar to Case 4 developed in the fifth week. Ulcers were present on lips and tongue also with excoriation of lips. Prednisolone 30 mg. daily was given initially and the dose reduced to 10 mg. daily later and continued for a total period of 3½ months. Desensitization with streptomycin and PAS were unsuccessful, and INH and oxy-tetracycline (2 G. daily) were continued till April 1963, that is, for one year, when nicotinaldehyde thiosemicar-

bazone 60 mg. daily was successfully introduced in the second attempt, and continued with INH 240 mg. daily (Tebafen-Geigy-2 tablets three times daily). Sputum became negative after April 1962. Serial radiographs showed excellent regression of lesions (X-ray films dated February 17, 1962 and March 29, 1963-Plates 3 and 4). The patient left the hospital on May 23, 1963.

Case 6. HL aged 26 years was admitted on October 20, 1962 in this hospital. He was similar to Case 5. Reactions appeared on November 23 and were more severe. He was treated on similar lines. Desensitization to streptomycin and PAS was unsuccessful. Prednisolone was discontinued after three months. He was continued on INH (300 mg.) and oxy-tetracycline (2 G.) till Tebafen (see above) two tablets three times daily (each tablet contains 10 mg. thiosemicarbazone and 40 mg. INH) was introduced in April 1963. Sputum, which was originally positive on smear in the forwarding hospital, was negative on smear and culture after admission to this hospital and remained so. Radiologically there was excellent regression of lesions (X-ray films

Case 5

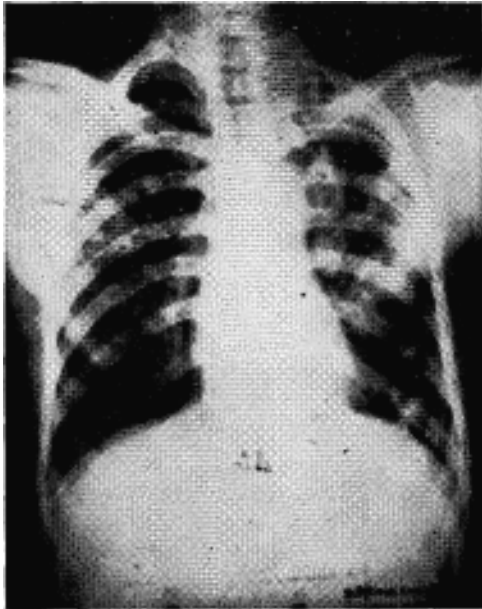


PLATE 3 (Film dated 17-2-62)

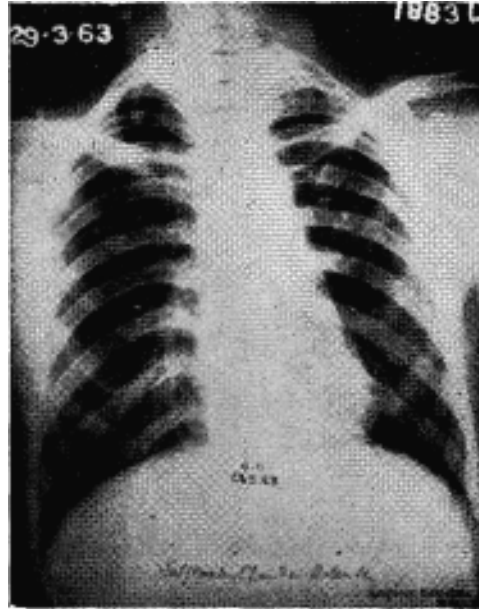


PLATE 4 (Film dated 29-3-63)

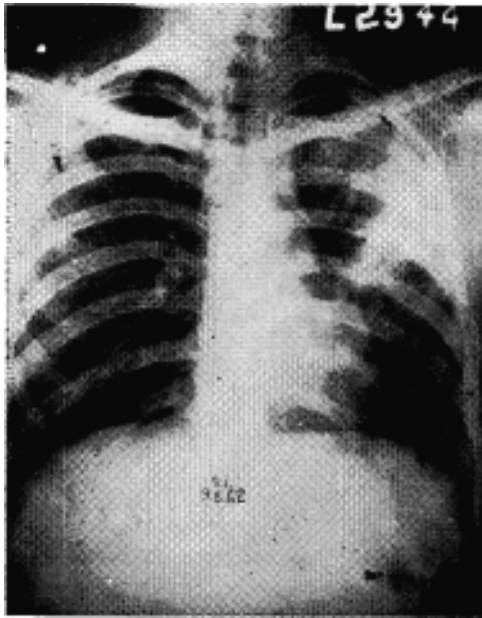
Case 9

PLATE 5 (Film dated 9.5.62)

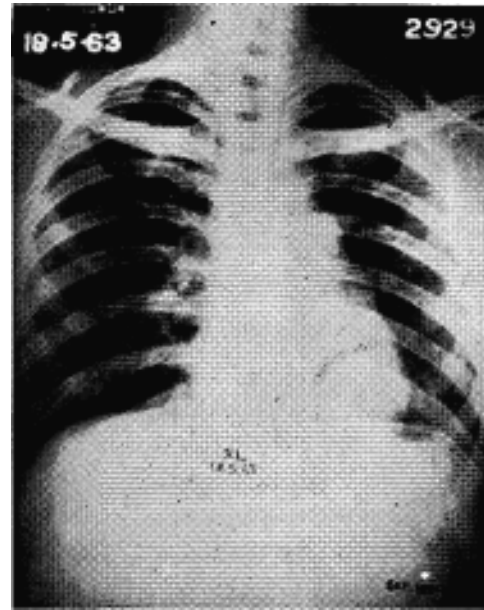


PLATE 6 (Film dated 18-5-63)

dated May 9, 1962 and May 18, 1963—Plate 5 and 6). Multiple cavities seen in tomograms originally disappeared. He was observed till June 17, 1964.

