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Guest Editorial

INTEGRATED MEDICAL CURRICULUM AND MODULAR TEACHING

There is absolutely no controversy about the type of product which medical education should aim at. The product should be a competent and caring doctor who bases his diagnosis and treatment on sound scientific knowledge. The scientific judgement and the humane approach are woven into the personality of the doctor through complex and intangible mechanisms and expressed in the form of an integrated behavioural output. How to achieve a perfect blend of the different streams of knowledge that go into the making of a doctor has never been settled. The controversy arises from the basic limitation that the educational course has to be delivered over a period of five years, whereas the service to an individual patient has to be sometimes delivered, as an integrated package, within five minutes. The problem of integration is to find the best way in which the curriculum can equip the doctor to bring together during those five minutes something that he might have learnt in the first year and something that he might have learnt only in the fifth year of his course. Naturally, there is no perfect mechanism by which this goal can be guaranteed.

Traditional medical education, of which Sir William Osier is probably the finest recent example, was primarily based on bed-side teaching and learning. However, the emphasis gradually shifted following the Flexner report which laid stress on basic science courses as a pre-requisite to learning clinical medicine. Although, to a certain extent, that was a shift in the right direction, it led to an uncontrolled growth in the share of basic sciences in the undergraduate medical curriculum. Artificial barriers were set up in the curriculum, with certain topics being relegated to specific departments. The needs of the undergraduate medical student were often overlooked in the enthusiasm for making the course more scientific. The medical course became so overcrowded that creative and critical thinking ability of students were adversely affected. Thus, paradoxically, the greater scientific content of the medical course robbed the students of their scientific temper. The recent information explosion has further strained the cognitive capacities of students. Effective management of information has, therefore, become critical.

Subject centered curriculum is the most widespread model for medical education currently practised in our medical colleges. This model assumes that physicians must be scientifically oriented and that they need extensive introduction to biological and physical sciences before undertaking the clinical experience. Unfortunately, the emphasis is on learning the basic disciplines rather than then-application to the practice of medicine. While the rationale of the present structure of the medical curriculum is apparently logical, the consequences are not entirely desirable. For the students, it means getting all the factual information in independent disciplines, without much relevance to patient care. The answer of the medical educationists to these problems has been the integrated curriculum.

The integrated curriculum attempts to fuse independent disciplines into a better unified whole. The

elements of the curriculum are integrated into a conceptually meaningful structure. The students study the biological and biochemical foundations of an organ system, its structural properties, reactions to disease and injury and response to treatment with minimum possible time gap in the delivery of different elements. The impact is further heightened by providing the relevant practical and patient care experience. In practice, the integrated curriculum gets translated into either the modular approach or the problem based learning approach.

The All India Institute of Medical Sciences (AIIMS) has pursued both these to varying extents, as is evident from the Leading Article in this issue dealing with a module designed for teaching tuberculosis. Tuberculosis is undoubtedly one of the most important problems in our country, and is becoming important even globally once again. Pathologists, physicians and public health specialists were asked to first define exactly what a student should know about tuberculosis. Then they came to an agreement on the best sequence in which knowledge on tuberculosis should be presented, and determined which discipline would deliver which portion of the module. Details of this unique exercise and the encouraging response it evoked among the students suggests that modular approach makes learning student-centered and more meaningful. A carefully planned module takes the teaching-learning process as close to the real life situation as one possibly can. However, tuberculosis is only a very small part of the curriculum. Considering the enormous amount of planning and effort needed to execute this module, one can imagine the effort that would be required for converting the entire course, or even a significant portion of the course, into modules. It will require an exceptional commitment on the part of an enlightened, broad minded interactive faculty. Further, it has been generally seen that even when the curriculum is integrated, assessment tends to be discipline-based. The system of assessment provides important clues which determine what and how the students really learn. Therefore, if the modular approach has to achieve real integration of knowledge in the minds of students, assessment should also be module-based and inter-disciplinary in nature.

To make the modular approach more acceptable, there is also need to define a 'core' curriculum which all graduates must know. Students can learn at their own pace if these integrated teaching modules can be converted into learning resource materials. Another essential element is to inculcate in the students the habits of self learning and taking responsibility. They can then intelligently manage and apply the ever increasing information load to health care delivery, meeting the expectations as well as needs of the society. The exercise on the modular approach reported in this issue is only the beginning of a long process. If it could be done for a small portion of the curriculum, it gives us hope and assurance that it could be done on a much larger scale.

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CURRICULUM DEVELOPMENT FOR INTEGRATED TEACHING OF INFECTIOUS DISEASES INCLUDING TUBERCULOSIS

Introduction

It seems reasonable to believe that an educational programme has better chance of being effective if its purpose has been clearly expressed. Furthermore, it is not possible to measure the results obtained from an educational system if its objectives have not been clearly defined. The act of writing it all down makes it open to inspection and improvement.

The prevalence of tuberculosis in India is said to be about 10 million of which 2.5 million are infectious. Nearly half a million patients die as a consequence of pulmonary tuberculosis per year. As there are 525,600 minutes in a year, we can also say that every minute of the year one person dies as a consequence of this infection. *Mycobacterium tuberculosis* can and does affect all organs of the body. Tuberculosis was, therefore, chosen as the first unit for developing an integrated objective-oriented programme for its teaching.

Unit: Tuberculosis

Keeping in mind the task analysis of an MBBS doctor posted at a Primary Health Centre (PHC), the group entrusted with developing the integrated module decided that a medical student must know about the:

1. Magnitude of the problem,
2. Microbiologic characteristics of the pathogen,
3. Epidemiology of the disease,
4. Pathophysiology,
5. Clinical profile,
6. Laboratory investigations that could help in diagnosis,
7. Management of cases,
8. Prevention of spread of infection,
9. Education of patients, relatives as well as community,
10. National control programme, and
11. Continued learning about the progress made in the control of the disease.

Twenty five specific objectives were written up to meet these requirements.

These objectives were then classified according to the behavioural change they were intended to achieve (Cognitive, Psychomotor, Attitudinal) as well as the desired level of the knowledge content (A = Must know, B = Good to know).

The 25 objectives could then be classified into:

	Must know (A)	Good to know (B)
Lower Cognitive (LC)	10	3
Higher Cognitive (HC)	7	2
Psychomotor (PSY)	3	-

At the end of the teaching unit, the MBBS student should, then, be able to:

1. State the importance of tuberculosis as a major health problem of the country and give the magnitude thereof. (LC; B)
2. Outline the importance of the host, environment and the agent factors in the epidemiology of tuberculosis. (LC; A)
3. State the common characteristics of mycobacteria which differentiate them from all other groups of bacteria. (LC; A)
4. Enumerate all the mycobacteria capable of causing disease in man and place them into respective recognized groups. (LC; B)
5. Indicate major differences between these mycobacteria. (LC; B)
6. Perform Ziehl Neelsen staining (ZNS) on a sputum specimen and identify the AFB on bright field microscopy. (Psy; A)
7. Demonstrate familiarity with relevant laboratory procedures other than ZNS for the isolation, identification and antibiotic susceptibility of *M. tuberculosis*. (LC; A)
8. Describe the mode of infection, pathogenesis, virulence, role of induced hypersensiti-

- vity, immunity and genesis of granulomatous reaction in tuberculosis. (LC; A)
9. List common symptoms; elicit important signs and make clinical diagnosis of pulmonary and extrapulmonary tuberculosis (disseminated, tuberculous meningitis, abdominal, genitourinary, bone and joints, lymphadenopathy) in children and adults. (LC;A)
 10. Enumerate differences in the clinical presentation of and recognize the development and morphology (gross and microscopic) of primary, progressive primary, miliary, disseminated, fibrocalcific tuberculosis in lung and various other organs in immunocompetent and immunocompromised hosts. (HC;A)
 11. Plan investigations (including microbiological, pathological, bio-chemical, radiological examinations and Mantoux test) in a suspected patient of tuberculosis. (HC; A)
 12. Choose the appropriate specimens to be collected at various stages of the illness and from different sites, for making a laboratory diagnosis. (LC; A)
 13. Carry out a Mantoux test and correctly interpret the results of the test, in a child. (Psy;A)
 14. Interpret the following specific investigations in the context of tuberculous disease (HC;A)
 - * Staining for AFB,
 - * Mantoux test,
 - * Cerebro spinal fluid (CSF): Cells, bio-chemistry, culture, serology, and
 - * Pleural fluid : Gross, microscopic, bio-chemical, cytology and ZN staining.
 15. Describe the radiological features of pulmonary and extrapulmonary disease and interpret a chest X-ray for presence of a primary, progressive primary, miliary and fibrocalcific lesion. (LC; A)
 16. Describe antituberculosis therapy in the following forms of tuberculosis in children and adults, giving doses, regimens and duration of therapy: (LC; A)
 - * Pulmonary disease
 - * Tuberculin positive school child
 - * Tuberculous meningitis
 - * Adenopathy
 - * Miliary disease
 - * Disseminated forms
 - * Bone and joint tuberculosis
 - * Genitourinary tuberculosis.
 17. Advise adjunctive and supportive management. (HC; A)
 18. Recognise those cases of tuberculosis which, on the basis of complication/complexity, require the opinion of a specialist or referral to a higher level of care. (HC;A)
 19. Plan further investigations if there is no satisfactory improvement after six months of treatment. (HC; A)
 20. Advise the patient about appropriate steps if the laboratory report indicates isolation of mycobacteria other than tubercle bacilli. (MOTT). (HC; B)
 21. Analyse the impact of the disease on the individual, the family and social and occupational life and advise measures to ameliorate the effects. (HC; A)
 22. Advise regarding BCG vaccination to children; administer the vaccine to a child and interpret the “take response” of the vaccine. (Psy;A)
 23. Describe the management of a pregnant patient, lactating case as well as the neonate born to such a mother. (HC; B)
 24. Describe the salient features of the National Tuberculosis Program (NTP). (LC; A)
 25. Describe the role of a medical officer of a PHC in the implementation of NTP. (LC;A)
 - * “If you give each learner a copy of the learning objectives, you may not have to do much else. – Mager”

Teaching and Learning Activities

An integrated curriculum involves coordination of different teaching and learning activities to ensure a harmonious functioning of the educational process for more effective

Table 1 *Integrated curriculum on teaching of tuberculosis: teaching-learning activities*

Content	Method	Hours	Department	Objectives
Mycobacteria	L	1	Micro	3,4,5
ZN staining	P	2	Micro	6
Pathogenesis and clinical presentation	S	2	Path,M,P,S	8,9,10
Gross and microscopic pathology	P	2	Path	8
Radiology	SGL	1	Radiol	15
Laboratory diagnosis	P	2	Path, Micro, Radiol	11, 12, 15
Management	S	2	Pharm,M,P,S CM	16,17,18,20, 21,23
Case studies and management exercises-I	SGL	2	M,P,Path (4 cases)	-do-
Case studies and management exercises-II	SGL	2	S, G, Orth, Path (4 cases)	-do-
Case demonstration (TB hospital)	SGL	2	CM,M,P	-do-
BCG & Mantoux test	SGL	2	CM,P	13,22
Public health National Control, Programme	L	1	CM	1,2,24,25
Visit to DTC	SGL	2	CM	-do-
CPSCR	SGL	4	CM	-do-

Learning opportunities:

L = Lecture, P = Practical, S = Seminar, SGL = Small Group Learning, CPSCR = Clinico, Psychologico, Social Case Review

Total: L = 2 hours, S = 4 hours, SGL = 13 hours, P = 6 hours)

Departments:

S = Surgery, M = Medicine, P = Pediatrics, Micro = Microbiology, Path = Pathology, Pharma = Pharmacology, Radiol = Radiology, Ortho = Orthopedics, CM = Community Medicine, G = Obst. & Gynecology. DTC = District tuberculosis centre.

training. It entails exposure of the student to interconnected concepts through a series of learning opportunities, scheduled one after the other. The educational content is, thus, delivered in a rational and stepwise manner.

The curriculum proposed above requires about 25 hours of formal teaching/learning compared to over 30 hours at present. The emphasis is on acquiring skills and on interactive learning. The didactic sessions (lectures/seminars) have been reduced from 15 to 6 hours. On the other hand, inter-departmental sessions extend to 14 hours, instead of 6 hours at present. The detailed schedule of teaching - learning exercises is shown in Table 1.

The formal teaching/learning exercises are

supplemented by self-learning modules, such as tape-slide programme, video and computer aided learning. Also, case discussions during clinical postings complement and reinforce the learning of students, initiated by the above module. The opportunity to actually manage a case during internship is the final step in learning.

The above teaching/learning schedule is flexible and subject to modifications based on discussions with the participating departments and on the feedback from students from time to time.

Evaluation

While preparing this module, the empowered

group thought deeply about the best possible "tests" (evaluation tools) to evaluate the course content of the Module on Tuberculosis which it had prepared, keeping in mind the laid down objectives.

<i>Objective</i>	<i>Suggested "test"</i>
1.	MCQ
2.	SAQ
3.	MCQ
4.	MCQ & SAQ
5.	MCQ
6.	Practical
7.	MCQ
8.	SAQ & MCQ
9.	Bedside case presentation
10.	Case study, practical, Viva voce and specimen identification
11.	MCQ
12.	MCQ
13.	Practical
14.	Viva voce
15.	Viva voce and MCQ
16.	SAQ & MCQ
17.	SAQ
18.	SAQ
19.	SAQ
20.	MCQ
21.	CPSCR
22.	Practical
23.	SAQ
24.	Essay
25.	Essay

(MCQ = Multiple choice questions; SAQ = Short answer questions; CPSCR - Clinico, Psychologico, Social Case Review)

The total "unit" could finally be assessed by long/short cases in which many of the above mentioned facets are examined and the students' ability to synthesise information assessed.

Experience

Having written up this programme, we made a number of presentations to interested

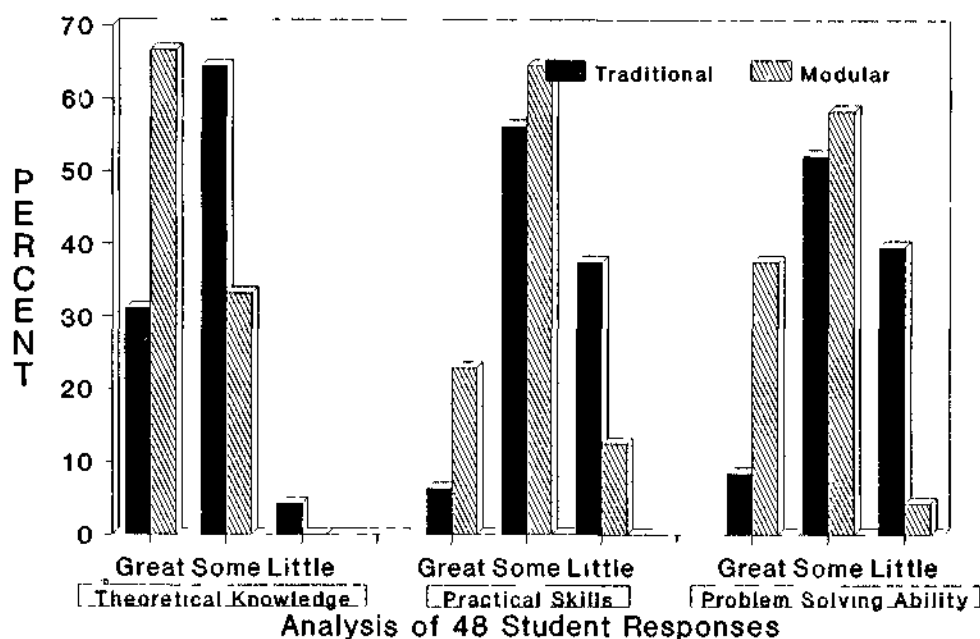
educationists. While some of the merits of this modular approach were self-evident, many reviewers expressed doubts regarding the feasibility of the programme. To answer them, we decided to administer the whole module to MBBS students of medical colleges of Delhi. A group of nineteen teachers was identified and each teacher was provided with the whole document as well as the specific objectives that each was to cover during his presentation.

For our modular teaching, Unit : Tuberculosis, we had anticipated 50 volunteer students; in fact, 58 had to be accommodated. The students were from All India Institute of Medical Sciences (AIIMS) (27); Maulana Azad Medical College (MAMC) (15); University College of Medical Sciences (UCMS) (10) and 6 foreign students doing their electives at AIIMS (4 from Oman and one each from USA and Canada).

At the start of the course, the students were asked regarding the traditional teaching which they felt helped to some extent in acquiring theoretical knowledge, practical skills, problem solving ability and holistic view of the subject.

The students were then provided the objectives of the course as well as the specific objectives to be achieved during each session (the same objectives had been provided to the teachers during the planning stage) and explained how this module was developed. The first day was devoted to providing basic background information regarding mycobacteria and the pathological changes that they can bring about. The students were given response sheets and encouraged to evaluate each session. They were also encouraged to write in any comment that they felt like making. Though the teaching was in the form of didactic lectures, attempts were made to make them interactive. The students responded enthusiastically, with 30% finding the first day's presentation "excellent". On the other hand, 2.7% of the students rated some parts of the presentations as unsatisfactory.

During the second day, there was a seminar on clinical presentation, small group learning of radiological features and then the students were first demonstrated and then encouraged to perform Mantoux test and BCG vaccination. Finally, each student had to make smears from the sputum specimen provided and to stain and



Graph. Comparison between traditional and modular teaching

examine them for the presence of acid fast bacilli : 95.1% of the students found the presentations to their satisfaction, but the level of dissatisfaction rose to 4.9% level.

On day three, the session began with a lecture on public health with additional comments and explanations provided by Prof. L.M. Nath, Dean, AIIMS. There was a fair amount of interaction and the students responded enthusiastically. This was followed by three seminars, one after the other, on laboratory diagnosis, management I (medical aspects) and management II (surgical aspects). A total of 16 faculty members made their presentations which the students had to sit through. This led to some amount of restlessness, with the students writing in that they were super-saturated with the mass of information provided to them. However, only 2.3% found the presentations unsatisfactory. The message was very clear: the organisers must provide for free time between sessions and allow the students time to stretch their legs. But the students were willing to forego these due to the rich fare dished out to them.

In defence of the organisers, it may be said that their idea was to fill the students with

knowledge so that subsequent interactions would be more fruitful. It was appreciated that the pace of teaching on the third day should have been slower.

The fourth day was a visit to the TB hospital. The main purpose of the visit was to provide an opportunity to learn signs and symptoms of the disease clearly manifested in the patients in advanced stages. A few discussions on management strategies would also be more fruitful. This was followed by reading of the Mantoux test. The students were then divided into four groups and each group worked up four case studies, two on the fourth day and two more on the final day. The final day's programme included a CPSCR presented by one of the students. The percentage of satisfied students during these two days remained high (96.4%).

A large number of students exercised their right to write in comments. The main thrust of the comments was that the pace of the module should be slower and that it should be offered to senior students, as add-ons, to integrate their information and to provide them a holistic view of the subject.

Finally, a post-workshop questionnaire was

administered, with the same questions as were in the pre-workshop questionnaire, but the students were asked to comment on the modular teaching that they had just undergone (Graph).

