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Editorial

IN SEARCH OF TB RESEARCH

Not very long ago, it was the consensus opinion among tuberculosis workers in this country that more than adequate amount of information on tuberculosis was available for undertaking effective care of individual tuberculosis patients as well as bringing the disease under control. In fact, several writers in the sixties had stressed the need for concentrating on fuller utilization of the available information than collecting more information. Research for the sake of doing research was not favoured.

Fortunately, the all important aspect of having 'better' knowledge had been taken care of reasonably well during the 'golden era of tuberculosis research' in India in the immediately preceding decade or so. Therefore, the advice for giving low or no priority to TB research made a lot of sense, then, in view of the pressing demands on scarce resources for a nationwide tuberculosis programme.

The golden era came soon after independence through a fortuitous nexus that developed between some outstanding scientists and public health specialists as well as administrators and some visionary politicians as well as a towering statesman of that era. The Indian TB researches were of high quality which helped to dispel many a myth embodied in the large volume of information on tuberculosis which was gleaned from Western sources. For example, the Madras studies of the fifties proved beyond dispute that tuberculosis patients could be treated as effectively in their homes, and without the feared public health consequences, as in sanatoria and hospitals. The finding demolished a strongly held opposite view and provided the scientific basis to the 'Organised Home Treatment' that had been advocated *a priori* since the forties by the New Delhi Tuberculosis Centre. Other similar examples could be given. What needs to be highlighted is the multi-dimensional perspective provided by NTI, Bangalore, to the profile of tuberculosis in a community. To the mainly epidemiological delineation considered so far were added the equally important sociological, economic and administrative dimensions. NTI demonstrated that without an organised and integrated nationwide programme, based on all the dimensions, the hope of controlling tuberculosis could remain a dream. In structuring the National Tuberculosis Programme, NTI used the technology of Operations Research and arrived at an elaboration which incorporated the known and tried-out technical interventions, introduced in a manner which met the felt needs of the people, were practicable as well as feasible, and were widely acceptable. In fact, 'felt need', 'feasibility' and 'acceptability' became buzz words and health administrators began looking at health problems from the people's view-point as well, instead of purely in terms of technical interventions. By demonstrating the true importance of the infectious cases, especially the smear positive ones and the high proportions of them already attending general health institutions on own initiative, the NTI made the stress placed on MMR surveys of communities, in order to find the early cases, quite meaningless. In fact, the present WHO policy on tuberculosis control embodies several of the Indian research findings.

Nonetheless, all is not well. And the bell rings again for more TB research, in India, to make India's fight against tuberculosis more successful.

The NTP introduced in the country in 1962 has not performed according to expectations. Are the expectations too high? Are the activities in reality not feasible? Or, is the manner of implementation of NTP unrealistic? During the last 10 years or so, 4 comprehensive reviews of NTP have been made: the first by the ICMR and the last by a joint Government of India, WHO and World Bank team. All the reviews have highlighted, more or less, the same shortcomings: lack of priority accorded to the integrated NTP, among other largely vertical health programmes that tend to monopolize the health staff, weak suprastructural support and poor budgetary provisions, even for the essential drugs needed for treatment and supervision over field activities. No major defect could be found in the technical structuring of the NTP. In this connection, it was particularly noted that very similar programmes in other developing countries had succeeded far better. The purists, however, might call the conclusion a heresy and even a misunderstanding of NTP. Unlike the proverbial curate's egg, NTP cannot be good in parts. An integrated multi-dimensional composite programme can hardly be defended in this manner. It can be justified only by insisting on a system re-analysis, more operational studies in the areas where expectations have been belied, and re-formulation. Just the way NTP was formulated in the first instance.

It goes to the credit of the government that the poorly performing NTP was not swept under the carpet and forgotten. A revised NTP has in fact been introduced in the country since 1994. Financial assistance and technical advice was sought from the World Bank and WHO. One of the reasons for looking beyond the shores of India could be that recommendations for the revised formulation, based on solid operational studies as already mentioned, could not be made available to the government on time. And, to ensure that financial assistance goes to the vital points of the programme, the international agencies appear to have borrowed heavily from experiences gained in other countries, where sociological and operational conditions could be very different. The revised strategy was introduced as a pilot project in phases I and II, and phase III may follow soon (details elsewhere in this issue). It is to be noted that the new strategy, which looks good, is born out of *ad hocism*, typical of the Western interventional approach of yore. Tuberculosis workers in India, therefore, are keenly awaiting the outcome of phases I and II. It is to be hoped that the review of the pilot phases would be comprehensive, touching on all the relevant aspects and not cure rates alone.