Case 7. JR aged 37 years was admitted in this hospital on June, 30 1962. His anti-tubercular chemotherapy with Streptomycin and INH was started in the previous hospital on June 19, 1962. In this hospital, PAS was added on June 30. From July 17, that is, four weeks after treatment was started, he started running high temperature. He also complained of burning sensation in the epigastrium and a feeling of swelling over the body. Temperature continued in spite of stoppage of anti-tubercular chemotherapy, and all relevant investigations as for a case of pyrexia of unknown origin, including muscle biopsy, were negative. On July, 25, he was given prednisolone 30 mg. daily with Streptomycin 1 G. and INH 300 mg. daily. Temperature subsided after two days, but Streptomycin had to be stopped as he developed itching, generalised erythema and maculopapular rash five days later. It was replaced by oxy-tetracycline 2 G. daily. Prednisolone dose was reduced 10 mg. daily

Ind. J. Tub., Vol. XII, No. 1

and continued for a total period of about 3½ months. During the later period he was desensitized to PAS and thereafter continued on INH and PAS. Serial radiographs showed good regression of lesions (X-ray films dated June 22, 1962 and July 20, 1963—Plates 7 and 8). The disease which was seen in practically the whole of left lung and right upper zone with multiple cavitation in left upper zone responded well to treatment. No cavitation was seen and this was confirmed by tomography. He was observed till January 18, 1964.

Results

In one case (Case 1) desensitization was tried without steroids with success but after prolonged waiting for the reactions to subside and with considerable difficulty. One case (Case 3) died when steroid was commenced after waiting for the reaction to subside and after failure to desensitize by ordinary methods. These two patients were not, however, seen by us in the beginning. All other patients were treated with steroids, INH and oxy-tetracycline, and later with

Case 7

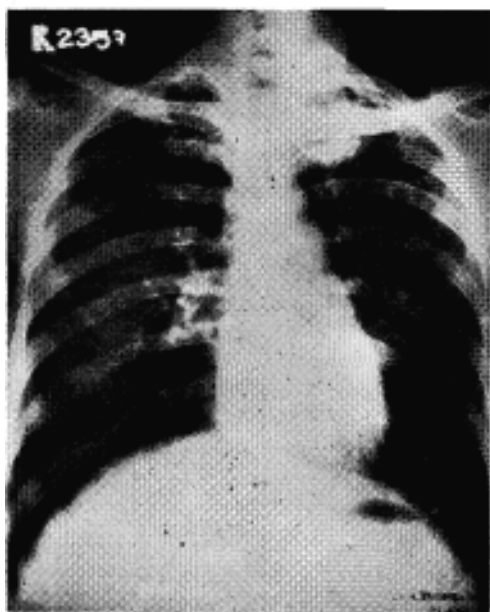


PLATE 7 (Film dated 22-6-62)

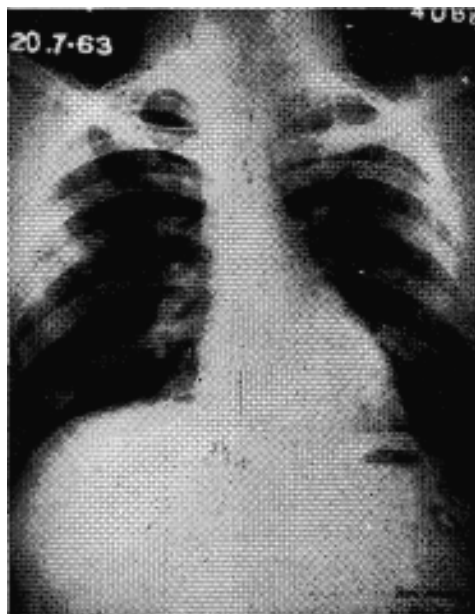


PLATE 8 (Film dated 20-7-63)

streptomycin, INH, PAS and thiosemicarbazone according to combination tolerated by the patients (In Case 2 oxy-tetracycline was not used).

All patients did well. Sputum became negative for Myco. tuberculosis and remained so. Radiologically the lesions regressed well.

Discussion

In severe hypersensitivity reaction steroids have to be used. These reactions occur in the first four to six weeks when normally all the three standard antitubercular drugs are employed. If full doses of all these or at least two of these drugs are to be used concurrently as are essential, the dose of the steroid has to be high for some time with its attendant hazards. It is not always possible to employ other antitubercular drugs as most of them are either toxic or have serious side effects. Besides these patients may be hypersensitive to these drugs also. Case 5 was found to be hypersensitive to thiosemicarbazone. Lower doses of steroids are

unable to suppress the reactions, as seen in Case 7, and desensitization under small doses of steroids in the beginning is not successful, as seen in Case 2. Therefore, moderate to high doses of steroid were used in the beginning till the reaction subsided. Isoniazid, the drug to which the patient is least likely to be hypersensitive, together with oxy-tetracycline 2 G. daily in four divided doses were given as antitubercular drugs. Oxy-tetracycline was used to prevent the emergence of resistance to INH and this was successful even with the 2 G. daily dose. According to available reports this has not been the experience of other workers outside India even with 4 G. to 5 G. daily dose in two divided doses. It is to be noted, however, that our patients had treatment with Streptomycin, INH and PAS for some time before hypersensitivity manifested when INH and oxy-tetracycline were administered together with a steroid. Home and Grant (1963) have reported recently development of INH resistance in two cases while desensitization was carried out. The dose of prednisolone the steroid used in these patients—was reduced gradually to a main-

tenance dose of about 10 mg. daily and continued to a total period of about three months. Desensitization to Streptomycin or PAS was attempted during the last six weeks or so of the steroid administration though not always successfully. When unsuccessful thiosemicarbazone in combination with INH was used later. It is felt that if the maintenance dose of the steroid is higher, say 15 mg. it may be possible to introduce Streptomycin or PAS or both.

There is, however, one danger in treating the cases in this way, that is, when the organisms are primarily resistant to INH. So, where such a probability exists, it is necessary to use a non-toxic drug like ethionamide in addition.

Nature of the reactions, time of onset, and the incriminating drug, is summarised in Table 1. Time of onset was between four and eight weeks as usually described. The incriminating drugs were streptomycin and/or PAS except in one case (PD) where patient was found to be hypersensitivity to INH also. It is felt that in such severe hypersensitivity reactions the patient is likely to be hypersensitive to drugs other than that which was originally responsible as seen in Case 5, who was so to thiosemicarbazone.

Summary

Severe hypersensitivity reactions to anti-tubercular drugs are rare but can be fatal.

Seven such cases are described and their management discussed.

Use of steroids is necessary in these cases. Antitubercular drugs used during the administration of steroid are INH and 2 Goxy-tetracycline daily. Oxy-tetracycline in this

dose prevented the emergence of resistance to INH for a period of three months or over during which steroid was used, and even afterwards. During the later period of steroid administration, desensitization to streptomycin and PAS was tried sometimes with success. Otherwise nicotinaldehyde thiosemicarbazone in combination with INH was used with success. Response of the patients both radiologically and bacteriologically was very good.

Nature of the reactions, time of onset, and the incriminating drugs are described.