A marked change was observed in a majority of the students indicating that, in their view, the modular teaching had, *to a large extent*, helped in obtaining theoretical knowledge, gaining practical skills and problem solving ability, providing self learning and a holistic view of the subject. They indicated that they would like to attend another module and hoped that the new module would incorporate changes suggested by them

Acknowledgement

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OCCUPATIONAL PNEUMOCONIOSIS AND TUBERCULOSIS***S.K. Kashyap****

Mr. President, Delegates, Ladies and Gentlemen,

I consider it a great honour and recognition of the National Institute of Occupational Health (I.C.M.R.) to have been invited to deliver the prestigious LUPIN-TAI ORATION, in spite of being an outsider to this discipline, during the 48th National Conference on Tuberculosis and Chest Diseases under the auspices of The Tuberculosis Association of India & TB Association of Madhya Pradesh in this beautiful historic city of Bhopal,

I take this opportunity to present my oration before this august gathering on the subject of "Occupational Pneumoconiosis and Tuberculosis".

Respiratory system is the target organ for the action of many environmental pollutants including dust and many inhaled microbes because it serves as the portal of entry for most of the pollutants in the work environment. There is a large number of chemicals and dusts which produce various types of reactions as a result of their entry into the respiratory system. These reactions vary from collection of a few macrophages at the one end to extreme to severe degree of pulmonary fibrosis at the other end.

Fibrosis of lung (Pneumoconiosis) resulting from exposure to free silica in the dust is probably the oldest known and most commonly studied of all occupational diseases of lung.

Silicosis is caused by inhalation of fine respirable particles of free silica. The distribution of silicon in nature is similar to the distribution of carbon among organic matter. Silicon constitutes about 28% of the lithosphere. Earth's crust is composed almost entirely of silica and silicates. They constitute the bulk of most kinds of rocks, sands and clays. Silicon occurs as silicon dioxide (SiO₂) which is known as "free silica". It is the free silica form which is most fibrogenic. About 12% of the earth's crust consist of free silica, mostly quartz. In the earth's crust, free silica is

only next to feldspar in abundance. Since the earth's crust contains such a large amount of free silica, mining and tunnelling required for sandstone industry, quarrying, granite industry, slate quarrying and dressing, grinding of metals, iron and steel foundries, silica milling, flint crushing and manufacture of abrasive soaps are occupations which may lead to silicosis. Some of the lesser known occupations, important from the silicosis point of view and peculiar to India, are the small scale industries like slate-pencil cutting, quartz crushing, agate grinding, etc.

It should be noted that only those airborne particles which are capable of reaching the alveolar region of respiratory system can cause silicosis. The size of these particles is usually less than 7 microns. They are commonly known as "respirable" particles. The silica particles induce fibrosis in the lungs, i.e. the normal lung tissue is replaced by non-functioning fibrous tissue. The fibrosis in non-complicated or simple silicosis is in the form of fine nodules varying in size from 1.5-3.0 mm, developing later into pulmonary massive fibrosis.

For the following reasons, occupational health problems arising from exposure to free silica dust occupy the most important place in India in the list of occupational diseases:

1. Minerals containing free silica are ubiquitous in nature and, therefore, they may be encountered in a variety of industrial operations.
2. A serious risk may exist, if its presence is not recognised and if the fact that even a short exposure to intense concentrations of dust containing free silica can lead to the development of rapidly progressing silicosis is not understood.
3. The unique place of silicosis as an occupational disease in developing nations is because unlike other forms of pneumoconiosis, it predisposes to the

* Lupin-TAI Oration delivered at the 48th National Conference on Tuberculosis and Chest Diseases, Bhopal, 9-12 December, 1993.

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occurrence of tuberculosis, which is still an important cause of mortality and morbidity in India

There are more than 30 studies on the prevalence of silicosis in our mines and surface industries. The most important of them were reviewed in the ICMR Technical Report Series No. 4. These studies provided important firsthand information regarding the severity of the problem of silicosis in the mines and industries. However, in most of these studies a standardised technique was not used.

During the last decade, the National Institute of Occupational Health (NIOH) has conducted studies on silicosis/pneumoconiosis in a number of industries, like slate pencil making in Madhya Pradesh, quartz crashing and agate industries in Gujarat, stone cutting industry in Uttar Pradesh and coal miners' pneumoconiosis in surface and underground mines in Bihar and Bengal.

A. Silicosis in Unorganised Sector in India

1. Silicosis in Slate Pencil Industry

The slate pencil making industry is localised in the Mandsaur district of Madhya Pradesh. There are about 100 slate pencil cutting units. The number of workers employed by each unit varies from 4 to 20. Cutting of slate pencils is essentially a dry process during which dust is generated in a cloud that pervades the factory atmosphere.

The environmental and medical surveys carried out by the NIOH (Annual Report, 1981) in this industry revealed that the total and respirable dust levels in the breathing zone of the cutter were 46.5 mg/m^3 and 10.4 mg/m^3 respectively, with 56.5% of free silica. The medical survey of 593 workers revealed that 324 (54.6%) of the workers were suffering from silicosis, of whom 105 (17.7%) had progressive massive fibrosis (PMF). The average duration of exposure required for development of silicosis was 7 years. Repeat examination of these workers after an interval of 16 months showed that 23 (21.9%) of the workers, who had been diagnosed as suffering from PMF had died during the intervening period. This reflects the rapidly progressive nature of the disease.

To control the dust exposure, a local exhaust system was prepared by Bharat Heavy Electricals

Limited, Bhopal, which was installed in 10 cutting machines. The industrial hygiene survey conducted after installation of the local exhaust system showed that the total and respirable dust levels were 2.25 and 0.32 mg/m^3 of air respectively.

2. Silicosis in Quartz Grinding Industry

Quartz grinding is one of the few industries where there is an exposure of workers to almost 100% free silica dust. Even short and intense exposure to higher concentrations of free silica dust, particularly in its finer form, may result in rapidly advancing, fatal silicosis.

Quartz grinding industry is widespread in the country. In Gujarat State, it is relatively a new industry employing a small number of workers. Many of the units at the time of our survey were not covered under the purview of the Factories Act. Quartz grinding is essentially a dry process. A large quantity of dust is generated during the processes of crushing and disintegration of stone and sieving, weighing and bagging of the powder. Most of the work carried out by the workers in this industry involves heavy physical labour resulting in deep and rapid breathing.

Environmental and medical surveys carried out in eight quartz grinding units (NIOH Annual Report, 1985-86) revealed that the mean values of total dust concentrations were between 81 and 660 times higher than the threshold limit suggested by ACGIH. The mean values of respirable dust concentrations were between 12 and 243 times higher than the threshold limit values (TLV). Medical survey of 75 workers from these units showed that 9 (12%) were suffering from silicosis. In a few of these workers having silicosis, the exposure to dust history was even less than 1 year.

After the implementation of dust control measures, i.e. enclosure of work process, a repeat survey of the above units was carried out. The industrial hygiene study showed that the reduction in the total dust levels was from 77% to 92%, and in respirable dust from 67% to 94%.

3. Silicosis in Agate Industry

Decorative carving of agate stone is a traditional household industry localized in the

Khambhat area of Gujarat. The job of breaking, grinding, drilling and polishing of agate stone is carried out in small units employing 2 to 4 workers. There are about 10,000 workers employed in this industry. During the process of grinding of agate stones, dust is generated which pervades the factory environment. Inhalation of this dust containing high proportion of free silica leads to the development of silicosis.

Our environmental survey showed that mean total and respirable dust concentrations at the nose level of the grinders were 14.75 and 2.35 mg/m³, respectively, with 60% free silica. The threshold limit values suggested by ACGIH for the total and respirable dusts containing 60% free silica are 0.48 and 0.16 mg/m³ of air, respectively. Medical examination of 470 agate workers showed that the hazard of silicosis was limited to the grinders only. Of 353 (241 male and 112 female) grinders examined, 135 (38.24%) had radiological evidence of silicosis. More than 60% of the sufferers were below 30 years old and their duration of work as grinder was less than 10 years. A local exhaust system with an air cleaning device developed at NIOH was installed at two grinding units. It was found that the dust levels after the installation of the local exhaust system were close to the ambient dust levels. The reduction in the total and respirable dust levels was about 94%.

4. Silicosis in Stone Cutters

The stone mined in the Bundelkhand area is known as 'slab stone'. It is used for road and building construction. The largest number of mines are located in Lalitpur district of Uttar Pradesh. An environmental and medical survey of this industry (NIOH Annual Report, 1986-87) revealed that the total and respirable dust concentrations during the process of stone cutting were 22.4 mg/m³ and 1.6 mg/m³, respectively. Examination of 125 stone cutters showed that the prevalence of silicosis and tuberculosis were 22% and 48% respectively. The average duration of dust exposure for the development of silicosis was 12 to 15 years. The total and respirable dust levels after installation of the control device, which operates on the principle of enclosure, were 3.4 mg/m³ and 0.8 mg/m³, respectively. This dust control device also

gives protection against eye injuries.

B. Coal Miner's Pneumoconiosis In India

Coal mining is playing an increasingly important role in our national development, particularly in the fields of power generation and metallurgy to overcome the shortage and high cost of crude oil

The "Study of Pneumoconiosis in Coal Miners in India" was initiated as an international collaborative study between the ICMR and International Development Research Centre (IDRC). The broad objectives of the study were to assess the environmental conditions in selected mines in respect of respirable dust concentrations, and to assess the effect of environmental conditions on miners. The study was undertaken in coal miners in West Bengal and Bihar. The study population consisted of 5777 underground coal miners with 1236 surface coal miners as referents. The coal dust levels were higher than the prescribed TLV in all the underground mines studied. The free-silica content of coal dusts were below TLV. The prevalence of simple pneumoconiosis and PMF were 6.91% and 0.05% respectively. Majority of the cases of pneumoconiosis were Category 1. This low prevalence of simple pneumoconiosis and PMF, as compared with other reports, is attributed mainly to the unexplained geographical differences. A significantly higher ($p < 0.01$) prevalence of non-pneumoconiotic respiratory morbidity consisting of persistent respiratory symptoms, along with mainly obstructive type of pulmonary function abnormality was observed in underground coal miners compared with surface coal miners. The difference in the prevalence of respiratory morbidity persisted even after taking into account factors such as age, dust exposure, duration of work and smoking habit.

Prevention of Occupational Respiratory Diseases: Some Practical Examples

From the foregoing discussion, it is evident that for the control of dust in industry, different measures may be needed for different work processes. After the epidemiological surveys which helped in defining the magnitude of the

respiratory morbidity and mortality, the NIOH scientists have developed certain dust control devices on the principles suggested earlier. These dust control devices are as follows :

Slate-pencil Industry

Local exhaust system with filter bags for cleaning the exhaust air. This device is essential for the prevention of air pollution problem.

Agate Industry

Local exhaust system with a water-pump which mixes the dust laden air with water. The dust particles become heavy after mixing with water and are removed.

Stone Quarrying Industry

The non-availability of electric power in this industry excludes the possibility of providing local exhaust systems for dust control. The Institute scientists have developed a simple dust hood made of an iron frame covered by a plastic shield at its roof and cloth on its side walls. This device has been tried in the field for its acceptability and the workers have found it suitable. Another advantage of this device is that it prevents eye injuries also. Efforts are being made to improve the efficacy of the device.

Stone Crushing Industry

The source of dust generation in this industry is diffused and local exhaust systems cannot be used for dust control. Therefore, the measures applied were:

- Enclosure of grinding process
- Humidification of work environment
- Improvement in general ventilation

Tuberculosis in Dusty Industries

Tuberculosis, a communicable disease highly prevalent in India, does particularly afflict the working populations in dusty industries. The occurrence of tuberculosis has been reported from the nineteen 40's onwards in workers exposed to silica and coal dust. In earlier times, it had been labelled as dust phthisis or rock tuberculosis. The prevalence of tuberculosis in the pottery, ceramics, brick making, metal grinding industries and among coal miners has been reported as from 3.6% to 19.0%. Our own observations in a number of industries have shown that, at times, tuberculosis is much more common in workers exposed to silica than the specific disease 'silicosis', particularly in the small-scale industries, i.e. slate pencil, quartz crushing, agate and stone cutters, whereas we have observed the prevalence of tuberculosis in the range of 4.8% in coal miners to 48.0% in stone cutters. Most of the silicotics are prone to develop tuberculosis. Because of the peculiar nature of their work environment, the spread of tuberculosis infection is facilitated. Some of the earlier reports mentioned that 40-70% of silicotics die due to tuberculosis. It is a very frequent observation that in early stages the workers engaged in silica related industries are more often than not treated for tuberculosis on developing respiratory symptoms, probably due to lack of understanding and awareness of the conditions like silicosis and pneumoconiosis.

Acknowledgement

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INTERSTITIAL LUNG DISEASE*

D.D. Kulpati¹

I am extremely grateful to the Tuberculosis Association of India, and Ranbaxy Laboratories for giving me an opportunity to give this oration.

I would like to dedicate this oration to my patients who have provided me the distillate of the knowledge concerning the clinical approach to interstitial lung disease which has been developing in my mind and practice. The use of this fundamental approach, avoiding the current, almost sensational, newer data cascading from research, will provide the framework for dealing with this disease. It is not a dissertation on pathology or physiology but a combination of relevant fragments from these and other disciplines, such as physical diagnosis, roentgenology and laboratory tests interwoven into an approach for the management of this problem. A clinician does not need to know the sophisticated nuances of physiology and pathology to become successful but must know how to piece together the fragments of other disciplines to create a meaningful, coherent pattern for his purpose. In this sense, the clinician is truly the new person of medicine.

Tuberculosis and chronic obstructive airways disease will remain the major public health respiratory problems. Interstitial lung disease (ILD) is also important to the wary clinicians in so far as early diagnosis and proper management are of paramount importance in order to prevent late irreversible fibrosis. Such patients are usually treated as pulmonary tuberculosis or even as bronchial asthma-bronchitis and the early stages of the disease are usually missed when therapeutic intervention may have arrested or reversed the disease.

Introduction

Diffuse interstitial pulmonary disease is a heterogeneous group of disorders of diverse

etiology, which primarily, but not exclusively, involve the pulmonary interstitium or peripheral gas exchanging parts of the lungs diffusely. They are grouped together because of the common clinical, roentgenographic, physiologic and pathologic features. Most patients have a history of insidious exertional dyspnoea and a chest roentgenogram that shows a diffuse infiltrative pattern. The classic physiologic features of these diseases are those of restrictive ventilatory defect with reduced lung volume and compliance but with airflow generally maintained. The pattern of interstitial disease mainly involves the supporting tissues of the lung. In most, but not all, there is an inflammatory cellular infiltration and fibrosis of alveolar septa while, in some, inflammatory cells also occur within alveolar air spaces. These disorders may also be accompanied by airways disease, pulmonary vascular disease and even pleural disease. These diseases have been variously named as diffuse interstitial lung disease, diffuse interstitial pulmonary fibrosis, diffuse fibrosing alveolitis, cryptogenic fibrosing alveolitis (CFA) and Hamman-Rich syndrome, etc.

There is a large number of conditions of known and unknown causes which may result in diffuse interstitial pulmonary fibrosis. The causes can be categorized into the following broad groups.

Etiology

Unknown causes

Classical interstitial pneumonia-fibrosis [cryptogenic fibrosing alveolitis].

Known Causes

1. Inflammatory:

Infective: Bacterial [tuberculosis], viral [in-

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fluenza], fungal [histoplasmosis], parasitic [filariasis, ascariasis].

Non-infective : Chronic inhalation pneumonia [oils, fumes, gases], haemosiderosis.

Cytotoxic [Bleomycin, Cydophosphamide, Methotrexate] or hypersensitivity reactions to drugs [Nitrofurantoin and Sulphasalazine].

Immunological or connective tissue disorders : Systemic sclerosis, rheumatoid arthritis, dermatomyositis, polymyositis, chronic hepatitis, renal tubular acidosis, Sjogren's syndrome, coeliac disease, etc.

Chronic left ventricular failure [increased pulmonary venous pressure], chronic renal failure [increased pulmonary capillary permeability], alveolar proteinosis.

II. *Widespread granulomas:*

Extrinsic allergic alveolitis (EAA), pulmonary eosinophilia, sarcoidosis, berylliosis.

III. *Pneumoconioses:*

Inhalation of fibrogenic [silica, asbestos, talc] and nonfibrogenic dusts [tin, iron, coal].

IV. *Neoplasms:*

Lymphangitic carcinomatosis, alveolar cell carcinoma, multiple secondaries, lymphoma, pulmonary adenomatosis, neurofibromatosis, etc.

V. *Honeycomb lung:*

Associated with histiocytosis and tuberculous sclerosis.

Historical

Hamman and Rich reported five patients with dyspnoea, diffuse infiltration seen on chest roentgenogram, cor-pulmonale and death occurring within 6 months. However, it is now evident that this fatal form of the disease is uncommon. Idiopathic interstitial pneumonia, diffuse fibrosing alveolitis, cryptogenic fibrosing alveolitis, diffuse interstitial fibrosis is more often a chronic disease. A semantic variability, if not confusion, currently surrounds the whole subject

of diffuse interstitial inflammation and fibrosis. Scadding, and later Gough & Hinson, termed it "fibrosing alveolitis". Liebow and Carrington have encompassed a large number of interstitial diseases under the heading of "diffuse interstitial pneumonia".

Etiology & Pathogenesis

The etiology of CFA is unknown, hence it is referred to as cryptogenic.

The mean life expectancy of a patient after presentation with the disease is only four to five years. The review of the current data has shown that the number of deaths reported due to CFA has doubled over the previous decade and that the disease is an important contributor to the overall mortality from respiratory diseases. Some of the increase in mortality could probably be accounted for by more detailed investigation and greater diagnostic precision in the past decade resulting in more patients being recognised as having the disease. Death from the disease is more common in men at all ages (about 2.2 : 1 overall). The disease has been found to be predominant in men. There are no genetic factors, although familial fibrosing alveolitis may be transmitted as an autosomal dominant trait: B₅₁ & B₆₂ were significantly more frequent and B⁵¹, was associated with acute progression of the disease. Cigarette smoking is a potential factor in the higher mortality among men. Occupational exposure to unrecognized fibrogenic agents or occult or low exposure to known agents is also a possibility. The deposition of Ni in hilar mediastinal lymph nodes and of Si in lung tissue has been demonstrated. However, the disease is not etiologically homogeneous and is a stereotype response of lung to various undetermined factors. An immunological disturbance with deposits of immune complexes appears to be responsible for the initiation of fibrosis of alveolar walls in some patients. The arachidonic acid cascade metabolites may be playing an important role. The presence of non-organ specific antibodies, high titer of serum rheumatoid factor, circulating antinuclear antibody, raised gamma globulins, fibronectin, and antibody-complement complexes on the wall of the alveolar capillaries and over production of pulmonary surfactant (PAM) suggest auto-

immune reaction in other patients. Auto-allergic response, induced by virus (EB) or other agents is suggested by similar histopathological features following influenza pneumonia and in extrinsic allergic alveolitis. Types I, III and V collagen specific antibodies were demonstrated in 33%, 22% and 13% respectively. Auto-immunity to collagens, particularly that directed to type I collagen may be important.