Even though a revised strategy is in position, there is no gainsaying the fact that more TB research is needed. And in view of the urgency, all the noted research institutions could apply their shoulders to the wheel. It may be useful, nevertheless, to take a quick look at some of the areas where the resurgent research activity could concentrate, besides systems analysis, a task suitable for the NTI to undertake. Illness (and action-taking) behavioural studies need to be repeated. In addition, the behaviour and attitudes of the health care providers need attention, both in the government and private sectors. Illness behaviour studies could include the decision-making process (individual, family and community) and the resultant extent of utilization of the provided tuberculosis services. Collaboration and co-ordination between government, NGOs and private practitioners have defied the several *ad hoc* attempts made in the past. It needs a systematic study. Also, in the early days of NTP, training of microscopists, selected from the PHI staff, or the utilization of malaria laboratory workers was considered sufficient for the diagnosis of infectious cases in rural areas. The strategy does not appear to have worked well. The alternative of setting up simple rural laboratory services needs to be explored seriously. In summary, we must give a new lease of life to TB research.

D.R. NAGPAUL

ABDOMINAL AND PELVIC TUBERCULOSIS (WADIA SYNDROME)*

Boms J. Wadia¹

I am deeply honoured for being selected to deliver this oration, and fully appreciate the faith reposed in me by the organizers. I thank Lupin Laboratories for their magnanimous hosting. In my gynaecological practice, the tuberculosis patient almost always presents with sterility as the most common symptom. For this reason, the treatment should revolve round preventing fibrosis which would kink the fallopian tube giving rise to sterility or ectopic pregnancy due to improper transport of the ovum after fertilization. My worthy colleagues in the audience, the chest physicians, want to promote fibrosis in the lungs, specially if there is cavitation. I want you to appreciate that the fallopian tubal healing should be by primary intention and not by secondary intention, as is encouraged in the lung tissue. Gynaecologists are, therefore, of diametrically opposing view with that of physicians as far as healing of tissue after tuberculosis infection is concerned. I have learnt from my professors, all of them good friends, specially Prof. Mohanty with whom arguments and reasoning have become legendary on the J.J. Hospital campus for the past almost 2 decades. The truth, which I want to publicly acknowledge today is how useful these heated discussions have been, to give my patients better results, and today I hope to learn more from you, my audience, and from your vast experience in treating tuberculosis. With these feelings, I stand here before you for this oration in all humility. I hope to come up to your expectations and have put together my own personal data collected since 1968, which I'll share with you today. I remember Prof. V.N. Shirodkar coming from his trip abroad in 1968 and showing me an instrument with which to directly visualize the abdomen. He informed me that it was called a "laparoscope", and described to me the way it was to be used. Being adept in giving pneumo-peritonium for tuberculosis patients, I

started to use it, encouraged fully at JJ Hospital by my unit-chief, Prof. O.J. Shah, and in my private practice by Prof. V.N. Shirodkar. This laparoscopic intervention fulfilled the dream of Prof. Mehra Wadia (my late mother) of using modern techniques in our specialty. These two seniors supported me by sending me cases of sterility where no cause could be determined with the diagnostic procedures available at that time. The first three cases I did (all in my private practice) were relations of doctors. They had no findings to explain sterility. And all of them showed typical tubercles, which upto that time we could only see by laparotomy. In those pre-laparoscopic days, it was common to find tubercles, on laparotomy, in cases of unexplained infertility. This made me think of gathering data, and computerizing them since the 80's-from the most primitive models to the 486 and pentium computers of today. I was also very fortunate in taking live video clips during endoscopies, from the early 80's (some of the first in the world) with support from Storz of Germany. I realized that some lesions not previously described or documented in literature appeared with persistent regularity. This we started showing at various medical fora. Now, some of my colleagues affectionately started calling it the "Wadia Syndrome". With the Chair's permission, I will share with you, my audience today, some of the typical video clips.