Four more such patients were admitted in 1963. Oxy-tetracycline in 2 G. daily dose (in four divided doses) has been able to prevent the emergence of resistance to INH.

Acknowledgements

I am grateful to Lieut. General C.C. Kapila, Director General, Armed Forces Medical Services, and Major General T.R. Pahwa, Director of Medical Services, for permission to publish this paper, and to Major General P.N. Bardhan, Commandant, Armed Forces Medical College, for his helpful guidance in the preparation of this paper. I wish to thank Brigadier Inder Singh, Consultant in Medicine, for his suggestion to use "Tebafen," and Lieut. Colonel M.L. Gaiind, Adviser in Dermatology, for his help in treating some of the patients.

REFERENCES

1. Crofton, J. (1960), *Brit. Med. J.*, 2, 370.
2. Heaf, F., and Rusby, N.L. (1959), *Recent Advances in Respiratory Tuberculosis*, J. & A. Churchill Ltd., London, pp. 101 and 107.
3. Home, N.W., and Grant, I.W.B. (1963), *Tubercule, Lond.*, 44, 1, 180.

| <i>Patient</i> | <i>Nature of Reaction</i> | <i>Time of Onset</i> | <i>Incriminating Drugs</i> | <i>Remarks</i> |
|----------------|--|---|---|---|
| Case 1 PD | Exfoliative dermatitis.* Discomfort in upper abdomen, papular rashes and itching, watering of eyes, and running from the nose | 8th week | Streptomycin, PAS and INH. | |
| Case 2 PKM | Fever* Difficulty in breathing, burning sensation all over the abdomen, fever, fall of blood pressure. | 6th week Within 2J hours of giving Streptomycin, INH and PAS about 2 weeks later | PAS. Sensitivity to Streptomycin not tested. | Had difficulty in breathing, burning sensation in abdomen half an hour after 600 mg of amodiaquine during the first rise of temperature.* |
| Case 3 BP | Exfoliative dermatitis* | 4th week | Streptomycin and PAS. | |
| Case 4 KPS | Erythema and Vesicular eruptions over whole body. Swelling of the face | 5th week | Sensitivity to PAS not tested Desensitizing doses of Streptomycin used under cover of steroid. | |
| Case 5 CB | As in Case 4. Lesions were seen in mouth also | 5th week | Streptomycin and PAS | Later found to be hypersensitive to thiosemicarbazone also. |
| Case 6 HL | As in cases 4 and 5 | ----- | Streptomycin and PAS. | |
| Case 7 JR | Fever, burning sensation in the epigastrium, feeling of swelling over the body | 5th week | Streptomycin. PAS not tested. (Desensitizing doses to PAS used under cover of steroid). | |

Nature of the hypersensitivity reactions to antitubercular drugs, their time of onset, and the incriminating drugs

GASTRIC FUNCTION STUDIES IN PULMONARY TUBERCULOSIS

MRS. S. KULDEEP AND K.S. GREWALL
(Ispat General Hospital, Rourkeld)

It has, for some time, been known that pulmonary tuberculosis and peptic ulcer are found in association more frequently than can be accounted for by chance alone.

Pulvertaft (1952) was the first to draw attention to this relationship and noted in one follow-up study 8 deaths due to pulmonary tuberculosis out of 23. Anderson (1955) in a follow-up study also noticed higher incidence of deaths due to pulmonary tuberculosis.

Thorn and Brookes (1956) found that in cases with normal X-Ray chest before partial gastrectomy operation, 11 out of 616 men developed tuberculosis. It was also found that the prevalence rate of pulmonary tuberculosis in men with gastric ulcer was 10.5% and in men with duodenal ulcer 5.3%, a highly significant difference (Heaf and Rusby 1959). Collman (1956) also reported occurrence of serious complications developing in peptic ulcer cases after surgical treatment for pulmonary tuberculosis.

Thorn (1956) investigated various factors which might have led to this result—position of ulcer, extent of resection, weight and symptomatic outcome—there was little doubt that low pre-operative weight was decidedly most important.

Pulvertaft (1952) and Anderson (1955) also regarded the loss of weight and general debility to be the cause for it.

However, Johnson (1951) in a follow-up of cases of gastrectomies noticed an increase in weight in 58 per cent, no appreciable change in 33 per cent and a decrease in only 9 per cent of cases.

In view of the above interesting relationship reported, this study was undertaken to find out any disturbances of gastric secretions in patients of pulmonary tuberculosis.

Methods and Materials

Thirty cases of active pulmonary tubercu-

losis attending the chest department of this hospital were studied. Only fresh virgin cases who had not received any anti-tubercular drugs were taken up. All were sputum positive for A.F.B.

The analysis carried out relates to (a) fasting gastric juice (quantity, free and total acidity, and chloride content) (b) fractional gastric analysis and residual juice (c) Cystological study. Smears of the gastric sediment were taken and stained by Papanicolaou method (1942) and presence of bacteria, mucous, epithelial cells and blood cells noted.

Ten persons, normal on clinical and radiological examinations were, also studied as controls.

Results and Comments

It is seen from Table I that the total quan-

TABLE I

| | <i>TB Patients</i> | | <i>Normals</i> | |
|--------------------------------------|--------------------|-------------|----------------|-------------|
| | <i>Range</i> | <i>Mean</i> | <i>Range</i> | <i>Mean</i> |
| 1. Quantity in cc. | 12-85 | 28.0 | 10-130 | 38.4 |
| 2. Free Acidity (Units per cent) | 0-54 | 13.0 | 0-63 | 20.6 |
| 3. Total Acidity (Units per cent) | 2-70 | 17.4 | 2-74 | 29.3 |
| 4. Chloride (Gram per cent) | 0.5-1.2 | .72 | .2-1.3 | .75 |

tity and the free and total acidity of the fasting juice are lower in the TB patients than the normal values. Similarly the fractional analysis results (Table II) also show a lowering of the free and total acidity values—both as regards the maximum and minimum levels.