In our country, the awareness about interstitial lung disease is increasing as is evident from the frequent reports in our literature. In Czechoslovakia, the prevalence has been estimated as approximately 3 patients per 100,000 inhabitants, as also seen in a Japanese study. In USA, approximately 11,000 hospitalizations, every year, are due to these diseases.

The algorithmic synthesis for CFA will consist of history, physical examination, chest radiography & CT-studies, pulmonary function profile, laboratory studies, BAL and transbronchial biopsy and other histopathological studies.

History-taking

A careful, incisive history is the most decisive element in the process of evaluation of these disorders. The presenting symptom is nearly always exertional dyspnoea. Most of the patients are ambulatory, usually with histories of chronic and or subacute disease. Exertional dyspnoea, not uncommonly, is preceded by a flu like illness. Dry distressing cough accompanies dyspnoea in more than 70% of cases but in 20%, cough and fever may be the sole presenting complaints. Constitutional symptoms such as fever, weight loss, weakness may accompany other clinical features but are often completely overshadowed by the relentless dyspnoea and cough. These constitutional symptoms are probably more common in India.

Physical Examination

The physical examination may be normal in the early stages of certain disorders e.g. sarcoidosis. However, the typical breathing pattern is shorter duration, both on inspiration and expiration, frequently associated with

tachypnoea, either at rest or with exercise. By contrast, those having idiopathic interstitial-pneumonitis fibrosis are generally dyspnoeic; manifest restrictive breathing patterns and, on auscultation, manifest classic "velcro" rales (dry, superficial end-inspiratory crackles described as being close to the ears) at the lung bases. The digital clubbing is observed in more than 50% of cryptogenic fibrosing alveolitis cases. Rales and clubbing are notably absent in sarcoidosis, while these are regularly seen in patients with cystic fibrosis. Central cyanosis is a variable finding and depends upon the severity of the disease. Midway to late, in the course of the disease, jugular venous pressure may be raised and pulmonary second sound may be loud, indicating pulmonary arterial hypertension. Diastolic gallops may be associated with either left or right ventricular failure. Cardiac arrhythmias and wet rales may indicate left ventricular dysfunction with consequent passive congestion of the lung. A meticulous search should be made for the presence of extra-pulmonary manifestations of the disease process.

Chest Radiography

The location of infiltrates depends upon the pathogenesis of disease. The haematogenous spread leads to diffuse densities in both the lungs although basal dominance is usually observed. In the lower regions, the lymphatic drainage is slow and this localizes the disease in the lower zones.

Some secondary effects produced by the ILD may modify the basic radiological pattern e.g. emphysema secondary to bronchiolar obstruction or compensatory to pulmonary fibrosis. Similarly, loss of volume and crowding or reticular markings may distort the original pattern and may make them unrecognizable.

The amount of interstitial infiltrate seen on chest radiogram may seriously underestimate the parenchymal involvement and is less accurate than the physiological tests to determine the extent and severity of interstitial inflammation and damage.

Pulmonary Function Profile

The characteristic changes in pulmonary function include uniform reduction of the static

pulmonary volume (vital capacity and residual volume) usually with varying degrees of impairment of diffusion. This is the characteristic restrictive pattern. There is greater reduction in forced vital capacity (FVC) than forced expiratory volume in one second (FEV_1) resulting in normal or super-normal FEV_1/FVC ratio. The decrease in RV is not as much as TLC with the result that RV/TLC is more than 30% as compared to normal for which RV/TLC is less than 30%.

Laboratory Investigations

As the etiology and manifestations are diverse, the laboratory tests have to be individualized. However, a systematic approach will be useful. This is summarized in the table below:

Table 1. Laboratory & serologic correlates in interstitial lung disease

1. Hypersensitivity pneumonitis	Precipitating antibodies
2. Tropical pulmonary eosinophilia	Peripheral blood eosinophilia
3. Sarcoidosis	ACE
4. Rheumatoid lung disease	%Rheumatoid factor > 1:80
5. SLE	ANA + ve (speckled > 1:160)
6. Polymyositis	Muscle enzymes

CT-Images in Interstitial Lung Disease

Although standard AP and lateral chest roentgenograms still remain indispensable in routine evaluation of ILD, the marked superimposition of opacities over bronchovascular bundles and poor definition of pleural basal shadows and mediastinal/hilar shadows, besides the 10-15% occurrence of normal roentgenograms in ILD suggest the need for more sophisticated investigations.

CT scan of thorax provides a window by which the lung parenchyma and bronchovascular bundles can be studied without the problem of superimposition of shadows, in cross section. The etiological diagnosis can be suggested by a particular predominant type of opacities and their distribution.

A radiologic-pathologic correlation study showed the following patterns:

- A. Patchy or homogenous increased density [A_1 (68%) lazy density, A_2 (14%) high density.], thickening of alveolar septum and/or intra-alveolar exudate.
- B. High density with a decrease of lung volume and atelectasis due to alveolar collapse (5%).
- C. Micronodular or granular densities, dilatation of alveolar ducts and/or granular densities, irregular fibrosis (86%).
- D. Air bronchiogram with high density, atelectasis due to alveolar collapse and dilatation of the bronchioles (14%).
- E. Confluence of various sized ring like shadows, 2 to 10 mm in diameter, the so called reticular pattern. Various sized dilatation of bronchioles and/or bronchi (86%).
- F. Confluence of coarse ring like shadows, 5 to 15 mm in diameter, honeycombing (18%).
- G. Subpleural bullous changes : subpleural bullae (59%).

The distribution, in a vertical direction, was in all upper, middle and lower lung fields in all the cases. The cross sectional planes showed that lesions existed predominantly in the dorsal area (100%), followed by ventral (72%) and mediastinal (73%) areas. Subpleural area was involved in all the cases but middle and inner areas in 64% and 23% of cases respectively.

Magnetic Resonance Imaging

MRI scans showed significantly higher T_1 and T_2 relaxation times in patients who showed 'active' disease as defined by (1) clinical and radiographic parameters and (2) need for intensive treatment. Lower T_1 and T_2 relaxation times were seen in cases who had a stable future course.

BAL and Transbronchial Lung Biopsy

Broncho Alveolar Lavage (BAL) assesses the disease activity and helps in decision making regarding therapy and prognosis of these disorders.

Lavage cellular analysis reflects the inflammatory and immune status of the parenchymal cells. In IPF, polymorphonuclear dominance suggests active disease and more likelihood of response to therapy. Therapy usually lowers the counts. So, normal lavage means quiescent stage of the disease. In sarcoidosis, BAL count of more than 28% lymphocytes indicates that disease will progress if not treated, and a fall in lavage cells occurs with improvement.

In collagen vascular disease (CVD) and IFF, more than 11% lymphocytes indicate response to treatment while the polymorphonuclear leucocyte increase indicates poor prognosis.

As with any clinical test, BAL cellular analysis is hardly flawless. Its role is properly viewed as one facet of the composite clinico-pathologic evaluation of ILD. BAL analysis provides information comparable in value to that of bone marrow aspirate in assessment of anemia. Transbronchial biopsy should be performed at the time of BAL. However, in all but the most compromised patients, the diagnosis of IPF should be made only after surgical lung biopsy to complete the exercise of exclusions.

Transbronchial lung biopsy (TBB) is particularly useful in excluding infections or neoplastic diseases that mimic chronic progressive interstitial disease, in excluding a more treatable disease e.g. hypersensitivity pneumonitis and for assaying the activity of the disease. It should be performed early in the disease, before the end stage of fibrosis obliterates any identifying hall-marks of the disease. In the management of ILD one will never regret obtaining a lung biopsy but is bound to repent if the occasion is missed and the biopsy is not secured in time.

Transbronchial lung biopsy gives 60-80% yield and provides tissue diagnosis in more than 70% of patients of undiagnosed diffuse pulmonary fibrosis.

Course of the Disease

The progression of dyspnoea involves a spectrum extending from an acute fulminant illness to a more indolent evolution of respiratory impairment, extending over several years. The progression of dyspnoea may be punctuated by

recurrent respiratory tract infections. Pulmonary arterial hypertension and/or cor pulmonale may complicate the clinical course in the midway or late stages of the disease. While the tempo of the disease may vary, a fatal outcome is virtually certain without intervention.

The patients with early disease with an active alveolitis and minimal fibrosis respond well to therapy. In contrast, patients with minimal alveolitis and severe fibrosis do not respond to therapy. TBB cannot be performed repeatedly and, therefore, the activity can be decided by BAL, Gallium-67 scanning, positron emission scanning, TcDTPA inhalation, collagen turnover markers, etc.

Management

The various approaches have varying degrees of sensitivity and specificity for the evaluation of alveolitis of the interstitial lung disease. However, the basic principles of therapy include the following:

- (1) Identify and remove the injurious agent. In early hypersensitivity pneumonitis, the disease will often regress as the source of the antigen is removed. Specific therapy of alveolitis can be instituted during exacerbation.
- (2) Suppress the inflammatory response to prevent the progression of the disease and irreversible damage to alveolar capillary units.
- (3) Palliate the complications of the disease.
- (4) Therapy must be aggressive and has to be for a long time.

The definition of good response is : reduced breathlessness, a more than or equal to 10% increase of FVC and improved chest radiogram maintained for at least a year.

Therapeutic approaches

Corticosteroids are the mainstay of the treatment. Some symptomatic benefit may be obtained in about 50% of cases of cryptogenic fibrosing alveolitis but objective radiographic or physiologic improvement is obtained in only about 15% of patients.

The factors associated with good prognosis include:

- (i) A younger patient
- (ii) Less severe radiologic disease
- (iii) Initial lower FVC combined with a short history of breathlessness (i.e. < 2 years)
- (iv) A more cellular content hi biopsy (TBB)
- (v) A greater collagen type III.

Prednisolone is the preferred steroid and is generally recommended for the acute inorganic dust exposure diseases and acute effects of radiation and drug induced clinical disease, particularly if there is hypoxemia. In chronic interstitial diseases, the use of this therapy is limited. The National Heart Lung Blood Institute of USA has advised the following schedule of prednisolone therapy:

- (i) Initial Prednisolone 1 mg/kg/day for 2-4 weeks.
- (ii) Tapering 2.5 mg/week until maintenance dose of 0.25 mg/kg is reached.
- (iii) Long term therapy is advised according to stage of alveolitis (BAL and Ga-67); if alveolitis disappears, taper Prednisolone to zero; if alveolitis remains, stable-maintenance dose is continued.
- (iv) If alveolitis worsens, high doses of Prednisolone (a) may be given and tapered or (b) repeated as and when required.
- (v) All precautions for the side effects of this therapy must be taken and the dose adjusted accordingly.

Immunosuppressants like Azathioprine, D-penicillamine, Cyclophosphamide, Chlorambucil and Vincristine have been tried in CFA but long term controlled trials do not support this approach..

The response rates with corticosteroids are variable and the benefits are short-lived. Only one third of IFF patients demonstrated a significant clinical benefit at the cost of significant steroid induced morbidity. Steroid induced polymyopathy and/or bone demineralization will compromise the respiratory "pump" and /or the "lever" (ribs and vertebrae) of the "pump" and worsen the respiratory function.

Alternatively, Cyclophosphamide is more effective and less morbid than glucocorticosteroid therapy when used appropriately in IPF patients especially in neutrophilic alveolitis and after failure of steroid therapy. Oral Cyclophosphamide in doses of 1.5 to 2.0 mg/kg/day often provides disease control, with minimum morbidity as compared to oral Prednisolone therapy. In absence of serious morbidity, this therapy is usually given for 18 months.

"Pulse therapy" with large doses of Methylprednisolone is an useful adjunct to Cyclophosphamide therapy. The Methylprednisolone bolus in doses of 10 mg/kg intravenously is administered on three consecutive days, after which it may be repeated at weekly intervals. More frequent schedules may pose a major risk of opportunistic infection.

Azathioprine and Methotrexate have failed to produce similar benefits, probably due to a difference in the degree of immunosuppression achieved by this drug rather than any substantial difference in these two toxic agents.

Strategies ranging from probing of stimulus-secretion coupling in phagocytic cells to the analysis of oncogenic expression are currently being employed. Clinicians have reason to expect significant progress along the continuum of clinical research in this area of pulmonary medicine.

CIPROFLOXACIN IN RETREATMENT OF PULMONARY TUBERCULOSIS: EXPERIENCE WITH 16 PATIENTS

Sukhesb Rao

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Summary: Ciprofloxacin, a 4-quinolone was administered to 16 retreatment cases of pulmonary tuberculosis. Of these, 13 patients showed an adequate bacteriological and radiological response in terms of sputum conversion and radiological resolution. A larger clinical trial is warranted to assess the real anti-tuberculosis potential of this drug.

Introduction

Treatment of resistant tuberculosis or retreatment of failure cases often fails inspite of multiple drug therapy. This is mainly because of poor adherence to treatment, increased cost, drug toxicity, etc. Hence the search for newer drugs.

Among the newer anti-tuberculosis drugs which have shown promising results are Rifabutin¹ and Ansamycin² and 4-quinolones which is another group which has shown promising antimycobacterial activity in the recent past^{3,4}. Ofloxacin has been shown to be very effective both *in vitro*⁵ and *in vivo*⁶ against *Mycobacterium tuberculosis*. It has also proved to be quite safe⁶. Another quinolone, Ciprofloxacin, has also shown encouraging *in vitro* activity⁷, but reports of clinical trials with it are sparse.

Hence, this study was undertaken to study the role of Ciprofloxacin in retreatment of cases of pulmonary tuberculosis.

Material and Methods

This study was conducted on 16 patients of sputum smear positive pulmonary tuberculosis. The criteria of inclusion in the study were :

1. Past history of inadequate or irregular treatment or therapy with multiple drugs.

2. Bacteriological failure on standard chemotherapy.
3. Serious side effects to standard anti-tuberculosis drugs.

An informed consent was taken from each patient for the use of Ciprofloxacin. All these patients were kept on Ciprofloxacin, 500-750 mg daily in single dose (depending on body weight) together with some other drugs (Thioacetazone and Isoniazid in 13 patients and Ethambutol, Isoniazid and Thioacetazone in the remaining 3 patients). All patients were hospitalized prior to inclusion in the study. Sputum examination for acid fast bacilli by smear was done for 3 consecutive days every month, for 6 months or till sputum conversion occurred, whichever was earlier. If sputum failed to convert, patient was treated as a failure and managed accordingly. Out of the 3 failures, 2 patients were persuaded to send their sputum to a referral centre for culture and sensitivity testing. Both the samples grew *M. tuberculosis*, resistant to all standard drugs. Hence they were shifted to a regimen containing Kanamycin, Isoniazid, Cycloserine and Ethionamide. One patient responded well and is under follow up. The other patient did not turn up for follow up after 6 months. The third patient's sputum could not be sent for culture and hence he was empirically kept on the same regimen. He too has shown improvement and is under follow-up. In respect of the patients whose sputum was converted, the same drugs were continued for one year (after sputum conversion) with sputum examination done every 3 months (except in 3 cases where Ethambutol was stopped after sputum conversion). Sputum examination by culture and sensitivity was not done because of non availability. Skiagram chest was done every 2 months till sputum conversion and afterwards

Table 1. Showing bacteriological response of patients

Patient No.	Past Therapy	Sputum Status							Other Drugs
		0m	2m	3m	4m	5m	6m	1yr	
1.	SHRZE	++	++	-	-	-	-	-	TH
2.	SHRZE	++	++	+	-	-	-	-	TH
3.	EHRZ	+++	++	++	++	+	+	NA	TH
4.	SHRZE	+++	++	+	-	-	-	-	TH
5.	SHRZ	++	++	+	-	-	-	-	ETH/TH
6.	SHRZ	++	++	+	+	-	-	-	TH
7.	SHRZ	++	++	-	-	-	-	-	ETH/TH
8.	SHRZE	++	-	-	-	-	-	-	TH
9.	SHRZE	+	-	-	-	-	-	-	TH
10.	EHRZ	+	+	+	+	+	+	NA	TH
11.	HRZE	++	+	-	-	-	-	-	TH
12.	SHRZE	+++	++	-	-	-	-	-	TH
13.	SHRZ	+++	++	+	-	-	-	-	ETH/TH
14.	SHRZ	++	++	++	+	+	-	NA	TH
15.	SHRZE	++	++	++	+	-	-	-	TH
16.	SHRZE	++	+	+	+	-	-	-	TH

S	=	Streptomycin
H	=	Isoniazid
R	=	Rifampidn
Z	=	Pyrazinamide
E	=	Ethambutol
T	=	Thioacetazone
NA	=	Not available

every 3 months till the end of treatment. A note was made of the side effects, if any.

Results

The clinical details of the patients and results are shown in Tables I and II. It is clear that all patients, except three (Nos. 3, 10, 14) showed satisfactory bacteriological and radiological response. The average time taken for sputum conversion was 3.7 months with minimum time being 2 months and maximum 5 months. Three patients were sputum smear positive even at 6 months and were classified as treatment failures and shifted to other drugs. None of the patients

had any significant adverse effect. Only 2 patients had slight giddiness and 2 had mild gastritis which disappeared on continuation of treatment.

Discussion

The treatment of resistant tuberculosis or treatment failures in pulmonary tuberculosis still poses many clinical challenges for chest physicians, despite many advances. This is mainly because of the use of multiple drugs which leads to drug toxicity and increased cost leading to default and non-response.

The interest in the 4-quinolones has added a new hope to the treatment of these patients. The

Table 2. Showing radiological response of patients

Patient No.	Past Therapy	X-ray Status				Other drugs
		2m	4m	6m	1 yr.	
1.	SHRZE	+	+	+	++	TO
2.	SHRZE	++	++	++	++	TH
3.	EHRZ	+	+	+	NA	TH
4.	SHRZE	+	+	++	++	TH
5.	SHRZ	+	+	+	++	ETH/TH
6.	SHRZ	+	+	+	+	TH
7.	SHRZ	+	++	++	+++	ETH/TH
8.	SHRZE	++	++	+++	+++	TH
9.	SHRZE	++	++	++	++	TH
10.	EHRZ	+	+	+	NA	TH
11.	HRZE	+	+	++	++	TH
12.	SHRZE	+	+	++	++	TH
13.	SHRZ	+	++	++	++	ETH/TH
14.	SHRZ	+	+	+	NA	TH
15.	SHRZE	++	++	++	+++	TH
16.	SHRZE	++	++	++	+++	TH

NA No t available
 + 25% improvement
 ++ 25-50% improvement
 +++ 50-75% improvement

fluorinated quinolones with their documented activity against mycobacteria³⁻⁵ and low toxicity are promising new drugs for the treatment of chronic mycobacterial diseases which do not yield to traditional antimycobacterial drugs. This group includes Ofloxacin, Ciprofloxacin, Norfloxacin, Pefloxacin, etc. Ofloxacin has shown promising results in the treatment of tuberculosis. Ciprofloxacin has been shown to inhibit the growth of *Mycobacterium tuberculosis in vitro*⁷, but when tested along with other antituberculosis drugs, it showed antagonism *in vitro*¹. Hence, its role *in vivo* in human beings remains to be assessed, barring a few trials⁹.