In the 40's, cases of sterility with pelvic tuberculosis had no chance of pregnancy. A stray case sometimes became pregnant. The first case with repeat pregnancy was reported in the literature from our unit. In the 50's, repeat pregnancies were rare: I estimated about 5%. This rate became 30% with newer antibiotics and prednisolone in doses of 20 mg per day. The pregnancy rates jumped to over 60% with larger doses of steroids and the newer

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antituberculosis drugs. Addition of Ciprofloxacin gave results nearing 75%. Today, the addition of gamma-globulins in the last 2 years has raised our success rate to almost 80%. These are the results in cases having no gross pathology.

The other side of the story is a study conducted on 10,000 serial cases, each having completed a family and coming to us for laparoscopic ligation. We were surprised to find that ESR was raised in them. Nearly a third had laparoscopic finding (without symptoms) of TB during the laparoscopic ligation. I cannot explain how these patients had repeated pregnancies without any treatment and ultimately came to us for tubectomy. I can only surmise that some became pregnant, maybe, because of having a better resistance to tuberculosis.

On this occasion, I would like to remember three famous gynaecologists who have shaped my medical learning and research. All of them were professors at the Grant Medical College & Sir JJ. Group of University Hospitals, Bombay. I have been privileged to be an undergraduate and postgraduate student in the same institution and then resident and consultant at my alma mater, ending up as Professor and Head of the Department. This institution is unique and probably one of the largest in the world with over 4,000 beds, 1,500 undergraduate and 650 postgraduate students. It is one of the oldest medical institutions of modern medicine in Asia and has its history stretching over 175 years. This background is important to us today, because Robert Koch worked in this very institution at the turn of the century.

The first of my three professors was the late Prof. Mehra Wadia who encouraged and cajoled me from my school, college and medical days to inculcate a sense of dedication in my academics. She taught me how to go from theory to the practical and ultimately to research; showed me the importance of instrumentation, gadgets, drugs, data collection and the most important human factor to give me a sense of professionalism with the most modern methods available. I was blessed to have her as my mother, and I was fortunate that, at least, I was M.B.B.S. but not M.D. before she passed away in 1960. She had kindled in me an inquisitive mind for newer things and kept my mind open to receive the latest thinking and technology, which has been the foundation of my oration today.

Her classmate and close colleague, who died 11 years after her demise was the world famous Prof. V.N. Shirodkar with whom I had operated for 3 hours, daily, including holidays and Sundays, for over 10 years till his demise in 1971. With his background of original surgeries, recognized worldwide, and his contacts, I was introduced to my international colleagues. He showed through laparotomy, that many unexplained cases of female sterility were due to tuberculosis of abdomen.

The last of the three professors died in 1985, and after that I had no senior person left with whom I could take counsel or guidance in my medical work. Prof. O.J. Shah was my chief for almost 12 years. He encouraged me in laparoscopy and allowed me complete freedom in the unit. I remember with nostalgia how he would accompany me to some of the camps in the beginning of my career, but not operate himself. His experience and expertise were always there. This gave me immense confidence, and he even encouraged me in my early work on abdominal tuberculosis. His directions and thinking, accompanied with a good mixture of theory, practical and therapeutics gave me impetus without responsibility towards experimental regimes.

Literature has proof that he gave corticosteroids with anti tuberculosis drugs way back in the 50's. How well I remember him attending my clinic, with his early cases for laparoscopy, and looking down the laparoscope giving his valued support to my diagnosing TB laparoscopically. He encouraged me to do second look laparoscopies, which has taught me how the disease and lesions regress and even disappear. It was unfortunate that we only started doing video-endoscopy after he retired in 1978. Video documentation is better than writing the most exhaustive notes. Different drug regimens used provided a recorded evidence under the eye of the video camera. In some clear cut cases hysterosalpingogram corroborated the laparoscopic findings.