However, the chloride content does not show any appreciable change. The amount of residual juice is also reduced in cases of pulmonary tuberculosis. There is no change in the patients of pulmonary tuberculosis as

Table II
Finding of Fractional Analysis

| | <i>TB Patients</i> | | <i>Normals</i> | |
|---|--------------------|-----------------|------------------|-------------|
| | <i>Range</i> | <i>Mea</i> " | <i>Range</i> | <i>Mean</i> |
| I. Maximum Values | | | | |
| 1. Free acidity (Unit per cent) | 2-84 | 23.00 | 14-92 | 34.00 |
| 2. Total acidity (Unit per cent) | 4-96 | 34.00 | 16-100 | 48.0 |
| 3. Chloride (Gram per cent) | 2-1.1 | .75 | 4-1.2 | .80 |
| II. Minimum Values | | | | |
| 1. Free acidity (Unit per cent) | 2-36 | 7.0 | 0-48 | 12.0 |
| 2. Total acidity (Unit per cent) | 2-90 | 34.0 | 2-54 | 16.00 |
| 3. Chloride (Gram per cent) | 5-1 | .65 | 1-7 | .45 |
| III Time for maximum acidity | 1/4-2 1/2 hrs | 1 1/4 hrs | 1/2-2 hrs. | 1 1/4 hrs. |
| IV Time for minimal acid level after peak | 1 1/2-2 1/2 hrs | 2 hrs | 1 1/2-2 1/4 hrs. | 2 hrs. |
| V. Residual juice | 4-20 cc. | 13 cc. | 3-26 cc. | 15 cc. |

TABLE III

Findings of Cytological Examination

| | <i>TB Patients</i> | <i>Normals</i> |
|---------------------|--------------------|----------------|
| 1. Epithelial cells | 75% | 70% |
| 2. Leucocytes | 80% | 85% |
| 3. Bacteria | 72% | 80% |
| 4. Mucous | 100% | 100% |

far as the time to reach the peak level of acidity and return to minimum levels is concerned. Similarly the cytological examination (Table III) showed no marked differences.

It is thus clear that the only change in gastric physiology seen in the patients of pulmonary tuberculosis compared to the normal controls is the occurrence of a mild degree of hypochlorhydria.

Summary

Gastric functions have been studied in 30 cases of active, sputum positive, non-treated cases of pulmonary tuberculosis and 10 normal persons. Studies of fasting juice, fractional gastric analysis and cytological examination of the gastric contents have been done.

The only change detected in the patients of pulmonary tuberculosis is a mild degree of hypochlorhydria.

REFERENCES

- Anderson, C.D. Gunn R.T., Watt J.K. (1955) Br. Med. J, 1, 508.
- Collanan J.O. (1956) Am. Rev. Tub. Pulm. Disease 74, 358.
- Heaf and Rusby (1959) Recent advances in Respiratory Tuberculosis. Churchill Lond. 247.
- Johnsons. (1951) Acta Medica. Scandinav 140, 12.
- Pulvertaft C N. (1952) Lancet, 1, 225.
- Papanicolaou G.N. (1942) Science 95, 433.
- Thorn P.A., Brookes V.S, Waterhouse J.A.H. (1956) Brit. Med. J., 603.

NEWS & NOTES

Our New Chairman

Dr. K. N. Rao has taken over as the Director General of Health Services, Government of India, and by virtue of that, he is Chairman of the Association.

The New Editorial Board

The new Editorial Board for the Indian Journal of Tuberculosis from July, 1964 consist of: Dr. P. K. Sen (Calcutta), Editor, Dr. N.L. Bordia (TB Adviser) and Dr. M.D. Deshmukh (Bombay), Co-Editors, and Dr. S.P. Pamra (New Delhi TB Centre) and Dr. H.B. Dingley (Mehrauli TB Hospital, Delhi), Associate Editors.

New Cover Page

From the March 1965 issue, the Indian Journal of Tuberculosis will have a new cover page.

TB Health Visitors' Course

The 1965 TB Health Visitors' Course opened at the New Delhi TB Centre, on 2nd January, 1965. At present, eighteen candidates are undergoing the one-year course.

TB Association of Goa, Daman and Diu

A TB Association for Goa, Daman and Diu was inaugurated in Panjim by the Lt.-Governor of Goa on 2nd October, 1964. Mr. B.M. Cariappa, Secretary of the Tuberculosis Association of India, addressed the inaugural meeting. The Goa Administration has promised a contribution of Rs. 25,000/- as the corpus of fund for this Association. The Tuberculosis Association of India gave an ad hoc grant of Rs. 5,000/- to enable them to start this Association.

TB Association of Madhya Pradesh

Considerable progress has been made in regard to the formation of a TB Association for Madhya Pradesh. It is gratifying to note that all formalities connected with the formation of this Association have now been completed. A draft model Constitution for this Association has been made available by the Central Association and it is hoped that the State TB Association will be formally constituted in the near future.

Rules and Regulations of Mysore Association

Rules and Regulations of the Mysore State Association have been recently revised on the basis of a model draft made available by the Tuberculosis Association of India. These rules are meant to ensure cooperation of all sections of the public and Government in the activities of the Association.

K.E.A.T. Fund of Rajasthan

The Central Association had been trying to persuade the Rajasthan Government to transfer to the State TB Association securities worth Rs 6,70,000/- representing balances available in the King Emperor's Anti-TB Fund returned to States now forming Rajasthan, as this amount was meant to be used for non-official anti-TB work in the State. The Rajasthan Government have now agreed to release a sum of Rs. 6,85,000/- for building two TB Hospitals in Jodhpur and Ajmer.

TB Workers Conferences in the States

West Bengal

Bengal TB Association organised its first TB Workers' Conference in Calcutta on 28th and 29th November, 1964. A Souvenir and a Directory of TB institutions in Bengal were brought out on the occasion. The Conference was attended by over 250 delegates.

Shri B.M. Cariappa, Secretary, Tuberculosis Association of India, addressed the inaugural session.

Besides, presentation of original papers there were two Panel discussions on "Medical Management of Pulmonary TB" and "Surgical Treatment of Pulmonary TB" followed by a Scientific Session.

Some of the important recommendations made at this Conference were: (a) Case-finding in rural areas by Sputum tests at peripheral centres while Referral System should be evolved for District Control Programme, (b) Patients from rural areas should have highest priorities for hospitalisation. (c) Good risk Surgical cases should be immediately admitted in hospitals and there should be special arrangements in separate institutions for the treatment of incurable cases, (d) In Chemotherapy single drug should not be used except under extreme conditions like "Single drug or no drug at

all", (e) The Government should provide necessary foreign exchange for the import of major drugs like PAS which are often in short supply, (f) A patient should be given the same diet he is used to thereby avoiding additional diet, (g) Patients are fit to be rehabilitated to their own jobs unless it is a very hazardous one. (h) Attempts should be made to give chemotherapy to all known cases of tuberculosis including minor collapse therapies like A.P. & P.P. if necessary, (i) To avoid misuse of free anti-TB drugs these may perhaps bear some special colour, (j) There should be adequate supply of second line drugs like Thiacetazone, Ethionamide, Pyrazinamide and Cycloserine to recognised TB institutions; (k) Gramsevaks should propagate among the rural people about the necessity of drug taking and availability of free anti-TB drugs.