This study has shown that Ciprofloxacin can be effectively used in the treatment of pulmonary

tuberculosis. All our patients showed satisfactory bacteriological and radiological clearance except 3 patients (No. 3,10,14) whose sputum failed to convert even after 6 months of treatment. It was relatively well tolerated and no patients experienced intolerable side effects.

Though the presence of other drugs along with Ciprofloxacin prevents us from drawing conclusions, but we also know that monotherapy in tuberculosis is an unacceptable proposition. Considering this fact and the fact that all our patients had already failed with the traditional anti-mycobacterial drugs, it can be inferred that Ciprofloxacin contributed significantly to the satisfactory bacteriological and radiological response.

The other drawbacks of this study are a small

study population and the absence of a long term follow-up. In spite of these drawbacks, the results give some hope about the role of Ciprofloxacin as an anti-tuberculosis drug. We recommend that this drug be tried further in a long term controlled clinical trial.

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IN VITRO ACTIVITY OF CIPROFLOXACIN AND OFLOXACIN AGAINST SOUTH INDIAN ISOLATES OF MYCOBACTERIUM TUBERCULOSIS

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Summary. *Mycobacterium tuberculosis* isolates from 104 south Indian patients, including 52 sensitive to Streptomycin (S), Isoniazid (H) and Rifampicin (R), and 52 resistant to SHR/HR were tested for their in vitro susceptibility to Ciprofloxacin and Ofloxacin on Lowenstein-Jensen medium, the geometric mean for minimal inhibitory concentration (MIC) of Ciprofloxacin was 2.00 mcg/ml for sensitive strains and 2.17 mcg/ml for resistant strains, the overall mean being 2.08 mcg/ml. Considering Ofloxacin, the MICs for the different categories of strains were again similar, there being no difference between sensitive and resistant strains, the geometric means being 2.00 and 2.05 mcg/ml, respectively.

Introduction

Despite the rapid advances in treatment and the availability of effective short course chemotherapy regimens, tuberculosis continues to be a common disease in the community. Tuberculosis is gaining increasing clinical relevance also because of its association with HIV infection¹. Treatment for disease due to drug-resistant *M. tuberculosis* is more toxic, more expensive and not as successful as in disease due to drug-sensitive organisms.² Effective treatment of patients with multi drug resistant organisms will be greatly facilitated by the development of newer anti-tuberculosis drugs.

Interest in the quinolone group of drugs has grown during the last decade with the development of new derivatives such as Norfloxacin, Pefloxacin, Ofloxacin, Enoxacin,

Lomefloxacin and Ciprofloxacin. Of these, Ciprofloxacin is among those with the lowest minimal inhibitory concentration (MIC) against *M. tuberculosis*³ and is more active than Norfloxacin and Enoxacin.^{4,5} A recent study at Tuberculosis Research Centre, Madras has given promising results with Ciprofloxacin on both drug-resistant and drug-sensitive isolates of *M. Tuberculosis, in vitro*.⁶

Ofloxacin has been reported to be active both *in vitro* and *in vivo* against mycobacteria.⁷ It was, therefore, proposed to test the *in vitro* activity of Ofloxacin on south Indian isolates of *M. tuberculosis* and compare it with that of Ciprofloxacin. The results of this investigation are reported in this paper.

Material and Methods

Strains : A total of 104 clinical isolates of *M. tuberculosis* from as many patients was tested. These included 52 isolates sensitive to Streptomycin (S), Isoniazid (H) and Rifampicin (R), and 52 resistant to SHR or HR. The standard sensitive strain *M. tuberculosis* H₃₇ Rv was also tested.

Drug concentrations : Ciprofloxacin and Ofloxacin were incorporated in Lowenstein Jensen (LJ) medium slopes to give final (pre-inoculation) concentrations of 0.5, 1, 2, 4, 8, 16, 32 and 64 mcg/ml.

Sensitivity testing : A standard suspension (4 mg/ml) of the strains, which were given code numbers to conceal their identity, was inoculated with a 3mm loop on to 2 drug free LJ slopes and one LJ slope each, with the different concentrations of the drugs. All slopes were

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Table 1. Minimal inhibitory concentrations of Ciprofloxacin against south Indian isolates of *M. tuberculosis*

	No. of strains	MIC* (mcg/ml)			
		0.5	1	2	4
SHR sensitive	52	1	11	27	13
SHR/HR resistant	52	1	4	35	12
Total	104	2	15	62	25

*No strain had an MIC > 4 mcg/ml.

incubated at 37°C. And, at the end of 4 weeks of incubation, the MIC was determined using the 20-colony end point.⁸

Results

MIC for Ciprofloxacin : The standard strain, *M. tuberculosis* H₃₇Rv, tested on three different occasions, gave an MIC of 1 mcg/ml. Considering the strains isolated from patients (Table 1), even though 21% (11/52) of SHR sensitive strains had an MIC of 1 mcg/ml, as against 8% (4 out of 52) of SHR/HR resistant strains, the corresponding proportions with MIC of 2 mcg/ml were 52% and 67% respectively. This shift could have been due to experimental variation since the proportions of strains with an MIC of 4 mcg/ml were nearly identical. The geometric mean MICs were 2.00 mcg/ml for sensitive strains and 2.17 mcg/ml for resistant strains, the overall mean being 2.08 mcg/ml.

MIC for Ofloxacin : The MIC of Ofloxacin for *M. tuberculosis* H₃₇Rv was 1 mcg/ml on the two occasions tested. The distributions of the MICs with the two categories of strains were very similar, their being no difference between sensitive and resistant strains, the geometric mean MICs being 2.00 and 2.05 mcg/ml, respectively (Table 2).

Discussion

Although the currently used treatment regimens for pulmonary tuberculosis are quite effective in patients with drug sensitive organisms, the patients with drug resistant

Table 2. Minimal inhibitory concentrations of Ofloxacin against south Indian isolates of *M. tuberculosis*

	No. of strains	MIC* (mcg/ml)			
		0.5	1	2	4
SHR sensitive	52	1	8	33	10
SHR/HR resistant	52	1	7	33	11
Total	104	2	15	66	21

*No strain had an MIC > 4 mcg/ml.

organisms, especially those resistant to Isoniazid and Rifampicin, do not respond well to these regimes.⁹ In view of the possibility of an increase in Rifampicin resistance among tuberculosis patients, there is an urgent need for investigations with the newer anti-tuberculosis drugs.¹⁰ These newer drugs include the aminoglycosides, such as Amikacin and Capreomycin, the long acting Rifampicin derivatives, the fluoroquinolones and combinations of beta-lactam antibiotics with beta-lactamase inhibitors.^{10,11}

Considering first the aminoglycosides, although Amikacin is effective against *M. avium-intracellulare* complex, its activity against *M. tuberculosis* is low and, as such, it might not be effective in the treatment of disease due to *M. tuberculosis*.¹¹ A recent study from this Centre revealed that 6% of SHR sensitive and 15% of SHR/HR resistant strains could be resistant to Capreomycin.⁶ As such, Capreomycin may have only a limited role in the treatment of patients with multiple drug-resistant organisms.

The rifamycin derivatives, Rifapentine and Rifabutin have been reported to be more active than Rifampicin *in vitro* against Rifampicin sensitive strains. Thus, Arioli and others¹² reported a 2 to 10 fold higher activity for Rifapentine than Rifampicin. Recent studies at this Centre revealed that although Rifapentine exhibited a significantly higher activity in Rifampicin sensitive strains, there was complete cross resistance in Rifampicin resistant strains. **On the other hand, Rifabutin was not only more effective than Rifapentine in Rifampicin-sensitive strains but also a small proportion**

(22%) of Rifampicin-resistant strains were susceptible to Rifabutin *in vitro*¹³. Thus, Rifabutin might not only be useful to some extent in the treatment of disease due to Rifampicin-resistant organisms but it could possibly delay the emergence of resistance to the companion drugs making it particularly suitable for intermittent chemotherapy due to its longer half-life.

The introduction of fluoroquinolones has broadened the range of therapeutic tools used against mycobacterial diseases. Being a new class of compounds, there is no cross resistance with the conventional anti-tuberculosis drugs.⁹ Of the various derivatives studied, Ciprofloxacin and Ofloxacin have been reported to be most active *in vitro* against *M. tuberculosis*.^{3,14,15} However, the absorption of Ciprofloxacin after oral administration is poor (mean C max 2.4 mcg/ml) with a relatively lower mean half life (4.1 hours) compared to that of Ofloxacin (C max: 11 mcg/ml; t 1/2 : 7 hours).^{16,17} Preliminary studies have demonstrated that Ofloxacin is effective against *M. tuberculosis*, *in vitro* as well as in experimental murine tuberculosis.⁷ In a recent uncontrolled study conducted by the Hong Kong Chest Services/British Medical Research Council,¹⁸ It has been reported that Ofloxacin is a relatively better drug in the treatment of drug-resistant pulmonary tuberculosis patients than Rifabutin.

The present investigation revealed that the *in vitro* activity of Ofloxacin was similar to that of Ciprofloxacin, the overall geometric mean MICs being 2.03 mcg/ml for Ofloxacin and 2.08 mcg/ml for Ciprofloxacin. The earlier reported lower geometric means of MICs from this Centre⁶ were perhaps a reflection of laboratory variations in medium preparation, batches of drugs used and doubling dilution concentrations shifting the mean by one step. It may be observed that the mean MIC for Ciprofloxacin is only slightly below the peak serum levels attainable with therapeutic doses of the drug. However, in pulmonary and other tissues the drug may attain levels in excess of those in serum which may be adequate to inhibit growth of strains.^{19,20} The mean MIC of Ofloxacin, however, is far below the peak serum level of 11 mcg/ml attainable at normal dosage.^{16,17} Moreover, our results showed that the MICs of both Ciprofloxacin and

Ofloxacin were within a narrow range of 1-4 mcg/ml for most of the *M. tuberculosis* strains tested. Further, since no differences in susceptibility to Ciprofloxacin and Ofloxacin were noted between strains sensitive or resistant to SHR, it can be concluded that there is no cross resistance between these quinolones and standard anti-tuberculosis drugs. Earlier studies at this Centre also showed no significant differences in the activity of Ciprofloxacin between SHR sensitive and resistant strains.⁶

The present investigation also suggests that Ciprofloxacin and Ofloxacin might be effective in the treatment of patients with multiple drug resistant organisms. But their use in patients could easily lead to the selection of resistant mutants. This, in turn, could mean resistance to the other quinolones, as cross resistance is a well-known phenomenon among the quinolones.⁷ Therefore, these quinolones might be useful in the treatment of multidrug resistant tuberculosis only if used in judicious combination with other drugs to which the strain is sensitive. Thus, the use of Ciprofloxacin or Ofloxacin in the chemotherapy of tuberculosis, including their role in the treatment of failures to standard regimens, can only be assessed after well planned controlled clinical trials.

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PRIMARY LUNG CANCERS IN TREATED PULMONARY TUBERCULOSIS PATIENTS

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Summary : Primary lung cancers occurring in treated pulmonary tuberculosis patients are frequently diagnosed and treated as relapse. In this study, 22 treated cases of pulmonary tuberculosis patients were found to have primary malignant tumours of the lung. In 12 patients (54.5%), the malignant lesions were at the site of the healed inactive pulmonary tuberculosis lesion : 8 of the 14 squamous cell carcinomas belonged to this category, Adenocarcinoma accounted for one patient only. The already treated, clinically and radiologically deteriorated pulmonary tuberculosis patients, especially in the vulnerable age groups, with a negative sputum smear result should be investigated for possible bronchogenic carcinoma,

Medicine Department, Govt. General Hospital, Madras during a period of two years (1990-1992). Those already treated pulmonary tuberculosis patients who had clinical and radiological deterioration during their follow-up were selected for the study if they fulfilled the following criteria:

1. Confirmed (pre-treatment) pulmonary tuberculosis patients who had successfully completed anti-tuberculosis treatment.
2. A residual healed inactive pulmonary lesion at the time of treatment completion.
3. Negative sputum smear for AFB on repeated (at least two) examinations.
4. Histo/cytopathological confirmation of primary lung cancer from the specimens obtained by flexible fiberoptic bronchoscopy or needle biopsy.

Introduction

Without modern chemotherapy of pulmonary tuberculosis, millions of pulmonary tuberculosis patients will not be leading an extended lease of life. However, a sizeable proportion of them suffer from post-treatment disorders depending on the extent of the healed residual lung lesion. Association of scar carcinoma with healed tuberculous lesions is recognised to be one such possibility. The irritative effect of a chronic inflammatory process leading to metaplasia and the trapping of carcinogens in the fibrotic tissue have been considered as possible cancer triggering factors¹.

The present study analyses the occurrence of newly developed primary lung cancer among treated pulmonary tuberculosis patients with inactive residual lesions.

Material and Methods

The study was undertaken at Thoracic

A detailed history and a thorough clinical examination had been carried out in each patient. Chest skiagrams taken at the time of treatment completion were compared with those taken at the time of diagnosis of cancer. Pattern of primary lung cancer was analysed in relation to age, sex, smoking habit, type of pulmonary lesion and site of residual lesion.

Results

In all, 22 treated pulmonary tuberculosis patients in whom primary lung cancers were detected during post-treatment follow-up were selected for this study. Of them, 21 patients (95.5%) were aged above 40 years with the mean age of all patients being 54.9 years; 19 patients (86.4%) were male and the rest female.

As many as 15 (68.2%) of the 22 selected patients were having prominent hilar glands and mass lesions. Pulmonary mass lesions and coin

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Table 1 Primary lung cancers in relation to cell type, smoking habit and site

Cell type	Primary lung cancers		% smokers	Site of carcinoma in relation to site of pul. Tuberculosis			
	No.	%		Same site		New site	
			No.	%	No	%	
Squamous cell	14	63.6	71.4	8	57.1	6	42.9
Large cell	5	22.7	60.0	2	40.0	3	60.0
Small cell	2	9.1	50.0	1	50.0	1	50.0
Adenocarcinoma	1	4.5	-	1	100.0	-	-
Total	22	100.0	63.6	12	54.5	10	

shadows were found in 22.7% and 9.1% patients respectively.

Squamous cell carcinoma was detected in 14 patients (63.6%), large cell carcinoma in 22.7%, small cell carcinoma in 9.1% and adenocarcinoma in 4.5% (Table 1). Ten (71.4% of 14 squamous cell carcinoma patients were smokers (all male) and the smoking patients with large cell and small cell carcinoma were relatively less (Table 1). There was only one adenocarcinoma patient and he was a non-smoker.

As many as 12 of the treated pulmonary tuberculosis patients (54.5%) had the carcinomatous lesion at the site of the healed inactive tuberculous lesion. In the remaining 10 patients (45.5%) primary lung cancer developed at new site (Table 1). The only adenocarcinoma of this study was found to arise at the site of pre-existing healed scar tissue. However, there were

no significant differences seen in other cell types, as far as the sites of origin were concerned.

Primary malignant tumours of the lung were found to occur in 13 patients (59.1%) within five years of stopping anti-tuberculosis treatment (Table 2). In 9 other patients, bronchogenic carcinoma was detected five or more years after treatment completion.

Discussion

The history of a well established diagnosis like pulmonary tuberculosis, even though adequately treated, tends to hold the attention of the physician away from the co-existing carcinoma until it has advanced². Quantitative clinical and radiological characteristics of patients with primary lung cancer are not different from those having both tuberculosis and lung cancer^{3,4}.

Healed pulmonary tuberculosis patients with accompanying parenchymal scarring can perhaps stimulate epithelial metaplasia and atypical cell proliferation in the mucosa of the main and segmental bronchi as well as the terminal air spaces with the dense scar tissue². In the present study, 54.5% of primary lung cancers were found to arise from the pre-existing healed residual tuberculous lesions. However, it is not possible to assert that they were 'scar-carcinoma' and not coincidentally occurring primary malignant tumour of the lung. An earlier study⁵ had shown that the association of pulmonary tuberculosis and bronchogenic carcinoma was perhaps a coincidence.

Table 2 Time elapsed between anti-TB treatment completion and detection of primary lung cancer

Time interval (in years)	Patients	
	No.	%
≤ 5	13	59.1
6-10	3	13.6
11-15	4	18.2
> 15	2	9.1
Total	22	100.0

Adenocarcinoma had been the most frequently seen (67% and 72%) scar carcinoma in two earlier studies^{1,6}. However, in the present study, 8 (66.7%) of the 12 primary lung cancers arising from healed tuberculous sites were of squamous cell type. An earlier study⁴ observed that chronic inactive pulmonary tuberculosis was seen more frequently in patients with squamous cell carcinoma, while active tuberculosis was more often associated with adenocarcinoma and anaplastic carcinoma.

Bronchogenic carcinoma is one of the most unrecognised post-treatment problems among treated pulmonary tuberculosis patients. The chances of restarting anti-tuberculosis treatment in these patients, as relapsed tuberculosis, are high. All the more so, when the primary cancers arise from the inactive healed tuberculous foci. Therefore, it becomes imperative to investigate all the treated pulmonary tuberculosis patients whose condition deteriorates clinically and radiologically for possible bronchogenic carcinoma, especially in vulnerable age groups, if

their sputum continues to be negative for tubercle bacilli.

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FEASIBILITY OF UTILISING ADDRESS CARD SYSTEM FOR OBTAINING ACCURATE ADDRESS OF PATIENTS UNDER PROGRAMME CONDITIONS

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Summary : An address-card, one on which patient's home address is asked to be recorded by a person knowing for sure the patient's address, was investigated for acceptability and efficiency, in two Government hospitals located in semi-urban areas and six Primary Health Centres located in rural areas in North Arcot district. In all, 394 address-cards were given to the patients from the eight centres, of which 374 were returned with the address filled in, showing an acceptability rate of 95%. In all, 373 Type A letters were then posted to these address-card addresses in respect of which acknowledgement cards were received back from 306 (82%) patients. For 140 patients, the recorded addresses were found to be the same as on the address-card and the treatment card : In the remaining 233, there was some difference between the two addresses. Type B letters were then posted to the 233 patients at their treatment card address. No definite information was available regarding the receipt of one or both types of letters in respect of 80 patients; so, an attempt was made to visit these patients in their homes to find out the fate of these letters. Of these, no information could be collected in 9 patients.

Out of 224 patients for whom information regarding the receipt of letter was available, 143 (64%) patients received both letters and 16 (7%) received neither type A nor Type B letter. Twenty-one (9%) had probably or definitely not received the Type A letter, but had received the Type B letter. Forty-four (20%) had definitely or probably not received the Type B letter, but had received the Type A letter.

sufficient attention is not usually paid to recording complete and accurate addresses of out-patients requiring prolonged treatment and warranting prompt follow-up action when they default for collection of drugs. When a patient fails to attend the clinic on the due date for treatment, a reminder post card is to be posted for defaulter retrieval, as prescribed in the manual of District Tuberculosis Programme. This action can be successful only if the patients' addresses are recorded accurately. To a sample of 'lost' patients i.e. those who had defaulted continuously for one month, home visits were made in North Arcot and Raichur districts, and it was found that the addresses recorded on the treatment cards were inadequate or incorrect in 15% and 13%, respectively¹. In another study, it was found that the accuracy of recorded addresses was poor in a city clinic, with 20% to 30% of the posted letters not reaching the patients². In a comparison of the address card system and the addresses obtained by interrogation by health visitors in urban patients, the letter was received in 91% and 84% of the cases, respectively³. A study was undertaken by Tuberculosis Research Centre, Madras, in North Arcot district (prior to bifurcation of this district) to find out the feasibility and effectiveness of this system in rural and semiurban areas, under programme conditions.