Punjab

The Second State Tuberculosis Workers' Conference of Punjab was held in the premises of Gulab Devi TB Hospital, Jullundur, on 17th and 18th October, 1964. Lt.-Col. Deepak Bhatia, Director of Health Services, Punjab inaugurated the conference. Apart from the Scientific session there was a meeting of officers of District TB Associations for discussing organisational matters.

The Conference made a strong plea for the adequate supply of all the second line drugs like Ethionamide, Pyrazinamide and Cycloserine to all recognised TB institutions, as also availability of first line drugs, e.g., Streptomycin, Isonicotinic acid Hydrazide for regular and uninterrupted treatment. The conference also recommended that Government be approached for the exemption from sales tax of TB drugs purchased by voluntary bodies and also for waiving income tax on donations.

The conference decided to revive the activities of district branches with the active help and cooperation of Chief Medical Officers and Deputy Commissioners in the districts. The conference also resolved to intensify its health education programme and help in the formation of Care Committees.

Maharashtra

The Third Maharashtra State Tuberculosis

and Chest Diseases Workers' Conference was held in Bombay from 12th to 14th December, 1964 in the premises of J.J. Group of Hospitals. Shri Shantilal Shah, State's Minister for Public Health, Law and Judiciary, inaugurated the conference. Over fifty delegates attended the conference.

Shri B.M. Cariappa, Secretary, Tuberculosis Association of India, was the guest speaker at the inaugural session of the conference.

The Scientific session of the conference included a Panel-discussion on "Control Programme for Tuberculosis in Maharashtra State". There was also a meeting of officials of District TB Associations in Maharashtra which was presided over by Shri B.M. Cariappa, Secretary, Tuberculosis Association of India.

Some of the important recommendations of the conference are: (a) Branches of State TB Associations should be organised in all districts and these should be representative of all sections of the community, (b) Government officials should fully cooperate with District Associations in all TB control programmes and in the Seal Sale Campaign, (c) Government should supply sufficient drugs to District Associations for their domiciliary treatment programme, (d) Government should give financial help to District Associations for their activities, (e) Corporations and Municipalities should earmark portion of their health budget for TB work, (f) Staff working in TB institutions run by TB Associations be accorded training facilities in the N.T.I., Bangalore, (g) State Transport authorities may give special travel concessions to TB patients as has been done by Railways, (h) Government may depute more delegates for the State Conference of TB Workers and (i) to help the "district programme" Government should have a panel of doctors willing to render voluntary help in cooperation with district TB Clinics and provide them with free drugs for treating patients.

International TB Conference, Munich

The XVIIIth International TB Conference will be held in Munich (Germany) from 5th to 9th October, 1965 under the auspices of the International Union Against Tubercu-

losis. Prof. Erich Schroder will preside over the conference.

Full details of the conference can be obtained from the International Union Against Tuberculosis, 15 Rue Pomereu, Paris (16e) France.

World Congress of Cardiology

The fifth World Congress of Cardiology will be held at New Delhi from 16th to 22nd October, 1966.

This Congress is being held in Asia for the first time.

Meeting of the Eastern Regional Committee

The fourth Regional meeting of the Eastern Regional Committee of the International Union Against Tuberculosis was held in Manila (Philippines) from 30th October to 2nd November, 1964. Delegates from Australia, Hong Kong, India, Japan, Nepal, Malaysia, Singapore, Sikkim, South Korea, Thailand and Philippines attended the meet-

ing. Dr. P.V. Benjamin, Dr. N.L. Bordia and Shri B.M. Cariappa attended the meeting from India.

The meeting decided to shift its headquarters from New Delhi to Bangkok. The new Secretariat at Bangkok will function from 1st January, 1965.

The meeting also elected Dr. W. Cotter Harvey (Australia) as its President, Dr. J. S. Sodhy (Malaysia) as its Vice-President and Drs. Luang Binbakya Bidabhed and Ninart Chinachoti as its Treasurer and Secretary respectively. Dr P.V. Benjamin and Shri B.M. Cariappa were elected members of the Executive Committee of the Regional Committee for 1964-66.

An informal meeting of the Regional Committee will be held, as usual, at the time of the International TB Conference at Munich during October 1965. The meeting also accepted the invitation of the Japan

Anti-TB Association to hold its next regular meeting in Tokyo in 1966.

The Indian Journal of Tuberculosis

ABSTRACTS

Vol. XII

December 1964

Abst. No. 1

A Controlled Comparison of Streptomycin plus Pyrazinamide and Streptomycin plus P.A.S. in the Retreatment of patients excreting Isoniazid Resistant Organisms

S. Velvet et al: Tub., Land., (1964), 45, 144.

A controlled comparison of Streptomycin plus Pyrazinamide (46 patients) and Streptomycin plus P.A.S. (36 patients) in the retreatment of patients with Pulmonary Tuberculosis is reported. All were excreting strains of tubercle bacilli resistant to Isoniazid but sensitive to Streptomycin and P.A.S. at the start of trial.

The disease status at one year was assessed in 44 patients on Pyrazinamide and 24 on P.A.S. and of these 29 (71%) and 12 (50%) respectively had bacteriologically quiescent disease.

Seven patients (2 on Pyrazinamide and 5 on P.A.S.) had the treatment terminated because of toxicity, 1 due to Pyrazinamide polyarthrititis, 2 on account of hypersensitivity to P.A.S. and 4 (1 on Pyrazinamide, 3 on P.A.S.) because of Streptomycin toxicity. Nine patients (2 on Pyrazinamide, 7 on P.A.S.) became uncooperative and stopped treatment and 2 patients (on Pyrazinamide) died, 1 of a non-tuberculous condition.

Streptomycin plus Pyrazinamide was slightly more effective therapeutically than Streptomycin plus P.A.S. and was not more toxic or less acceptable to the patients.

H.B.D.

Essai Clinique Controle de Trois Types de Traitement Oral de la Tuberculose Pulmonaire

Le Hir et al: Bull Wld. Hlth. Org. 1964, 30, 701-732

Trial based on 246 previously untreated

patients, sputum positive with sensitive bacilli is reported. The three oral drug schedules tried were:

1. INH 400 mg daily.
2. INH 300 mg and PAS 15 grams daily.
- 3 Three to five tablets daily of a mixture of INH 100 mg and Ethionamide 166 mg.

Patients were serially allocated to the three schedules. All the patients were adults, 167 males and 79 females. Cavitation was present in 97%. Choice of hospital or ambulatory treatment was left to the patients themselves and 73 patients were hospitalized for periods varying from 2 to 8 months. Ambulatory patients however attended the clinic daily for supervised administration of drugs except on Sundays. Patients were advised to stop working but it is not recorded how many accepted this advice.

Only 136 patients completed 4 months of treatment and of these 24%, 68% and 77% in the three schedules respectively were converted at the end of 4 months' treatment. INH resistance had developed in 93%, 45% and 9% respectively of the cases still unconverted in the three schedules at the end of 4 months' treatment.

The sputum conversion rates after 8 months' treatment (excluding patients with resistant organisms at 4 months) were 27%, 76% and 77% respectively. The rate of development of drug resistance among those who were still sputum positive at the end of 8 months was 68%, 20% and 2% respectively.

In the INH/Ethionamide series there was no difference between the hospital and ambulatory patients. In the INH/PAS group the hospital group fared somewhat better. This advantage was much more marked in the INH alone series.

Drug toxicity was practically non-existent

Ind. J. Tub., Vol. XII, No. 1

in all three series. In the INH/Ethionamide series, only one patient had to be taken off treatment because of toxicity.

Examination of urine for INH was not done regularly. However, 14 out of 60 cases examined gave a negative result. In view of the supervised drug administration this indicates the extent of "False Negatives".

A unique feature of the trial was that ambulatory patients were offered a free meal daily at the time of drug administration. Even this did not prevent premature defecations in a number of cases.

S.P.P.

Bed Rest and Institutional Treatment in Pulmonary Tuberculosis

A. A. Brace and E. A. Spriggs : Amer. Rev. of Resp. Dis. 1964, 90, 183

The results of treatment of patients with active pulmonary tuberculosis, some new cases and some previously treated, have been co-related with the quantum of adjuvant rest and exercise. In 141 the bed rest on an average was for about 7 days and Sanatorium treatment for 0 to 2 months (E Group) and the remaining 174 (R Group) were in the sanatorium for about 6 months with average bed rest for 2 months. The patients in the E group either continued to work or returned to work as quickly as possible, bed rest being advised only as long as fever was present. The results in the two groups were compared at 6 months, 2 years and 4 years after the start of treatment. The patients in R group had a slight advantage with regard to cavity closure at 6 months but this was not maintained at 2 years. On the whole results in E group were slightly more favourable at 6 months because fewer patients in this group required surgical treatment. R group, however, fared somewhat better at 2 years because this group had marginally fewer breakdowns.

The study has its limitations and bias in the allotment of cases could not be eliminated entirely.

Therefore, though it does not prove that rest and institutional treatment have no beneficial effect in pulmonary tuberculosis, one might reasonably have expected the effect to be more appreciable and apparent if of any

importance. Now that the treatment of tuberculosis gives such satisfactory results, the physician has a duty to accomplish it with the least possible dislocation of a patient's life.

S.P.P.

Drug Resistance in patients with Pulmonary Tuberculosis presenting at the Chest Clinics in Hong Kong

Hong Kong Government Tuberculosis Service I British Medical Research Council Investigation: Tubercle, Lond., (1964), 45, 77.

Of the 869 sputum specimens from the newly registered patients, 247 (28.4%) were negative on smear and culture, 47 (5.4%) were positive on smear but negative on culture and 571 (65.7%) grew on culture. The remaining 4 (0.5%) cultures were contaminated.

There were 5 anonymous mycobacteria. Of the 564 patients with sensitivity test results, 302 (54%) had no history of previous chemotherapy, 54 (10%) had a history of probable chemotherapy and 208 (37%) had history of definite previous chemotherapy.

Of the 302 patients with no history of previous chemotherapy, 20% had drug resistance to 1 or more drugs; to 1 drug in 35%, to 2 drugs in 25% and to all 3 drugs in 11%. The total resistance to isoniazid was 62%, to Streptomycin 41% and to P.A.S. 13%. Double drug resistance to Isoniazid and Streptomycin occurred in 23%, to Isoniazid and P.A.S. in 1% and Streptomycin and P.A.S. in 0.5% patients

Isoniazid resistance was found in 14% patients with no previous chemotherapy, in 40% of patients with a history of previous chemotherapy which did not include definite isoniazid and in 67% of patients with a history which included definite isoniazid therapy. Streptomycin resistance occurred in 11% of patients with no history of chemotherapy, in 27% of patients who received some injections and in 43% who had history of definite Streptomycin.

P.A.S. resistance was found in 3% of patients with no history of previous chemotherapy, in 10% with history of chemotherapy which did not include P.A.S. and

20% patients with history of definite P.A.S. therapy.

Patients whose sputum smears were graded as heavy or moderate on direct examination were more likely to be excreting drug resistant organisms than patients whose smears were graded as scanty or negative.

H.B.D.

The Incidence of Viable Tubercle Bacilli in Tuberculous Lesions following Chemotherapy

Joseph P. Kazlowski, James W. Raleigh and William S. Teensken: Tubercle, Lond., (1964), 45, 101.

Two culture techniques were compared using 286 lesions obtained from 108 patients. Of these 286 lesions, 30 were "Target Point", 27 "Closed Negative" and 229 "Open Negative" lesions. In one technique the lesion was homogenized in saline and in the other in 0.5% bovine albumin medium.

The results obtained from the two techniques do not show any significant difference taking the lesions as a whole, or separately according to their pathological status. Viable tubercle bacilli could be isolated from 20% of the "Target Point", 18.8% of the "Closed Negative" and 24% of the "Open Negative" lesions.

H.B.D.

Treatment of Patients with Cultures Resistant to the Primary Anti-tuberculosis Drugs

M. Zieraki: Tub., Lond., (1964), 45, 96.

Of 174 patients with cultures resistant to one or more of the commonly used anti-tuberculosis drugs, 106 were treated with 2 drugs for at least 3 months, most of them having Ethionamide. 33 had 3 drugs for at least 3 months, all receiving Ethionamide, Pyrazinamide and Cycloserine, followed by 2 drugs after the sputum had become negative.

In the group treated with 2 drugs, 87% of 73 had negative cultures after 6 months and 82% of 34 after 9 months.