Material and Methods

The address-card system consisted of giving a clinic-addressed stamped post card to the patient with a written and oral request to get his address entered on it by the local postman or any other

Introduction

In India and many other developing countries,

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literate person knowing patient's correct postal address. The study was conducted in two taluk hospitals and six Primary Health Centres located in semi-urban and rural areas. When patients attended these centres, they were given the address card by the local staff with instructions to get the complete and accurate address written on it and then post it to the Centre's field unit at Vellore. Once an address-card was received at the field unit, a Type A letter with a clinic-addressed stamped reply post card was posted to the address written on the address-card. The address written on the address-card was compared with that already available on the treatment card and in case of any discrepancy, a Type B letter with a reply post card was posted to the address entered on the treatment card. When no definite information regarding the receipt of the letters was available for some addresses, home visits were made to these addresses to find out the fate of the letters. These visits were done after a period of one month.

Content of letters

The matter in the address-cards, Type A and Type B letters, was in the local language (Tamil). Both Type A and Type B letters expressed concern about the patient's health and regularity of treatment and aimed at finding out whether

patients could receive letters, and requested them to post back the attached clinic-addressed post card immediately, on receipt of those letters, entering the date of receipt on the reply card. Though the content of both Type A and Type B letters was the same, they were marked Type A and Type B in order to differentiate the two.

Results

Acceptability and accuracy of address

A total of 394 patients attending two taluk hospitals and six Primary Health Centres including one Panchayat Union Dispensary, was given the address-cards (to be posted back to the field unit at Vellore). Of these, 374 (95%) cards were received back at the field unit with complete address (Table 1) showing that the system was acceptable in both semi-urban and rural areas. A letter with a reply post card was posted to 373 patients (one letter was not posted since the address was that of the work spot) requesting the patient to post back the reply card after entering the date of receipt of the letter. Of the 373 letters posted, 306 (82%) acknowledgement cards were received at the field unit; 9 (2%) were returned undelivered and, so, were definitely not received. Definite information was not available for the remaining

Table 1 *Response to postcards posted at the address-card address*

	GH [@]		PHC [@]		Total	
	No.	%	No.	%	No.	%
a. No. of address-cards given to patient	198	-	196	—	394	-
b. Cards received back from patients (% based on a)	185	93	189	96	374	95
c. Type A letters posted	184*	-	189	-	373	-
d. Type A letters definitely received by the patient (% based on c)	150	82	156	83	306	82
e. Type A letters probably not received by the patient (% based on c)	29	16	29	15	58	16
f. Type A letters definitely not received (% based on c)	5	3	4	2	9	2

[@] GH - Taluk Hospital; PHC - Primary Health Centre

* For one patient, the address was that of his work spot and hence type A letter was not posted.

58 (16%) letters (considered as probably not received).

Comparison of addresses on address-card and treatment card

The address entered on address-card was checked against that entered on the treatment card. It was observed that 140 (38%) addresses (Table 2) were the same in both. In the remaining 233 (62%), some form of discrepancy was observed between the two addresses. Of the 26, with inadequate address-card addresses, 16 (16%) patients received Type A letters (16 (62%) patients received Type B letters). Of the 156 with inadequate treatment card address, 134 (86%) received Type A letters (116 (74%) received type B letters). In 51, with inadequate address in both, 43 (84%) received Type A letters (29 (57%) received Type B letters).

Relative efficacy of address-card and treatment card addresses

Of the 233 patients for whom both types of letters were posted, 193 (83%) patients received

Type A letters and 161 (69%) received Type B letters, including 140 who received both (Table 3). Six (3%) had definitely not received Type A letters and 10 (4%) Type B letters. In 34 (14%), Type A letters were probably not received as against 62 (27%) of Type B letters.

Home Visit

Since no definite information (probably not received) was available regarding the receipt of one or both types of letters for 80 patients, an attempt was made to visit their homes to find out the fate of those letters. Forty-five patients had definitely received Type A letter, and probably not received Type B letter. Of them, no information could be elicited for 7 patients even after making a home visit, and from the remaining 38 patients, two Type B letters were collected. There were 16 patients who had probably not received either letter; for 2 more patients no information could be elicited even after making a home visit. Considering the remaining 19 patients, 1 Type A and 1 Type B letters were collected from one patient. For 18

Table 2 Adequacy and accuracy of address-card and treatment card addresses

No.	Type of discrepancy	GH [@]			PHC [@]			Total
		a	b	c	a	b	c	
1.	Inadequacy in address-card address in door no., street name, and/or village name.	10	2	0	6	7	1	26
2.	Inadequacy in treatment card address in door no., street name, and/or village name.	60	6	3	74	12	1	156
3.	Difference between address card and treatment card addresses in door no., and/or street name.	20	6	1	23	1	0	51
4.	Same address in address card and treatment card	60	15	1	53	9	2	140
Total		150	29	5	156	29	4	373

@ GH - Taluk Hospital, PHC - Primary Health Centre

a = Patients who had definitely received Type A letters

b = Patients who probably had not received Type A letters

c = Patients who definitely had not received Type A letters

Table 3 Receipt of Type A and Type B letters

Type B letter (Treatment card address)	Type A letter (Address-card address)			Total	
	Definitely received	Probably not received	Definitely not received	No.	%
Definitely received	140	18	3	161	69
Probably not received	45	16	1	62	27
Definitely not received	8	0	2	10	4
Total No.	193	34	6	233	100
%	83	14	3		

Table 4 Number of days taken to receive Type A and Type B letters

		Interval days for Type A letters				Total
		0-3	4-7	≥8	Not recorded	
Interval days for Type B letters	0-3	107	6	2	6	121
	4-7	9	0	0	0	9
	≥8	2	0	0	0	2
	Not recorded	6	1	0	1	8
	Total	124	7	2	7	140

patients (Type A letter probably not received, but Type B received), Type A letter could not be collected. For 1 patient (Type A letter definitely not received, but Type B probably not received), Type B letter could not be collected. Thus, out of the 24 patients for whom information regarding the receipt of either Type A or Type B letter was available, 21 had probably or definitely not received Type A letter but had received Type B letter and 44 had probably or definitely not received Type B letter but had received Type A letter. The difference in the receipt of the letters between the address card address and treatment card address is statistically significant ($P < 0.01$ -McNemar's test).

Interval between posting and receipt of letters

Of the 140 patients who had received both kinds of letter (Table 4), 124 (89%) Type A

letters had been received within 3 days as against 121 (86%) Type B letters. The letters were received within a period of 7 days by 7 and 9 patients, respectively. Thus, the majority of the patients who received the letters did so within 7 days of posting, and the interval was the same for the two types of letters.

Discussion

The study has demonstrated that it is feasible to introduce the address-card system under programme conditions in Taluk Hospitals (semi-urban) and Primary Health Centres (rural). The system was acceptable as shown by the fact that the filled up address-cards were returned by 374 of 394 (95%) patients. The Address recorded on the address-card was accurate in 306 (82%) of 373 patients, since the acknowledgement/reply card enclosed in the letter posted to the

addresses was received back at the unit. These findings are similar to those reported by Radhakrishna et al.³, where the acceptability of the address card was 96% and accuracy was 85% in urban patients.

When the address-card address was compared with the address recorded on the treatment card at the respective centres, it was found that the addresses differed in 233 patients. Despite this, 140 of these 233 had definitely received both the letters posted; another 21 had received the letters sent to the treatment card addresses and an additional 53 had received the letters sent to the address-card address. The postal system in the area under study seems to be good since 124 (89%) address-card address letters and 121 (86%) treatment card address letters had been received within 3 days of posting. Since rural areas form a fairly closed community, letters were probably delivered to the patients even when there were slight difference in the addresses.

It was estimated that only 27% of the patients, started on standard chemotherapy during the period from 1.7.84 to 30.6.85 received 12 collections or more of the prescribed treatment⁴. Defaulter retrieval, a major factor in improved case holding, depends on posting a letter or visiting the patient, both of which require an adequate and accurate address. This study and earlier studies by Krishnaswami et al² and Radhakrishna et al³ have established that the accuracy of address can be significantly unproved by using the address-card system, which is an inexpensive, convenient and acceptable method. This study has also clearly established that the address-card system can be effectively introduced under programme conditions even in rural and

semi-urban areas.

Acknowledgements

We are grateful to Dr. A. Subramanian, District Tuberculosis Officer and the staff of peripheral health institutions in North Arcot district, for their co-operation in conducting the study. We thank Mr. M.S. Krishnamoorthy, Senior Research Officer (Retd.), and Dr. Rajeswari Ramachandran, Assistant Director, for their valuable guidance. We thank Mrs. Vanaja, Medical Social Worker and Mr. C.R. Sudheendra for their contribution in organising the home visits. We also thank Mrs. K. Saroja for her secretarial assistance.

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TUBERCULOUS EPIDIDYMO-ORCHITIS IN A THREE YEAR OLD CHILD

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(Received on 1.2.93; Accepted on 4.3.93)

Summary : A rare case of disseminated tuberculosis presenting as epididymo-orchitis in a 3 years old is reported. Tuberculous orchitis is unusual at any age and is virtually unknown in children. Scrotal swellings in childhood are usually malignant. The multisystem nature of the disease in this case led to the suspicion of a malignant process. The dilemma was resolved after magnetic resonance imaging and fine needle aspiration biopsy of the scrotal swelling. The child continues to improve on anti-tuberculosis treatment combined with steroids.

Introduction

Tuberculosis of the male genital tract is unusual in childhood. Only a handful of case reports describe this entity, usually along with miliary tuberculosis. We present a case in which a scrotal swelling was the initial manifestation of tuberculosis in a 3 year old boy and multiple investigations were needed to confirm the non-neoplastic nature of the disease.

Case Report

A 3 1/2 years old male child presented with 9 months' history of a progressive painless right scrotal swelling. Four months later, the child had developed weakness of the left half of the body including the face. The patient also had had 3 episodes of partial seizures and repeated episodic headache and vomiting. There was no history of fever, anorexia, cough or a significant weight loss. No contact with a case of tuberculosis could be established.

Physical examination revealed a well nourished child with anthropometric parameters within the normal limits. There was a right scrotal swelling which was smooth, non tender, with decreased testicular sensation. A nodular

enlargement of the epididymis could also be palpated. The vas was normal. The child had a left spastic hemiparesis and left facial palsy. Fundal examination of the eyes revealed congestion of both discs. There was a firm hepatomegaly of 3 cms and the spleen was palpable. Rest of the systemic examination was normal.

The full and differential white cell counts, liver and renal profiles were normal. ESR was elevated to 60 mm. Mantoux test was positive. Chest radiograph revealed a coin shadow in the right midzone, with right paratracheal lymphadenopathy. Scrotal ultrasound showed an enlargement of the right testis and epididymis. The testicular mass was predominantly solid with a heterogeneous echotexture.

In the CT Scan of the cranium, there was a large irregular ring enhancing lesion with massive surrounding edema in the right temporo-parietal region (Fig. 1). The ipsilateral lateral ventricle showed a significant mass effect with gross dilatation of the left lateral ventricle. There was another satellite lesion in the right parietal area. On MRI of the brain, multiple focal areas of granulation tissue were found in the right cerebral hemisphere, with the largest being in the parietal lobe.

Fine needle aspiration cytology of the testicular mass revealed necrotic material, degenerated cells and lining cells of the tunica. Occasional giant cells were also seen. The overall cytomorphology was suggestive of a granulomatous lesion, likely to be tuberculous, though AFB could not be visualised on smear or culture. The 24 hours' urine microscopy and culture for AFB were negative. Intravenous pyelography and ultrasonography revealed that the kidneys were normal in size and texture.

The child was put on a 3 drug antituberculosis regimen (Rifampicin, Isoniazid and Pyrazinamide) combined with steroids and

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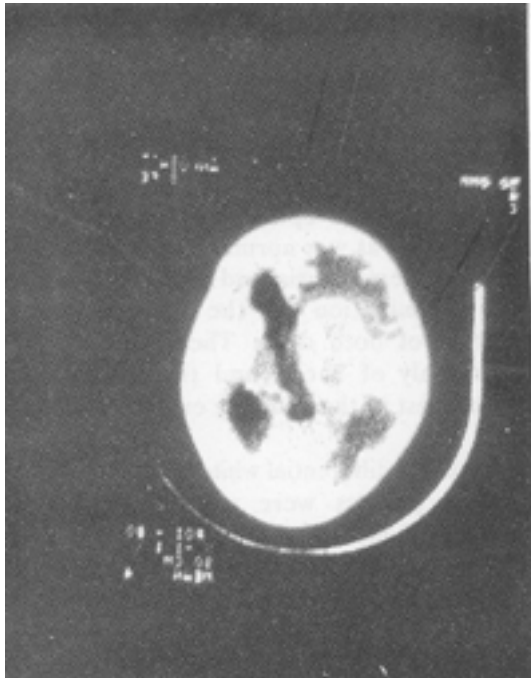


Fig. 1 CT scan showing a large ring enhancing lesion in right temporoparietal region and dilated left ventricle

anticonvulsants. CT Scan done after 3 months of therapy revealed a decrease in the size of the lesion (Fig. 2). The clinical course has been one of progressive improvement.

Discussion

The proportion of tuberculous patients having extrapulmonary tuberculosis has been constantly increasing but the number with genital tract involvement has remained relatively constant. In the series reported since 1900, the proportion of males with genital tuberculosis has ranged from 0.43-15%^{1,2,3}; the lowest figures being the most recent as they are based on clinical rather than autopsy data.

Genital involvement in children is virtually unknown in the prepubescent age as the average time interval between the development of the primary lesion and genito-urinary manifestation is rarely less than 5 years, and is usually more than 10 years⁴. Only stray case reports exist in literature. Lincoln followed the course of 942

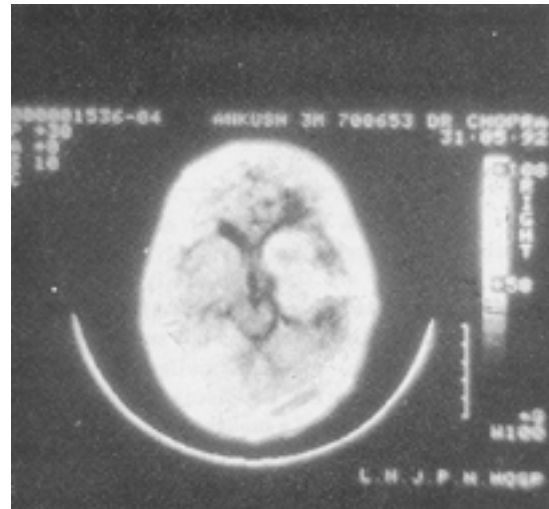


Fig. 2 CT scan done after 3 months showing decrease in the lesion size

children with untreated primary disease in the pre-chemotherapy era and discovered that only 12 developed genital disease⁵. Tuberculous orchitis was not seen in those children. Extragenital tuberculous disease including renal involvement is present in as many as 88% of the patients with genital tuberculosis^{6,7}. In children, genital tuberculosis is usually the localised manifestation of a disseminated disease. Miller et al⁸ described the association of miliary tuberculosis, tuberculosis lymphadenitis, and epididymitis in a 6 month old child. Milleneria⁹ has reported a 18 month old South African child with epididymitis being the sole manifestation of tuberculous disease and emphasized that since most chronic scrotal swellings in children are malignant, the tuberculous nature of a scrotal swelling must be decided on histology alone.

A relatively high percentage of patients with genital tuberculosis have evidence of quiescent or active pulmonary disease. This suggests that the initial site of disease in most cases is pulmonary and the subsequent spread to the genital tract occurs as⁹ descending infection from the urinary tract, direct extension from neighbouring organs, early or late haematogenous dissemination, lymphatic spread, besides primary tuberculous infection of urethra. Genital tuberculosis due to haematogenous seeding of the genital tract is more common in children than adults and usually

involves the prostate and the epididymis because of their rich vascular supply. It is likely that the primary site of infection in our case was the lung and haematogenous dissemination led to the genital and neurological involvement. The presentation with tuberculous orchitis, which is rare at any age but virtually unknown in childhood, and neurological symptoms is the unusual feature of this case which led to all the sophisticated investigations.

Acknowledgements

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TUBERCULOUS OTTOS MEDIA AND SHORT COURSE CHEMOTHERAPY

V.K. Arora¹ and K. Gowrinath²

(Received on 1.6.93; Accepted on 24.10.93)

Summary : A case of tuberculous otitis media where diagnosis was made after surgical mastoid exploration is discussed. A high level of suspicion by the treating physician is mandatory to avoid long delay in diagnosis and increased complications in the modern chemotherapy era.

Introduction

Tuberculous lesions in the ear are rare and occur usually in association with pulmonary tuberculosis in adults. A tuberculous aetiology is not thought of in the absence of typical features like multiple perforations over the tympanic membrane, as described in literature. This is particularly so because of the low prevalence of isolated lesions caused by *Mycobacterium tuberculosis* in adults without any evidence of pulmonary disease. We report a case of tuberculous otitis media without pulmonary involvement where diagnosis could be made post-operatively.

Case Report

A 29 year old female attended our hospital for inability to close left eye and dribbling of saliva from the angle of mouth, of two weeks' duration. The patient gave history of intermittent left ear pain with serous discharge for the preceding three months. Examination of the left ear showed scanty serous discharge. The tympanic membrane was congested, with whitish granulation material in the attic area. There was no mastoid tenderness, nor nystagmus. All blood counts and urine examination were normal. Mantoux test reading was 10 × 10 mm. Chest

radiograph showed no abnormality. Left mastoid radiograph showed sclerotic changes. Neurological examination revealed left sided infranuclear facial palsy. Mastoid exploration was done as there was no response to antibiotics and the exploration material showed tuberculous granulation tissue (Fig. 1). The patient showed excellent response to 2 EHRZ/4HR therapy with subsidence of ear discharge and complete improvement of facial palsy within one month of chemotherapy. The patient is currently under treatment and follow up.

Discussion

Tuberculous otitis media is a rare condition and the exact incidence is unknown. There are a few selective reports in the literature^{1,2}. In view of the extremely low incidence (< 1%) of ear disease, it often precludes the diagnosis³, especially in the absence of concomitant tuberculous focus elsewhere. The characteristic feature of otitis media is multiple perforations in tympanic membrane with profuse otorrhea³. Most commonly, the disease is painless and the tympanic membrane is hyperaemic and bulging. In our patient, the symptoms were non-specific. The presence of ear pain pointed towards the diagnosis of pyogenic aetiology. Whitish granulation tissue in the attic area without tympanic perforation made the surgeon explore the mastoid and the histopathology provided the unequivocal diagnosis of tuberculous otitis media.