In the group treated with 3 drugs, the proportions were 91% of 33 and 97% of 32.

Treatment was interrupted because of

drug toxicity in 23% of the whole group of 174.

H.B.D.

Major Surgery for Pulmonary Tuberculosis

R. S. Francis & M. P. Curwen: Tubercle, 1964, 45, Suppl.

The report is of a National Survey of 8232 patients operated between April, 1953 and March, 1954 and followed for 5 years thereafter. The survey was remarkably complete and out of 8232, only 4.4% of the patients were untraced after 5 years. Satisfactory 5 years' results were achieved in 78.3% of the main series of patients. A further 7.6% were free from active disease though failing to achieve highest standard of recovery. Evidence of active disease was present in 4.2% in half of whom bacilli were drug resistant.

Major complications of surgery arose in 19% and 5% of the patients had died within 5 years. A striking difference is shown in the frequency of major complications after unilateral operation for cavitating or non-cavitating disease. The complications affected 11% of patients with non-cavitating disease, and 20% of those who had unilateral cavitation and 41% of those with bilateral cavitation. It may however be pointed out that the treatment of these patients (in 1953-54) would be considered inadequate by present day standards. Even so the relapse rates are not high; 6.8% relapsed within 5 years after all types of resection and 10.3% after all types of collapse operations.

S.P.P.

Comparative Study Between Bacteriologic Findings in Patients with Pulmonary Tuberculosis & Bacteriology of Surgically Resected Lung Tissue

Gladys Eaelina Amodio, Jose Antonio Perez, Nilda Cafure, Camilla Enrique Farias, & Remigio Caminas: Diseases of the Chest, 1964, 46, 37

The results of bacterial positivity and sensitivity prior to surgery were compared with bacteriological findings and guinea, pig inoculations of the resected lesions' in 57

patients of pulmonary tuberculosis admitted for surgery. All were suffering from moderately or far advanced disease; the age range was 13-54 years and nearly one third were women.

Before the operation, tubercle bacilli were isolated from 60% patients whereas 67% of the resected specimens were positive. Before operation, sensitivity study was carried out in 21 patients and the bacilli were sensitive to all the 3 drugs in 7; 7 were resistant to one drug, 5 were resistant to two drugs and 2 were resistant to all three standard drugs. No sensitive bacilli were however isolated from any of the 20 resected specimens where sensitivity studies were carried out. Fifty percent of the latter were resistant to one drug, 33% to 2 drugs and 17% to 3 drugs.

It was also noted that 6% of the cases before operation and 10.7% of the resected specimens were positive by direct smear but negative by culture which suggested a change in the growth character of the bacilli.

As for the guinea pig inoculation, concurrence was noted in 28 cases out of 53 and in the remaining 25, 5 were negative on direct smear and/or culture but positive by inoculation into guinea pig and in the remaining 20, the culture was positive but resected material was negative by guinea pig inoculation. It has been pointed out that in all these 20 cases, the bacilli were resistant to one or more drugs and in 83.34% bacilli were resistant to INH.

S.P.P.

The Present Status of the Serodiagnosis of Tuberculosis

Robert C. Parlett: Bull. Inter. Union Tub. 1964, 34, 9

Current immunological methods applied to the diagnostic and antigenic studies of mycobacteria are of two major types viz Hemagglutination test and Precipitation test. Both these tests possess advantages and disadvantages. The precipitation procedure is less time consuming, more easily controlled, and a direct measure of combination between antigen and mature antibody than is the hemagglutination procedure.

The hemagglutination test, although lacking uniformity in interpretation, has been

considered positive only if agglutination occurs in titers of 1:8 or greater. The biological false positive with known tuberculous sera ranged from 0 to 50% and positive tests with tuberculous sera ranged from 22 to 93%. This test can be useful as a diagnostic tool only after further improvements and adjustments in technique.

The most popular form of a precipitation test is "Gel Double Diffusion" reaction. The diffusion test may be unidirectional as carried out in a test tube or multidirectional when carried out on a plate or slide. The most recent method recommended for performance of the test and criteria of positivity are described.

The results from the initial study showed 84.2% positive reactions amongst 380 cases of far advanced active pulmonary tuberculosis. Amongst 245 cases of moderately advanced active pulmonary tuberculosis, 180 (73.5%) sera were positive. Amongst the minimal, 57.8% were positive. Out of 140 sera from patients from whom a typical acid fast bacilli were isolated, the test was positive in 104 (74.3%). In 78 cases of inactive tuberculosis, 56.4% were positive. In 41 cases of extra pulmonary tuberculosis, 18 (43.9%) were positive. All 9 cases of primary tuberculosis proved to be positive. There appears to be positive co-relation between presence of hyper-sensitivity demonstrated by the Gel Diffusion reaction. The author concludes that from limited evidence available Gel double diffusion test follows classical pattern of antibody responses to bacteriological antigens and is the most promising sero-diagnostic test procedure available at this time.

S.P.P.

The Gel Double Diffusion Precipitation Test in the Diagnosis of Tuberculosis

A. Lind: Bull. Inter. Union Tub. 1964, 34, 37

The objects of Gel Double Diffusion (G.D.D.) tests are to screen a large population with the intent of discovering unknown cases of infection, to obtain supportive evidence in favour of a diagnosis and basic research on immunology of tuberculosis. The G.D.D. test is inherently more sensitive

than simple diffusion and the unidimensional tube method is ordinarily 30% more sensitive than the multidimensional plate method.

Only 2% Mantoux positive without evidence of active disease show a positive reaction. The BCG vaccinated individuals showed only temporary positivity. Amongst 280 patients of sarcoidosis approximately 80% were positive. All patients of leprosy, as a rule, reacted negatively.

There are important clinical aspects having a bearing on the sensitivity of the test. Although it is difficult to predict in any individual case the co-relation between demonstrated antibodies in vitro and the severity of the disease or its duration, circulating antibodies are demonstrated *on the whole* at a higher frequency in relationship to the more advanced stages of disease. Statistically significant higher occurrence of precipitins in the sera of patients whose history of tuberculous disease was longer than 5 years was also found.

S.P.P.