Facial nerve palsy has been reported in some cases² and has been regarded as a pointing feature in a painless chronic otitis media. Residual disabilities like conductive deafness and facial nerve palsy have been reported after

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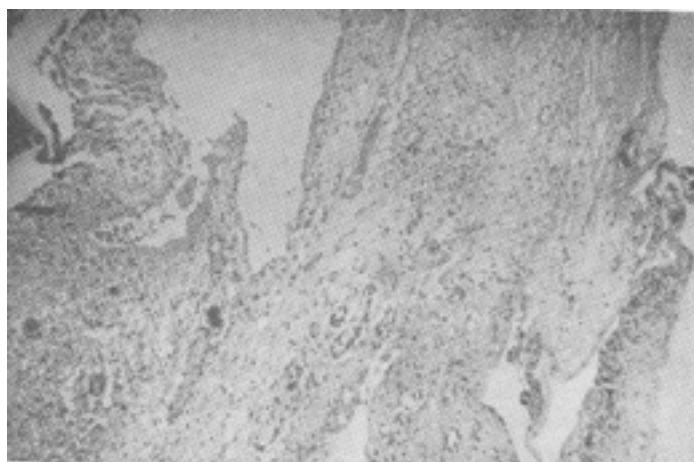


Fig. 1. Section showing bony spicules along with chronic inflammatory granulation tissue with focal areas of necrosis surrounded by Langhans giant cell and epithelioid cells (H & E x 100)

conventional chemotherapy². However, in the present case, short course chemotherapy of 2EHRZ/4HR showed excellent response both in respect of the serous ear discharge and the recovery of left facial nerve function within one month of chemotherapy, aided by clearance of the granulation tissue during the operative procedure. The authors feel that delay in arriving at the specific diagnosis increases the chance of conditions such as fistula formation, labyrinthitis, deafness and intracranial complications. This can be avoided by a high level of suspicion in the initial stages of this

curable condition with modern chemotherapy.

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RECURRENT HAEMOPTYSIS IN ENDOBRONCHIAL ACTINOMYCOSIS
SIMULATING BRONCHOGENIC CARCINOMAV.K. Arora¹, K. Gowrinath² and C. Ratnakar³

(Received on 12.7.93; Accepted on 22.9.93)

Summary : A case of recurrent haemoptysis due to endobronchial actinomyces simulating bronchogenic carcinoma is presented because of its rarity.

Introduction

Pulmonary actinomyces usually presents as a chronic localised inflammatory process with insidious non-specific symptoms such as fever, pain in chest and cough. Endobronchial lesions are extremely rare^{1,2}. We present here a case of endobronchial actinomyces with recurrent haemoptysis.

Case Report

A 45 year old farmer was admitted for recurrent haemoptysis of three years' duration. There was no other significant complaint. Occasional cough was associated with expectoration of small amount of blood stained sputum and at times frank blood. He had been treated with Trimethoprim without any relief. Four years back, the patient had sustained multiple rib fractures with left haemothorax due to a fall.

On examination, the patient was found to have poor oral hygiene, Grade II clubbing and signs of obstructive pneumonitis right upper lobe. The possibility of malignancy as a causative factor was considered. He had a smoking index of > 200.

TLC, DLC and urinalysis were normal. Haemoglobin was 14.5 gm% and ESR 45 mm/1st hour (Wintrobe). Sputum smear and culture

were negative for tubercle bacilli, pyogenic organisms, fungus and malignant cells.

X-ray chest showed a dense opacity over the right upper zone with signs of loss of volume (Fig. 1). Bronchoscopy revealed an intrabronchial growth in right upper lobe bronchial orifice. Biopsy of the growth showed sulphur granules with bluish filaments surrounded by acute and chronic inflammatory cells (Fig. 2) suggestive of actinomyces.

The patient was treated with Benzyl Penicillin 2 mega units six hourly daily for six weeks and then with long acting Penicillin. He showed symptomatic improvement and subsidence of haemoptysis. Repeat bronchoscopy demonstrated melting of the intrabronchial growth and X-ray chest showed just residual fibrotic lesions.

Discussion

Actinomyces in humans is caused by *Actinomyces israelii*. Several strains of Actinomyces are frequently found in human saliva, bronchial washings, tonsillar crypts and dental plaques. The disease affects only those who have these organisms as a part of their normal flora.

Actinomyces tends to colonize devitalized tissues and may occasionally co-exist with chronic tuberculous lesion and bronchogenic carcinoma. However, there is no direct relationship between actinomyces and other specific infections, cirrhosis or metabolic diseases³.

Recurrent haemoptysis due to actinomyces is rare⁴, though it is common in tuberculosis, aspergillosis, bronchogenic carcinoma and

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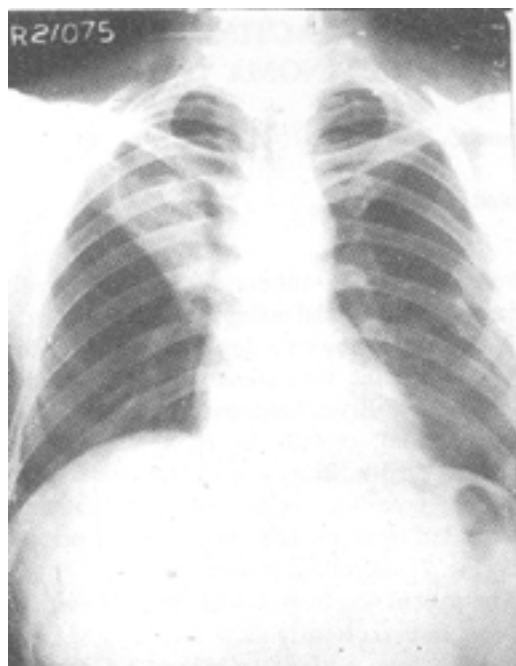


Fig. 1 X-ray chest showing dense opacity over right upper zone with signs of loss of volume, with evidence of healed fracture 5th, 6th and 7th posterior ribs on the left side

bronchiectasis. In our patient, recurrent haemoptysis appears to be due to erosion of neovascularized tissue within the area of fibrosis, since actinomycetes spreads by direct invasion, without regard to tissue planes and causing massive fibrosis.

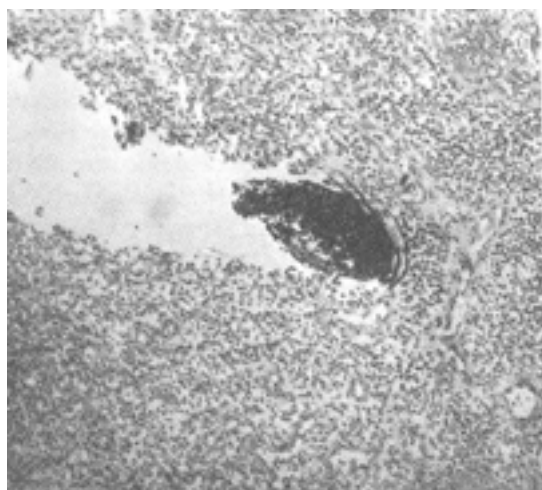


Fig. 2. Photomicrograph showing an abscess with actinomycotic colony in the centre (H&E x 100)

The disease is more likely to be detected incidentally on a routine chest X-ray and/or bronchoscopy. Variable clinical and radiological appearances pose a problem in the diagnosis of actinomycosis^{5,6}. Diagnosis is usually delayed till drainage or aspirated material is available for culture. Sputum culture is not helpful as the organism forms a part of normal oral flora.

The presence of sulphur granules and actinomycotic filaments on histologic examination and excellent response to penicillin therapy point to the definitive diagnosis of actinomycosis.

Penicillin is the drug of choice. Streptomycin, Tetracycline, Chloramphenicol and Cephalosporins have been found to be effective with variable beneficial results. Lincomycin has been used successfully as an alternative to penicillin⁷. But therapeutic response may be slower with drugs other than penicillin with more toxic effects on prolonged use. Though the duration of therapy depends upon the extent of the disease, 90% cure rate can be achieved with 6-12 months of treatment⁸.

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HEPATIC ENCEPHALOPATHY OBSERVED DURING SHORT TERM CHEMOTHERAPY

S.K. Gupta¹ and Sunita Tekchandani²

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Sammay: Acute hepatic encephalopathy In a 55 year old female patient of pulmonary tuberculosis on 12th day of treatment is reported. She had no previous history of liver disease, anti-tuberculosis or any other drug treatment Patient responded to withdrawal of drugs and conservative treatment.

Introduction

Considerable attention has been devoted to study the application of various short course regimens in the national tuberculosis control programme. Short course chemotherapy has been found highly effective in treatment of tuberculosis and majority of patients tolerate it very well. Drug induced hepatitis is occasionally seen in patients of tuberculosis administered both INH & Rifampicin. The incidence of hepatitis associated with jaundice has been estimated at 9-10% in Indian reports^{1,2,3}. We report a case of acute hepatic encephalopathy observed on 12th day of anti-tuberculosis treatment as a rare presentation. Physicians who are generally familiar with the spectrum of hepatitis with jaundice in their patients on short course chemotherapy should be aware of such a serious clinical condition wherein early recognition and prompt treatment would be rewarding.

Case Report

A 55 years old female was admitted with complaints of cough, low grade fever, loss of appetite and weight for two months. She had no history of liver disease and anti-tuberculosis treatment.

On examinations she was febrile (38° C), pulse

was 100/mt, BP). 120/80 mm of Hg. There was no lymphadenopathy, no pallor, no icterus and no rash. Examination of respiratory system revealed crepitations in left suprascapular region. Her pre-treatment investigations : hemoglobin 9.7 Gm/DL, ESR 70 mm in 1st hour, TLC 10000/cumm, DLC P 75, L 23, E 2. Total serum proteins 6.0 Gm/DL. SGOT 15 I.U., SGPT 20 I.U. Sputum for AFB was positive. Urine analysis was normal, chest X-ray revealed cavity and infiltrations left upper zone. The patient received Rifampicin 450 mg. INH 300 mg., PZA 1.5 gm. daily. On 11th day she was noted to be irritable and drowsy. She had jaundice and developed grade IV coma in next 24 hours. Fresh investigation revealed-hemoglobin 9 gm/DL, ESR 82 mm. In 1st hour TLC 11200/cumm. DLC. P 78, L 22. Serum bilirubin 4.2 mg/DL. SGOT 120 I.U., SGPT 150 I.U. HBsAg-negative, urine positive for bile salts and bile pigment. Anti-tuberculosis treatment was stopped and supportive treatment was given in the form of adequate vitamins, nutrition and expert monitoring. The patient regained consciousness after three days and recovered with return of liver functions to normal after two weeks (serum bilirubin 0.8 mg/dl, SGOT 17 IU, SGPT 26 IU, albumin/globulin ratio normal).

Discussion

Drug induced hepatitis is occasionally seen in patients of tuberculosis administered both INH and Rifampicin. This is quite consistent with many reports from India in recent years, since the use of Rifampicin has become widespread. It is more common in patients with previous history of liver disease and alcoholism⁴. In about 1% of treated patients, an illness develops which is indistinguishable from viral hepatitis.

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Approximately half of these cases occur within first 2 months of treatment while in the others, clinical disease may be delayed for months. Liver injury appears to be age related, increasing substantially after age of 35 years. The highest frequency is in patients over age of 50 and the lowest under age of 20 years⁵.

The present case highlights the following :-

1. Fatal reaction like hepatic encephalopathy may occur with anti-tuberculosis treatment.
2. One should monitor liver functions in patients on short course chemotherapy.

Review of literature did not reveal hepatic coma with anti-tuberculosis treatment and the present case illustrates an unusual presentation. The possibility of drug induced hepatic coma which is reversible if given timely attention should be kept in mind⁶.

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NGOs AS PARTNERS IN NATIONAL TUBERCULOSIS PROGRAMME: INDIAN URBAN EXPERIENCE*

D.R. Nagpaul

Introduction

The role of NGOs in the fight against tuberculosis during the early decades of this century had been a glorious chapter in the presently developed countries where tuberculosis is no more a problem and the developing ones where a lot remains to be done.

In that early phase, NGOs strived to create awareness about tuberculosis as a health problem; established model institutions for demonstrating to the government, as to others, how tuberculosis could be diagnosed and treated; trained medical as well as para-medical personnel in how to offer tuberculosis services and, above all, served as a symbol of the community's determination to conquer the disease. No wonder, NGOs were spoken of those days as "conscience keepers" of the Society

However, when governments realised their overall responsibility to the people and began to provide tuberculosis services, the importance of those pioneering NGO efforts and institutions became less. Yet, NGO institutions continued to play an important role because there was a large unmet demand for patient care. This state of affairs evolved into the so-called "complementing and supplementing" of public services role for NGOs. With the emergence of domiciliary treatment and implementation of National Tuberculosis Programme (NTP), however, NGO institutions got completely isolated because all kinds of health institutions started offering tuberculosis services. Financial compulsions have led to the closure of many of them. The few which have kept their doors open to the public are often dependent on government largesse. This scenario hardly befits the earlier pioneering role played by NGOs.

Surely, the health education service rendered by NGOs has remained pre-eminent all along. Besides, in affluent countries where tuberculosis

has declined, some NGOs have their mutual assistance programme to help out the developing countries. Nonetheless, the time has come for NGOs to turn over to the next chapter in their continued struggle against the disease.

A New Rote

In a number of developing countries, with reasonably well organised NTPs, the need is being felt for enlisting greater participation of the people in order to improve the present comparatively less satisfactory case-finding and case-holding rates to epidemiologically more desired levels. For example, in India the overall efficiency of case-finding under NTP has remained around 33% and that of case-holding around 45% for many years.^{1,2} These rates represent the average performance of around 390 District Tuberculosis Programmes (DTP), some including NGO institutions which report to NTP, but not that of the private sector since there is no general notification system in India. Several studies have shown that there is considerable under-utilisation of the public health services, including tuberculosis services. Why should that be so? The urban as well as rural patients' preference for the more accessible and acceptable private practitioner round the corner is well-known. For example, in a study in Maharashtra, among the chest symptomatics in 116 households, 92% had sought medical help for their symptoms. Of them, 67.8% of the rural and 54.1% of the urban symptomatics (overall 62.3%) had first consulted a private doctor while 32.2% and 19.7% respectively (overall 27.2%) had gone to a government/municipal run clinic/PHC facility for relief. Others had resorted to home remedies or collected drugs from pharmacies.³ The social preferences for making first contact with a private doctor, despite the cost of his service, emerges, therefore, as a

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Tables 1 & 2. Profile of two NGOs offering TB Services

	Maharashtra Lokhit Sewa Mandal	Ashwini Kumar Medical Relief Society
Registered	In 1975 for general health objectives	In 1969 for health & nutrition objectives
TB service	Started in 1979	Started in 1982
Objectives of TB Service	Helping poor TB Patients and Community welfare	Cooperation with local family physicians (around 2000), and treating their TB patients at concessional rates; Arranging TB seminars for physicians
Location	Six western suburbs of Bombay	Five suburbs and two central areas
Population	Around 2.5 million, in 3 municipal wards	Around 2.5 million
Funding	Donations by an international agency & drugs from Municipal Corporation	Donations; income form patients; drugs from Municipal Corporation
Facilities	Eight TB sub-centres; average 1 km travel distance. One medical and three paramedics full time in each sub-centre X-ray/sputum examination, treatment and case-holding offered free of charge	Treatment sub-centre in each suburb, within 1 km travel distance, with entire staff of two full time physicians and 6 part time paramedics Extent of concession for each patient (varying from 100% to 60%) recommended by family physicians
Clientele	Attending on own initiative & referred by family physicians	Case-finding done by cooperating family physicians (quality not known) Treatment done by Society on part payment or completely free; 30 family physicians run own treatment sub-centres with the concessional drugs provided by Society
Performance	<p>Case-finding :</p> $\frac{\text{New cases} \times 100}{\text{New outpatients}} \quad 40\%$ $\frac{\text{Sputum positives/New Cases}}{\quad} \quad 30\%$ <p>Case-holding :</p> $\frac{\text{Collected drugs} \times 100}{\text{Expected to collect drugs}} \quad 80\%$ <p>Treatment :</p> $\frac{\text{Completed treatment} \times 100}{\text{Put on treatment}} \quad 85\%$ <p>Case fatality 2.5 to 3.0%</p>	<p>Case-holding :</p> $\frac{\text{Collected drugs} \times 100}{\text{Expected to collect drugs}} \quad 70\%$ <p>Treatment :</p> $\frac{\text{Completed treatment} \times 100}{\text{Put on treatment}} \quad 41\%$
Remarks	From 1979 till 1993, 20,924 new cases treated and average Rs. 1300/-spent per patient,. Average yearly achievement 1,500 cases	From 1982 till 1992, 8, 042 patients treated. Yearly average a little over 1,000. Case-holding and treatment completion poor

significant factor. However, when symptoms become more severe or the funds dry up, many of them go to the public service institutions where the attitude of the staff and the quality of service leaves much to be desired. There are, in fact, multiple and complex reasons for this state of affairs' and an intervention by NGOs, as representatives of the people, could provide a way out of the difficulty.

Mathematical models constructed with the help of the relevant parameters in India have shown that with the present less satisfactory levels of case-finding and case-holding, the decline in tuberculosis could not be better than the natural decline of the disease.⁴ This conclusion is supported by several small epidemiological surveys carried out since the National Sample Survey of 1955-58 which show very little or no decrease in prevalence rates. Assuming, therefore, that the said mathematical model is realistic, it has been calculated that the case-finding efficiency must improve to around 70% and treatment efficiency to around 80% in order to reduce tuberculosis by around 10% per annum.⁴ That may not be possible without further expanding and considerably strengthening the NTP infrastructure and inputs. This becomes all the more compelling in view of the AIDS epidemic which is knocking at the doors of India and the neighbouring developing countries. One way of doing so would be to invite NGOs to help more directly in the NTP.

In September, 1991, the Government of India held a high level national workshop to review the problems facing the NTP. Among the accepted recommendations of that workshop is the provision for inviting NGOs to help in programme planning, implementation and assessment as partners in NTP.⁵

Urban experience

However, even before NTP came under closer scrutiny of the government, a few NGOs in the metropolitan cities of Bombay and Delhi had started taking new directions during the last decade or so in the true spirit of NGO work. Projects were started to remove the weaknesses of NTP according to their perceptions and felt needs of the community. A few examples can be given:

Table 1 is the profile of the Maharashtra Lokhita Sewa Mandal project modelled on the traditional complementing/supplementing effort of NGOs. Though helpful, the effort suffers from similar weaknesses as that of NTP because the pattern of work is similar. However, case-holding and treatment completion are much better.

In Table 2, the profile of Ashwini Kumar Medical Relief Society's project shows what could be achieved by providing a case-holding service to the private practitioners and tailoring the cost of treatment to the financial status of TB patients. It can be seen that there is no control over case-finding and case-holding as well as treatment completion are relatively poor.

In Table 3 is shown how the C-Ward Medical Association of the local private practitioners went about dealing with diagnosis and treatment compliance of their patients. While case-finding is poor, case-holding and treatment completion are better but the yearly output is small.

Table 4 shows the paradigm effort of the Disaster Relief Project of the Delhi Cheshire Home, an NGO that has its headquarters overseas. The project's mobile van takes tuberculosis service to the doorstep of urban slum dwellers who do not have a proper access to NTP service, at a time convenient to the poor wage earners. Case-finding as well as case-holding are good but the output could have been better, if the slum dwellers had cooperated better.

These examples underline (1) the useful role that small local NGOs can play, (2) how desperately private practitioners need assistance in providing good case-finding and case-holding service to their patients and (3) the crucial importance of ensuring an adequate and free supply of anti-tuberculosis drugs.

The Indian urban experience suggests two areas where NGOs can step in smoothly and help extend as well as upgrade case-finding and case-holding in the cities:

(1) As a first step towards enlisting people's participation in NTP, to convince and involve in NTP the local private practitioners, who are more acceptable to the people. In fact, practitioners in Bombay have already tried to put up projects in that direction but do not seem to have succeeded too well. Later, these private practitioners can be made the entry point for

Tables 3 & 4. Profile of two NGOs offering TB Services

	3 C-Ward Medical Association	4 Delhi Cheshire Home Mobile TB Clinic Project
Registered TB Service	In 1950 with general health objectives Started in 1981	Started in 1989 in selected Delhi Slums
Objectives of TB service	Free SCC to poor TB patients of C-Ward Medical Association members; Improving treatment compliance by arranging treatment through family physicians	Case-finding through Community symptoms-screening, twice/thrice weekly, efficient sputum/X-ray diagnosis; efficient case-holding/treatment; health education-people's participation
Location	C-Ward of Bombay Municipal Corporation	Five slums without a TB service
Population	About 1.5 million	0.1 million
Funding	Donations; membership fee from 500 physicians; drugs from Municipal Corporation	Donations by international agency, contributory X-ray diagnosis by another NGO; contributory drugs from Government
Facilities	One centre with X-ray and sputum examination pay facility, where volunteer experts make the diagnosis and prescribe treatment; poor patients get drugs free, others buy drugs; own physician gives injections and supervises treatment compliance, with follow up done from Centre	Mobile Clinic with microscopy, working in the evening hours One part time TB specialist and 6 paramedic
Clientele	Mainly 80 member physicians refer cases for confirming diagnosis and prescribing proper regimen; drugs are sent to own physician who ensures treatment compliance	Symptomatics in the Community
Performance	<p>Case-finding:</p> $\frac{\text{New cases} \times 100}{\text{New Patients Investigated}} = 6\%$ <p>Case-holding :</p> $\frac{\text{Collected drugs} \times 100}{\text{Expected to collect drugs}} = 86\%$ <p>Treatment :</p> $\frac{\text{Completed treatment} \times 100}{\text{Put on treatment}} = 80\%$ <p>Case fatality 3%</p>	<p>Case-finding :</p> $\frac{\text{New cases} \times 100}{\text{New symptomatics}} = 18\%$ <p>Case-holding :</p> $\frac{\text{Collected drugs} \times 100}{\text{Expected to collect drugs}} = 85\%$ <p>Treatment :</p> $\frac{\text{Completed treatment} \times 100}{\text{Put on treatment}} = 70\%$ <p>Case fatality 3%</p>
Remarks	From 1982 till 1988 around 15,000 patients investigated, 820 patients treated and 660 completed treatment. Average yearly achievement 137 cases	From October 1989 to March, 1993, total 3248 symptomatics examined, 605 cases diagnosed and treated. Average yearly achievement 200 cases

convincing and involving the people in the programme through a change in their health behaviour.

(2) In large cities, sizeable gaps exist in the NTP coverage of the population. Large chunks of population in slums and outgrowing urban fingers do not have either access to established services or private practitioners, often not even civic amenities and transportation. Since tuberculosis may be breeding more rapidly in such places, NGOs must step in to provide the service till, eventually, the public services reach them.

People's Participation

Studies have shown that one of the main reasons for under-utilisation of the provided services is health behaviour, which at present is not commensurate with the much higher levels of awareness of the people about the disease and the facilities that have been provided to deal with it. Therefore, NTP managers have been suggesting for quite some time that greater people's participation could correct under-utilisation, but without coming up with concrete plans how that could be done. One way of doing so has already been discussed. Namely, making the area private practitioners a part of the NTP network. For doing so, several principles have to be kept in mind because it has already been seen that expecting private practitioners to merely refer their cases to the Area Tuberculosis Centre (ATC) is expecting too much. Actually, a pattern of involvement has to be evolved which is acceptable to both the public and private sectors. In respect of case-finding by private practitioners, it has to be ensured that the diagnosis is scientifically correct and not just clinical. The drug regimens prescribed too have to be scientifically correct and proven. Supplies of anti-tuberculosis drugs have to be sufficient, so that every patient, irrespective of who treats, can get free drugs for the entire period of treatment. There has also to be an effective case-holding mechanism, in which responsibility for registering default and taking defaulter action is clearly demarcated and shared. And, lastly, there must not be undue financial or organisational load on the private practitioners, who invariably tend to avoid them.

Small local NGOs, as evidenced by our urban experience, hold the best promise of bringing Area Tuberculosis Centres and private practitioners closer, within the overall NTP network. This simple step may increase case-finding performance by 50% to 100% numerically and raise the treatment completion rate from around 45% to around 80%. The gains in case-finding and case-holding apart, it is difficult to see how people's participation in NTP could be obtained without taking their private doctors along.

Small local NGOs can also set up, without much difficulty, subsidiary drug distribution centres for each ATC, to enable their patients to collect drugs nearer their homes and at more convenient hours. This step will directly upgrade case-holding of ATCs. Besides, friends and relatives of the patients who come to collect drugs, and happen to have suggestive symptoms could be referred to the ATC for a check-up. These drug distribution centres are to be staffed by the volunteers of the local NGO and shall work in close collaboration with the ATCs.

A Suggested Plan of Action

Encouraged by our urban experience, the Government of India has accepted in principle that the Tuberculosis Association of India (TAI), as the national NGO, shall be the umbrella organisation to join hands with them in the planning, implementation and assessment of NTP. The TAI has an infrastructure that extends within all the States in the country in the form of 25 affiliated State TB Associations. There is a large number of district Associations as well, which is expected to greatly facilitate the partnership role already mentioned. The strength of an NGO lies at the grassroots because of its social service inspired by altruism. Today's NGOs are organisationally reasonably strong. Besides the "do gooders", there is an adequate number of professionals who join NGOs in search of careers, besides becoming an instrument of social change. And, increasingly, the NGOs are having more liberal access to funds, national as well as international, because their functioning is highly cost effective. NGOs are therefore worthwhile partners in NTP.⁶

On its part, the TAI has accepted the

responsibility for identifying all such NGOs in the field of health, mostly in the cities, which are already engaged in or are ready to take up anti-tuberculosis activities and for coordinating and assisting their activities.

The fulcrum, however, has to be the small local/suburban NGO, in each area. These may have to be set up, *de novo*, with the help of local influential people and the natural community leaders. After being set up, a local NGO should start collecting funds by the sale of TB seals and enlisting donations, till the results of its activities become visible enough to ensure a regular and automatic flow of funds. The local NGOs must establish rapport and close working relations with the area private practitioners and the ATC. Then, it can explain to them how it will function as a liaison between the two and the people. Under the scheme, those TB patients who prefer to take treatment from practitioners of their 'choice' will be allowed to do so. However, the local NGO will ensure that such patients have access to proper sputum microscopy and x-ray, if necessary, without repeated visits and prolonged waits. After scientific diagnosis, the ATC shall arrange the required supply of antituberculosis drugs for each patient. And, if a patient has to receive treatment from the private practitioner, ATC shall route his drug supply through the local NGO. Full responsibility for storing drug supplies, distributing drugs fortnightly to private practitioners and keeping records of regularity of treatment of each such patient will be that of the NGO. Over and above this, the NGOs reimburse

a token, agreed payment to private practitioners for each patient who is properly diagnosed and, later, completes his treatment, in order to partially compensate him for the time and efforts spent by him. The responsibility and liability for making such payments is that of the NGOs alone. One such plan of action is about to be started in Delhi. The close networking involving all concerned, and extending right upto the TB patient, is bound to boost NTP performance as well as attract people's attention leading to their participation in NTP.

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COHORT STUDIES

G.P. Mathur*

Historically, the term "Cohort" was first used in the construction of life tables. In this context it meant, originally, a group of persons, all born on the same day, who were followed for a certain period (ideally, through life) to obtain information about such vital statistics as probability of death (or survival) in successive years, probability of attaining any particular age, probability of dying between any two selected ages, expectation of life, etc. All these concepts were of great interest to actuaries and those concerned with life insurance. By extending the definition of cohort, such life tables could also be constructed for all persons born, say, within any particular calendar year. It can be seen that such a cohort analysis could provide useful indices about mortality and survival rates, unaffected by the age structure of the population. Also, such an analysis could facilitate comparisons between one place and another, one period and another, one community and another, and so on. However, since the construction of cohort life tables necessarily entails a long period of waiting in order to collect data, it is seldom resorted to in actual practice and an alternative method, 'the current life table method' is usually employed.

The term 'cohort', is now used in an even broader sense than before in medical statistics. A cohort can now be described as a group of

subjects which is precisely defined at the outset and of which the composition remains unchanged throughout the study except for losses due to death, migration, lack of follow up data etc. but to which no new subject may be added. Thus, for example, a group of patients suffering from the same disease and completing the same treatment successfully at a particular institution during 1990 may be said to form a cohort. If we were interested in finding the probability of relapse or death or any other event which can happen only once, we could observe this cohort for the necessary period. Suppose we were interested in calculating relapse rates for the ensuing three years, we could collect data as shown in Table 1. As we can see, of the 400 patients who formed the cohort, 14 were lost sight of, 2 died of causes not related to the disease (e.g. road accident), 32 relapsed and the remaining 352 were still healthy at the end of the first year. Since the 16 persons who were lost sight of or died of irrelevant causes were exposed to the risk of relapse only for part of the year, we may assume, as an approximation, that they were present and exposed to the risk of relapse for half a year and, therefore, in effect the number of persons at risk was $400 - 16/2 = 392$. Thus, the probability of relapse during the first year was $32/392 = 0.082$. The probability of not relapsing during the first year can now be

Table 1. Calculation of cumulative probabilities of relapse during 3 years' follow up (Hypothetical data)

Year	Persons at start of year	Lost sight of during year	Died of other causes during year	Relapses during year	Relapse rate during year	Non-relapse rate during year	Cumulative non-relapse rate upto end of year	Cumulative relapse rate upto end of year
1	2	3	4	5	6	7	8	9
1	400	14	2	32	0.082	0.918	0.918	0.082
2	352	13	3	20	0.058	0.942	0.865	0.135
3	316	10	2	12	0.039	0.961	0.831	0.169

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obtained as $1-0.082 = 0.918$. After excluding the persons who were lost sight of or died or relapsed during the first year, we have 352 persons available for study at the start of the second year. Proceeding as before, we may calculate the probability of relapse during the second year as $20/344 = 0.058$ and the probability of not relapsing as $1-0.058 = 0.942$.

Similarly, the probabilities of relapsing and not relapsing during the third year are found to be 0.039 and 0.961 respectively.

We can now proceed to calculate the cumulative probabilities of not relapsing or relapsing. Since the chances of not relapsing in the first and second years may be regarded as independent of each other, the cumulative probability of not relapsing in the first two years is calculated as $0.918 \times 0.942 = 0.865$. The probability of relapsing in either the first or the second year is complementary to this i.e. $1-0.865 = 0.135$. Again, by the same logic, the probability of not relapsing in the first three years is calculated as $0.918 \times 0.942 \times 0.961 = 0.831$. The probability of relapsing in either the first or the second or the third year is therefore $1-0.831 = 0.169$. In percentage terms, the cumulative probabilities of relapsing by the end of the 1st, 2nd and 3rd years may, thus, be expressed as 8.2%, 13.5% and 16.9% respectively. If it is necessary to make a comparison between two groups e.g. patients treated with short course chemotherapy with those given conventional treatment for whom data similar to Table 1 are available, this can be done using cohort analysis.

It is necessary to sound a note of caution regarding the persons 'lost sight of in the above example. The calculations proceed on the assumption that these are a random lot and their dropping out of the study is not related to the

probability of relapsing. If this assumption is open to doubt, the entire basis of the calculation collapses and the results would be biased. For this reason, it is important to ensure that their number is as small as possible.

Cohort studies, although difficult to organise and usually time consuming, can also be used to investigate the association between a certain risk factor and a particular disease. Theoretically, they are better suited for this propose than case-control studies which, inspite of their many practical advantages, are often exposed to several kinds of bias that may occur in selection, misclassification, etc. and which require comparatively sophisticated analysis and in which the choice of appropriate controls is not always easy.

In cohort studies, a sample of individuals, some exposed to the risk factor under study and some not so exposed, is followed up for an appropriate length of time and the incidence of a disease in the two groups during this period furnishes the basis for making a comparison and drawing conclusion regarding the strength of association between the risk factor and the disease. Thus, for example, we may follow a group of 3,000 healthy family contacts of TB patients and a control group of 5,000 healthy persons who have had no such contacts, for a period of three years, the two groups being more or less similar in all respects except this 'risk factor'. Suppose further that the number of new cases of TB developing in the two groups during this period is as shown in Table 2. One can see that 4% of the contact group and 1% of the control group developed the disease leading to a Relative Risk (incidence among exposed/incidence among non exposed) = 4.0. Obviously, the farther the Relative Risk (RP) is from 1, the stronger the association between the 'risk factor'

Table 2. *New cases of TB developing among family contacts of patients and persons without such contact (hypothetical data)*

	Developed TB	Did not develop TB	Total
Family contacts	120	2880	3000
Persons without family contact	50	4950	5000
Total	170	7830	8000

and the disease. To determine whether this association is real or merely a chance phenomenon, we carry out a "test of significance", in this case the usual χ^2 test which, gives $\chi^2 = 79.7$ for 1 d.f. $P < 0.001$. Incidentally, this value of χ^2 can also be used to give an approximate estimate of the confidence interval for the RR calculated earlier, viz. 4.0. The lower limit of the 95% confidence interval is given by $(RR)^{1-1.96/\chi}$ and the upper limit $(RR)^{1+1.96/\chi}$, χ being the square root of the χ^2 value already

obtained i.e. $\sqrt{79.7} = 8.93$. In this particular instance, the approximate 95% confidence interval can be calculated as $(4.0)^{1-1.96/8.93}$ to $(4.0)^{1+1.96/8.93}$ i.e. 2.95 to 5.43. Thus, we can conclude with 95% confidence that the Relative Risk lies somewhere between 2.95 and 5.43.

The examples of cohort analysis given above are only illustrative. Research workers can think of other situations in their field of speciality where such studies may provide the best method of dealing with data while avoiding bias.

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I, Ashok Sachdeva, Secretary-General of the Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001, hereby declare that the particulars given above are true to the best of my knowledge and belief.

ASHOK SACHDEVA

On behalf of the Tuberculosis Association of India.

AIDS KALEIDOSCOPE

CD 26

Researchers at the Pasteur Institute in Paris have recently identified a new molecule which enables the HIV to invade a human cell, and have labelled it as CD 26. The role of this molecule remains the same for the different strains of the HIV isolated so far. Until now, the existence of only a receptor molecule called CD 4 was known. The CD 4 enables the HIV to attach itself to the human cell but what enables HIV to infect the cell was not known. Now, the enzyme CD 26 - Depeptidyl Peptidase IV - provides the missing link. Independently, Australian researchers have cloned and genetically mapped this molecule, opening up the prospects for exciting future discoveries.

The discovery of CD 26 has immediate implications in the twin fields of a vaccine against AIDS and chemotherapy to cure AIDS : If a vaccine or drug could inhibit the activity of CD 26 in the body, then the virus would not be able to enter human cells even when introduced into the body. This proposition appears fairly similar to the already observed "superimmunity" found in some people who despite indulging in high-risk behaviour with HIV positive persons remain free of infection. Work on a vaccine against AIDS had until now focused on enabling the body immune system preventing the multiplication of the virus in the body rather than blocking its access to human cells.

Genetic Key

The genetic mapping of the CD 4 and CD 26 molecules has "opened the way for a potential manipulation of body's locks" against HIV. Besides, a synthetic protein has been found which inhibits the *in vitro*- growth of HIV in the laboratory. Both "protein therapy" and the genetic key hold the possibility of preventing the HIV seropositives developing into full blown cases of AIDS.

Kits

Two of the most widely used ELISA kits in

India and one of the rapid tests, Immunocomb, have been found to be not so reliable, after a cross-checking done in France. Such faulty kits could be the reason why a batch of anti-RHD injections was found to be HIV positive after all the precautions had been taken. Besides the Immunocomb process, which is probably the cheapest available, there are several others tests, such as the Recombinant DNA process, Immune-fluorescent Antibody Technique, Nucleic Acid Tracing and the Western Blot Test.

In the context of the problem posed by "defective" AIDS kits which have comparatively lower sensitivity and specificity, allowing some HIV positive persons to escape detection and others to be wrongly labelled, it must be mentioned that several serious errors have already occurred in France and Germany besides India, presenting a nightmarish, scenario. "Tainted" blood products have been transfused to scores of patients, who cannot now be traced back, before these products were found to be defective. It has been estimated that in India as many as 12% of HIV seropositivity may be due to transfusion of "tainted" blood products because of the known less than rigorous controls, especially in some commercial blood banks.

Australia's contribution towards detecting HIV seropositivity has been in the direction of reducing the time of testing to two minutes. It comprises the addition of a reagent to a drop of blood. The sensitivity of the quick test is said to compare well with the standard ELISA test although it may declare a slightly higher proportion of specimens as false positive.

DISEASE AND GENETICS

The human leucocyte antigen (HLA) in the nucleus of the human leucocyte cells has been found to be responsible for determining the natural susceptibility or resistance of people to diseases like tuberculosis, leprosy, etc. The HLA derived from genes, inherited from parents, appears to regulate the immune response in the body and is highly specific even in similar ethnic groups. Thus, people having the DR₂ gene in the leucocytes were found to be more prone to develop tuberculosis, and yet why all those having

DR₂ gene did not do so is not understood. Perhaps, one of the 11 sub-types of DR₂, already recognised, determines this characteristic. Thus, finding of the DR₂ role in natural susceptibility needs further scrutiny.

It has been reported, for example, that people of Indian, Pakistani and Bangladeshi origin living in England and Wales have a 40 percent higher than average risk of developing coronary heart disease. And, diabetes is five times more common among South Asians than Europeans. Also, Asians under 40 years of age are three times more prone to heart attacks than the national average rates. The usual risk factors related to heart disease-smoking, high blood cholesterol and stress level, etc.-were found to be similar or even lower among the Asians compared with Europeans.