Significance of Carcinoma Cells in the Blood Relative to Surgery of Pulmonary Carcinoma

Yoshihiro Hayata, Motonobu Hayashi, Kenkichi Oho. & Kingo Shinoi: Diseases of the Chest 1964, 46, 51

The study is based on 160 histologically confirmed cases of lung cancer admitted to the Tokyo Medical College from 1958 to 1962. Carcinoma cells in the blood could be demonstrated in about 20% cases but if repeated examinations were possible this percentage could have risen to 30%. Arterial blood samples are more suitable for cancer cell detection. Positivity rate is higher in cases with central than peripheral tumour; and the larger the tumour the higher the positivity rate. Circulating cancer cells are seldom found in coin lesions and in the silent phase of the tumour. Cases presenting with haemoptysis had a higher rate. The rate is also high for cases with lymphatic or haematogenous metastasis. Close relationship between histological malignancy and the positive rate has been demonstrated. The value of the test lies in selecting cases for surgery as close co-relation was observed

between positive rate and operability and survival rates.

S.P.P.

Mediastinoscopy in Bronchogenic Cancer

H Reynders: Diseases of Chest, 1964, 45, 606

Results of 122 consecutive mediastinoscopies performed on patients with cancer of the lung are described. The technique of mediastinoscopy as introduced by Carlens consists of a small low collar incision in the jugular notch. Through the incision a channel is made on the ventral surface of the trachea which reaches up to the tracheal bifurcation. Through this channel the mediastinal structures are palpated with the index finger and tissue biopsies done from suspicious looking structures with a biopsy forceps through an inserted mediastinoscope. This procedure is now practised in several countries and the results are reported to be satisfactory. The value of the procedure lies in deciding about the resectability of cancer lung without thoracotomy. The resection rate in those without evidence of cancer in biopsy specimens rose to 90%.

S.P.P.

Byssinosis Antibody to Cotton Antigens in Normal Subjects and in Cotton Card-Room Workers

Aly Massoud, M.B. & Geoffrey Taylor, M.D.: Lancet, 1964, ii, 607

Byssinosis is supposed to be allergic in origin. The nature of the antigen though unknown as yet is believed to be not fungal but probably chemical in origin. Significant co-relation has been found between the amount of antibody produced and the duration of exposure to cotton dust both in non byssinotics and in byssinotics. The amount of antibody produced also depends on the worker's own inherent ability to produce it. The symptoms of byssinosis are produced either directly by the antigen antibody complex or indirectly by the release of pharmacologically active substance.

In view of the chemical nature of the antigen it may be possible to remove the

antigen from the raw cotton before it is carded. Treatment of the crude cotton with alkalis would remove a large proportion of the antigen as in the manufacture of medical cottonwool (which explains non occurrence of byssinosis in carders employed in this industry) but this procedure is not practicable in the cotton industry as a whole.

S.P.P.

Right Middle Lobe Abscess Due to *E. Histolytica*

I. Opekin and E. Cheslen Dwases of the Chest, 1964, 6, 649

Despite a fairly high incidence of pulmonary complications in cases of hepatic amoeb-

biasis, right middle lobe involvement by direct extension is rare because the liver and the diaphragm come into direct contact with the right lower lobe. Perforation of the diaphragm by an abscess is therefore much more likely to involve the lower lobe.

Two cases of abscess in the middle lobe following amoebic hepatitis are described. Both reported with haemoptysis. Neither coughed out the typical anchovy-sauce pus or bilestained sputum. Haepatomegaly, tenderness, in the right hypochondrium as well as elevation of the right diaphragm were conspicuous by their absence. Pneumo-peritoneum was used as a diagnostic procedure.

S.P.P.

BOOK REVIEW

PULMONARY TUBERCULOSIS: by Walter Pagel, F.A.H. Simmonds, Norman Macdonald & E. Nassau 4th Edition, Oxford University Press, London, 1964. Pp. 520. £5.5. Far reaching changes in the management of pulmonary tuberculosis have taken place during the last decade following the 3rd edition and the new edition naturally reflects to a very large extent these changes and their impact on the epidemiology of tuberculosis and the control measures. Many of the chapters especially on clinical aspects are almost completely re-written to bring the book in line with current thinking.

A short account of drug resistance, chemistry, metabolism and typing of the bacillus and anonymous bacilli have been added to the chapters on pathology and bacteriology. Chapter on Evolution of Tuberculosis which has been a distinctive feature of all previous editions, is retained more or less in its original form. However, for a clinician who does not have the time and patience to go through this exhaustive section, a short chapter incorporating the essentials of morbid anatomy has been included.

The section on 'Management' is almost completely re-written and considerably pruned. Prominence has appropriately been given to chemotherapy and much of the details about the general and sanatorium treatment, rest, diet etc. have been considerably curtailed. Tissue reaction and the pattern of healing attributable to antimicrobial drugs is a welcome addition. A short account of the second line drugs and corticosteroids and their role in the present day treatment of tuberculosis have been included. The chapters on surgical treatment have been completely omitted except for a short account of resection of the lung. This is in keeping with the greatly diminishing role of surgery in the control of disease, as a result of successful chemotherapy and early diagnosis. However, one may not agree with the authors about the virtually complete elimination of an account of minor collapse measures. No doubt, cases suitable for these are extremely few, but that is not to say that the minor collapse measures are obsolete. This book, besides being a standard work

of reference for the specialists, also serves as a text book for the post-graduate students, and therefore a short chapter on minor collapse measures should have been retained. In a book of this type, it is not surprising that some statements creep in which may not be rational or widely acceptable in the present state of knowledge. For example, one may not agree with the authors in recommending two drug chemotherapy in chemo-prophylaxis for fear of resistance. The statement regarding re-examination of contacts every 3 to 6 months if they are below 35 years of age and none at all after the first examination if older in age seems to be contrary to present knowledge and is probably being carried over from the last edition. Again, opinion may vary whether tuberculosis of organs other than the lungs is really a complication of pulmonary tuberculosis. Pregnancy is dealt with under the heading "non-tuberculous complications and associated diseases" although pregnancy is neither a disease nor a complication of tuberculosis.

One of the justifications for this new edition, according to the authors, is that tuberculosis is still very much of a problem especially in the under-developed countries. Problems of tuberculosis in under-developed countries especially domiciliary treatment should therefore have received greater emphasis in this edition. Although the Madras Chemotherapy Centre studies have been quoted here and there, a fuller description of the requisites, achievements, problems and failures of domiciliary treatment would have been desirable. A statement like "patients with a positive sputum by direct smear should preferably be admitted to hospitals *as a routine* (italics ours)" should have been either avoided or qualified.

All in all, the new edition fulfils a clear need and will maintain the reputation enjoyed by this book ever since its first edition came out 25 years ago.

The get up of the book and quality of reproductions of skiagrams and photographs of sections and pathological specimens are excellent as in previous editions.

S.P.P.