The French Academy of Sciences has claimed to have developed a map of the human genome which could help in the detection and cure of many crippling diseases. Each segment of the DNA molecule contains about 100,000 genes, scattered among an enormous number of DNA base pairs. For genome mapping, the DNA was cut into pieces and each piece was cloned and cut further into smaller fragments. Each fragment was then "finger printed" to detect overlapping, if any, and the process was repeated till each fragment was pure and ready for putting it back together again, thus enabling the determination of the exact location of each gene in the genome. Further genetic research and genetic engineering are expected to revolutionize not only diagnosis and therapeutics but allow even prediction of diseases a new born child may suffer from later in life, by studying his genetic map. The last possibility is fraught with risks as it is also likely to raise many an ethical controversy and pose many legal problems for the medical profession.

TUBERCULOSIS: THE EGLECTED EPIDEMIC

According to WHO, "decades of national and international neglect of tuberculosis have led to the death of tens of millions of people". The disease now kills annually 3 million people worldwide, leading to WHO declaring it as a

"global emergency" in April, 1993, to undo the "past neglect of TB by Governments in all, WHO regions together with a declining scientific interest in infectious diseases that seemed no longer important in the industrialized world". It appears to WHO that a primary cause of the resurgence of TB in the rich countries has been the inadequate funding of international programmes for combatting tuberculosis in the developing world where 95% of TB sufferers reside. Isolationist public health policies, obviously, do not pay. In the US, where the number of TB cases was declining at 6 per cent per annum till 1985, the decline has been halted and the yearly incidence has doubled. The resurgence in TB in U.S. has been linked with the HIV epidemic, but now an epidemic of "multidrug resistant TB" is posing an equally grave threat there. According to WHO sources, "It will be impossible to control TB in industrialized nations unless it is sharply reduced in Africa, Asia and Latin America". The WHO global TB programme, therefore, aims at cutting the estimated 3 million deaths yearly to 1.6 million in the next 10 years. For this, it is estimated, about \$ 100 million need to be spent each year in providing microscopes, drugs and infrastructure.

Keeping in view the resurgence of interest in tuberculosis, the IUATLD has restated its role and objectives as follows :

"The target of activities of the IUATLD in relation to tuberculosis is to provide the organizational skills and to help generate the resources needed to stop the transmission of tuberculous infection in society, to maintain the fight against tuberculosis until the last remaining heavily infected cohorts have completed their life span and thereby to ensure the elimination of this disease from the ecommunity".

ASTHMA AND AIR POLLUTION

A sudden upsurge in asthma, especially in children, has been reported in the western industrialized and many developing countries. In Britain, there are more than 3 million registered cases and the number of deaths among them has doubled in recent years. One out of seven

children in U.K. and one out of 10 in Delhi schools suffers from asthma. The rise has been ascribed to the alarming rise in air pollution, especially in and around cities where the number of cars keeps multiplying, and in the industrialised areas. But a detailed review of studies on air pollution conducted by U.K. Department of Health has failed to establish any connection. Smoking and household allergens are the alternative causes, but the reasons for the sudden upsurge in asthma are not clear. The radical change in policies required to dean up urban air pollution, which could provide the final evidence, appears to be beyond the capability of most urban authorities, here as well as in the west.

MOLECULAR DNA TECHNOLOGY AND TUBERCULOSIS

The advances in molecular DNA technology and their application in mycobacteria have given everybody a hope not only of understanding their biological properties but also of finding ways to control tuberculosis in the near future. The discovery of genes responsible for imparting drug resistance to two most important drugs, Isoniazid and Rifampicin, has already generated a lot of interest not only among molecular biologists but also in physicians who treat patients of tuberculosis, particularly multi-drug resistant tuberculosis (MDR-TB). These discoveries will make it possible for scientists to understand the mechanism of action of these drugs and also find out how these organisms develop resistance against these drugs. This will further enable us to find ways to counter these mechanisms or to modify or find new drugs, which can act on these resistant organisms.

The 'luciferase reporter mycobacteriophage' (LRM) test developed in Dr. W. Jacob's laboratory at Albert Einstein College of Medicine, Bronx N.Y. will help in finding out the drug resistance pattern of the bacilli in just two days instead of four weeks.

The LRM system, once made specific by using specific phages will help to screen the new drugs against mycobacteria in a very short time,

thus making available newer drugs faster. This system will also help to reduce the cost of

A recent report in *Science* (Vol. 261, Sept. 10, 1993, p. 1390) by the team led by molecular epidemiologist Dr. Lee Riley of Cornell University N.Y., will help to break the code for the invasion of macrophages by tubercle bacilli. They have created a recombinant *E. coli* that mimics some of the traits that make *M. tuberculosis* such a deadly pathogen. The team has, for the first time, cloned a DNA fragment from *M. tuberculosis* that allows the pathogen to invade, survive and multiply inside the macrophages. This will enable researchers to look through the waxy layers of AFB and get an insight into the molecular basis of virulence. To find the genes responsible for the bacterium's ability to invade and grow inside the macrophages, Riley's team inserted random DNA fragments from the *M. tuberculosis* genome into *E. coli*. The *E. coli* is not an intracellular organism and normally does not invade human cells, but Riley's team eventually found a 1535 base fragment of *M. tuberculosis* DNA which, when inserted into *E. coli*, could invade cultured human epithelial cells, called Hela Cells. The researchers further fragmented 1535 base fragment into two smaller units. The initial 850 base fragment was found to be responsible for cell invasion, while the remaining 685 base fragment seemed to help the organism survive and grow inside the macrophages. The researchers have discovered a protein that seems to be encoded by the 1535 based fragment. Once this 52 kilo Dalton polypeptide is purified, its functions will show how the invasion of the macrophages by *M. tuberculosis* can be stopped or impaired.

The work so far done is in a model organism and not in the TB pathogen itself. It may be years before this can happen because of the technical difficulties inherent in working with mycobacteria. The researchers are optimistic that ability to manipulate the mycobacterial chromosome will eventually lead to the development of a vaccine which can prevent the invasion of macrophages by tubercle bacilli.

FORUM

Sir,

I am happy to put on record the progress made by the *Indian Journal of Tuberculosis* and the revitalization of the working of the Standing Technical Committee of the Tuberculosis Association of India. Myself and my colleagues have just returned after attending the Bhopal Conference, which was a great success and highly educative.

The *Indian Journal of Tuberculosis* published by the Tuberculosis Association of India has undergone a sea change and looks almost like an international journal, both in its get-up and the standard of articles selected for publication.

Dr. C. Srinivasa Rao

TB Association of Andhra Pradesh

Sir,

The publications in the *Indian Journal of Tuberculosis* have been very useful to us as reference material for our clinical meetings at the RST Cancer Hospital and Research Centre, Laxminagar, Nagpur. We are now working on the co-existence of TB and lung cancer. Kindly give the references/articles published in the *Indian Journal of Tuberculosis* in order to help us in our project planning.

A.K. Anwikar
Nagpur

In recent years, the *IJT* has published 2 articles on the subject (1987, 34,204 and 1990, 37,157) and the references given therein may meet your need. A Medline search could provide additional material.

Editor

Sir,

I read the case report entitled "Allergic bronchopulmonary aspergillosis : progress of early disease to bronchiectasis - a case study" by Gaur et al¹ with much interest. While the article was in press, a larger series of ABPA-S (allergic bronchopulmonary aspergillosis seropositive without central bronchiectasis) leading later to ABPA-CB (with central bronchiectasis) was reported by Greenberger et al², an internationally acclaimed authority on ABPA. They concluded that ABPA-S represented the earliest stage or, apparently, a less aggressive

form of ABPA. It has also been reported that ABPA may complicate 1% to 2% of all cases of chronic asthma². Sometime back, while screening 330 asthmatics for aspergillus precipitin by agar gel double diffusion (DD), counter immunoelectrophoresis (CIEP), and enzyme-linked immunosorbent assay (ELISA) methods, we found that precipitins against *Aspergillus* species were detectable in 7.88% of cases by DD and CIEP, but ELISA method showed 20% of cases to be having antibodies to *A. fumigatus*³. We had then concluded that ABPA could be detected, in the early course of the diseases, in bronchial asthmatics using a highly sensitive technique like ELISA³. Part of the above jigsaw puzzle has now been solved by the long term follow-up of frank ABPA patient^{1,2}, i.e. ABPA-S leading to ABPA-CB. However, a similar, long term follow-up of seropositive chronic asthmatics, is required to prove definitely our earlier conclusion³, so that, we can authentically opine that seropositive chronic asthmatics, ABPA-S, and ABPA-CB are within the spectrum of the same disease, where serum conversion is the earliest phenomenon and ABPA-CB is the intermediate phase, which when untreated can end up in Stage-V, as per the clinico-radiological staging of ABPA, by Mendelson et al⁴.

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NEWS & NOTES

FORTYNINTH NATIONAL CONFERENCE

The 49th National Conference on Tuberculosis & Chest Diseases is scheduled to be held at Pondicherry from October 6-9, 1994. The Conference will be held at Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Pondicherry. The discussion-topics selected for this Conference are : (1) Management of bronchial asthma or fiberoptic bronchoscopy; (2) National TB Programme including its assessment; (3) Follow-up studies on patients completing short course chemotherapy; (4) Management of treatment failure cases under field conditions; (5) Newer diagnostic methods in tuberculosis and (6) Smoking and tuberculosis. Free communications would, as usual, be eligible for presentation. In addition, there is likely to be a Continuing Medical Education Programme during the Conference. Those who wish to present papers may kindly send three copies of an abstract of their paper before 29th April, 1994, to the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001.

COHORT REVIEW OF PAPERS RECEIVED

Readers may be interested in the findings of an exercise carried out recently to assess the number, nature and subject matter of papers received for publication in the Indian Journal of Tuberculosis. In all, 50 papers were received during 1993; 7 dealt with clinical trials, 8 with other clinical aspects of pulmonary tuberculosis, 8 with extra-pulmonary tuberculosis, 10 with bacteriology and other laboratory studies, 2 with epidemiology, 11 with case reports and 4 with other subjects. Of the 50 papers received, 16 were accepted straightaway and all except 4 of these have already been published. Another 20 were adjudged unsuitable and authors were informed accordingly. Three papers are still under consideration of the Editorial Board. The remaining 11 were referred back to the authors with suggestions for improvement on the basis of the peer review. Revised versions have so far been received from 7; out of 7, four were found

to be acceptable - three have already been published.

CONTINUING MEDICAL EDUCATION

The Tuberculosis Association of Andhra Pradesh organised a Guest Lecture on "Cor Pulmonale" by Dr. V.K. Arora, Director-Professor & Head, Department of TB & Chest Diseases, JIPMER, Pondicherry on 12th February, 1994.

TB DETECTION & BCG VACCINATION CAMP

Tuberculosis Association of Cuddapah district in Andhra Pradesh organised a TB Detection & BCG Vaccination Camp on 18th and 19th November, 1993, at Maddanur, Cuddapah District. The Camp was inaugurated by Dr. Purushotham Reddy, M.L.A.; Dr. R.N. Reddy, Honorary Secretary, District TB Association, Cuddapah, presided over the function. About 150 patients were X-rayed and their sputum examination was done.

HEALTH CHECK-UP CAMP

A general Health Check-up Camp was organised at Anneparthi Village, Nalgonda Mandal in Nalgonda district on 21st November, 1993, under the joint auspices of the Tuberculosis Association of Andhra Pradesh and the Cosmopolitan Employees' Cultural Association. The Camp was inaugurated by the District Medical & Health Officer, Nalgonda and presided over by Dr. C. Srinivasa Rao. About 20 doctors belonging to various disciplines of medicine (allopathy and homeopathy) participated. All the eligible children were given BCG vaccination. About 1,500 patients were medically examined out of which 18 TB cases were diagnosed. All these 18 persons were old cases.

TB WORKERS' CONFERENCE

The Tuberculosis Association of Kerala and

the Ernakulam TB Association jointly organised a state level Conference of TB Workers on 23rd January, 1994, at the International Hotel, Ernakulam. The Conference was inaugurated by Sri Gopalakrishna Pillai, IAS, Secretary to Government (Health and Family Welfare), and presided over by Mr. K.R. Rajan, Chairman & Managing Director, TELK.

HEALTH EDUCATION

The Government of the National Capital Region of Delhi and Health Care Foundation of India organised a public health education programme as "PERFECT HEALTH MELA" from 12th to 19th December, 1993 at Talkatora Gardens, New Delhi. The main objective was to disseminate the message of health to the general public. A commemorative

postal stamp was also released by the President of India. Many NGOs actively participated in this Mela.

Delhi Tuberculosis Association put up a stall in which health education panels on tuberculosis were displayed. Throughout the Mela, Video Cassettes were played on TV showing short health education scripts on tuberculosis. About 40,000 visitors from all walks of life visited the stall.

OBSERVANCE OF ANTI-TB WEEK - 17TH TO 23RD FEBRUARY, 1994

The Tuberculosis Association of India, Central Office, and the State affiliates observed the Anti-TB Week from 17th to 23rd February, 1994, as an important part of anti-tuberculosis work undertaken by them.

ERRATA

In the paper "Prevalence of pulmonary tuberculosis in a Periurban community of Bangalore under various methods of population screening", published in the January 1994 issue of the Indian Journal of Tuberculosis, the following may be added after the first sentence under 'Acknowledgements' on page 26:

The authors are thankful for the efforts put in by the staff of Sociology Section in the data collection of the population screened and the conduct of the study.

In the same paper, under References on page 27, SI. No. 4, instead of 'Chandrasekhar, A.K.', please read 'Chakraborty, A. K.'

The Indian Journal of Tuberculosis

ABSTRACTS

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BCG INDUCED PROTECTION IN GUINEA PIGS VACCINATED AND CHALLENGED VIA THE RESPIRATORY ROUTE

Lagranderie, M. et al. *Tubercle and Lung Disease*; 1993, 74, 38.

In order to verify and develop knowledge about the mode of action of BCG, which has shown variable results in protection against adult pulmonary tuberculosis (as seen in the Chingleput trial), and epidemiological evidence that inhaled *M. tuberculosis* do confer a degree of immunity on 90-95% of the population affected, an experiment was designed. This involved 44 purebred and uniformly reared guineapigs, vaccinated by aerosol (3 groups of 4 each) and intradermal routes (7 x 4) with BCG 10⁵ and one group of 4 given intradermal saline. After challenge with virulent organisms, the mean number of primary lesions was 0.75-2.25 among the aerosol vaccinated as against 3.00-4.75 among those vaccinated by intradermal route, and 6.25 among those given saline.

A further group of guineapigs was then given higher dose of aerosolised BCG (5 x 10⁶). Both groups showed numerous microgranulomas in lungs, containing lymphocytes, histiocytes and rare neutrophils, but no giant cells or necrosis, from day 7. These became more numerous till day 28, and then started regressing, disappearing by day 70. After higher dose vaccination, BCG colonies were recovered from lungs, hilar and cervical lymph nodes, none of which suppurred, and had similar granulomata, with similar behaviour.

Delayed hypersensitivity to PPD was similar in both aerosol and intradermal groups. The number of virulent bacilli recovered from primary lesions was significantly lower in aerosol group compared to the intradermal group.

S.C.K.

ACUTE RESPIRATORY INFECTIONS: CONCLUSIONS OF AN IUATLD WORKSHOP

Tubercle and Lung Disease; 1993, 74, 2

Based on lung aspirates from a Papua New Guinea series, it is concluded that mixed bacterial infections, including organisms of low pathogenicity, were the usual aetiological agents in children. As children develop immunocompetence with growing age, the spectrum becomes narrower. Meningitis can be regarded as a consequence of invasion by *S. pneumoniae* and *H. influenzae*, resulting in high mortality. Bacteraemia has been found in as high a proportion as 25%.

Simple colonization by potential pathogens does not necessarily lead to disease. Key risk factors for Acute Respiratory Infections in children are air pollution, overcrowding, undernutrition, Vit. A deficiency, poor breast feeding practices and bronchial hyper reactivity.

Effective vaccines against bacteria usually involved are important and must be developed to supplement the basic vaccination against measles and pertussis.

S.C.K.

ULTRASOUND GUIDED ASPIRATION BI-OPSY FOR PULMONARY TUBERCULOSIS WITH UNUSUAL RADIOGRAPHIC APPEARANCES

Aug Yuan et al., *Thorax*; 1993, 48/2, 167.

Pulmonary tuberculosis patients with abnormal radiographic appearances are often found to be negative on broscoscopic and even sputum smear examinations. In this paper ultrasound guided aspiration biopsy for diagnosis of pulmonary tuberculosis was assessed. Out of

13 patients, 10 who had negative sputum smear as well as negative bronchoscopic brushing smears were subjected to ultrasound guided aspiration or biopsy. Ultrasonographic examination could diagnose nine out of the ten patients. Five out of 13 were diagnosed by smear and culture examinations while bronchoscopy could diagnose only four out of nine patients. In patients where sputum and bronchoscopic results are negative, ultrasonography procedure, where needle can be directed to the most suitable part of the lesion, could add to the diagnostic yield.

V.K.C.

COHORT STUDY OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN PATIENTS WITH TUBERCULOSIS IN NAIROBI, KENYA - ANALYSIS OF EARLY (6-MONTH) MORTALITY

Paul Nunn et al. *Am. Rev. Respir. Dis.*; 1992, 146/4,849.

Among HIV infected tuberculosis patients number of deaths were more as compared with patients suffering from tuberculosis alone. A prospective cohort study was taken up in Nairobi to compare mortality rates, risk factors and causes of death among HIV positive and HIV negative tuberculosis patients. Out of 281 tuberculosis patients 107 were infected with HIV.

Mortality rate was significantly higher in HIV positive patients within 6 months of antituberculosis treatment. Patients put on "standard" regimen showed higher mortality than patients put on "short course" regimen. Risk factors for higher mortality included old age and less than one year of education. Mortality was significantly lower in women. Most of the excess mortality occurring after the 1st month of treatment was due to nontuberculous infections. The authors suggest that health workers in

developing countries need to adopt short course chemotherapy and also get experience in dealing with nontuberculous infections in patients with associated HIV infection.

V.K.C.

DETECTION OF MYCOBACTERIUM TUBERCULOSIS IN SPUTUM SAMPLES BY POLYMERASE CHAIN REACTION USING A SIMPLIFIED PROCEDURE

Tanil Kocagaz et al, : *Journal of Clinical Microbiology*, 1993, 31/6, 1435.

Bacteriological diagnosis of tuberculosis depends on the microscopic examination of sputum smears and cultural confirmation. Ziehl-Neelsen staining to identify acid-fast bacilli (AFB) being the most rapid method lacks sufficient sensitivity and specificity and it takes more than 4 weeks to culture pathogenic mycobacteria because of their slow growing nature. Polymerase chain reaction (PCR) for specific detection of many infectious agents has been successfully used for identification of *Mycobacterium tuberculosis*. For potential use of this diagnostic tool the complex procedure has been simplified in this study. For amplification by PCR instead of enzymatic lysis and phenol-chloroform extraction, heat was the only agent used to break down the bacteria and to get DNA released. Results of 78 sputum specimens examined by PCR were compared with the results of acid-fast smears, culture and clinical data. Besides detecting all smear and culture-positives and smear negative but culture positive cases, PCR could additionally detect four out of nine cases that were clinically suspected for tuberculosis but were found to be negative on both smear and culture. The authors are of the opinion that this simplified DNA isolation procedure could be used in routine clinical practice.

V.K.C.