The criteria for diagnosis of pelvic/abdominal tuberculosis have changed over the years. It used to be a macroscopic view of caseation and tubercles, which were biopsied and confirmed by histopathology. This criterion is also in the minds of many practitioners even today. This was definitely the only criterion in the 70's. Then came a group of doctors who felt it was worth trying anti-tuberculosis

drugs for many cases of unexplained sterility, empirically. Prof. O.J. Shah's unit at J.J. Hospital was one of the pioneers, and it worked, very often! We have been seeing such lesions endoscopically with definite regularity and found that these cases had similar symptoms and signs. Computer checks showed me that what I felt was a conjecture was actually a statistical reality and many of the lesions were occurring simultaneously. My changing criterion for diagnosing abdominal Koch's disease was scientifically crystallizing. We started looking out for (1) free peritoneal fluid, (2) periuteritis (a word which we coined), (3) blue uterus (again something we saw only on laparoscopy), (4) perisalpingitis (specially the fibrosis on the tubal ante-mesenteric border) and (5) the "Wadia elevator" which certainly gave us an advantage in viewing better posteriorly where all the disease is lodged, like caseation, flimsy adhesions, encysted fluid and uterine syneche.

In the camps also we saw very similar pictures and the study of 10,000 serially examined cases revealed to us a similar picture. Again, the "elevator" helped us in rapidly visualizing the lesions. So, the changing scenario leading to laparoscopic diagnosis of abdominal tuberculosis was confirmed with our past experience and the statistical backing with computer tick-off forms.

Laboratory investigations did not keep pace with the flood of these findings. Though we called for a battery of tests, some of which were rated specific for Koch's disease, these often showed disappointing results not in keeping with the claims made. Some of these specific tests were positive and others were negative or doubtful, in the same patient. Apart from the expense and time taken, the rarity of positive tests left us confused.

Along the whole spectrum of laboratory tests, we found the time-tested ESR extremely useful as indicative of the disease, and also for prognosis and progress of treatment, specially if done accurately. It could be conveniently done in the smallest medical set-up with the most basic equipment and manpower. We realize it is nonspecific, but very high readings in apparently normal individuals make it specific and indicative of disease. At the time of collection of the blood specimen, the patient should have no

fever, cough, cold, etc. For standardization of the collection, the patient was made to starve, even without water, for at least 6 and preferably 8 hours. The blood collection is done in Wintrobe bulb, which is used both for Westergren (which we feel is better in borderline cases) and Wintrobe methods. The bulb is meticulously prepared by taking 8 g Pot. Oxalate with 12 g Ammon. Oxalate dissolved in 1000 cc of distilled water. Only 0.3 cc of this solution is taken in a dry bulb and placed in a hot air oven to evaporate the 0.3 cc of distilled water. Blood collection is done in a dry syringe and exactly 3 cc of blood is put in this "evaporated Wintrobe bulb". In accurate results are got if the procedure is not followed to the last detail, and the prognostic value of ESR is lost.

The drawn blood is shaken immediately in the Wintrobe collection tube and mounted immediately onto either Westergren or Wintrobe tube rack and read exactly after one hour. For the Wintrobe reading, the anemia correction factor with Wintrobe chart is to be applied. It is my curious observation that laboratories do not do this test properly and most of them do not even have the Wintrobe Correction Chart.

In this way, we realized that in women the hourly ESR reading of 15-20 mm, Mild Raise, 21-30 mm/Moderate Raise, 31-40 mm, Severe Raise and over 40 mm, Extreme Raise has a lot of significance.

This simple test, if done properly, revealed to us an estimated projection of 98% accuracy for diagnosing pelvic tuberculosis. It would be interesting to see how the computer ESR tests would fare. I am sure, if properly standardized it could give a lot of good information.

In the laparoscopic sterilization camps, we found lesions in the pelvis which we used to see in sterility cases. But these women had already completed their family, were without any symptoms and had actually come for tubectomy. Did they have tuberculosis of abdomen? Were we doing an over-kill with TB abdomen diagnosis in our sterility cases? There was a lurking suspicion of this! Almost all these cases had thick tubes which were definitely noticeable when we were putting on the Yoon band.

In fact, we classified the thickness of the tubes, clinically, by the degree of difficulty we encountered in putting on the Yoon ring on the fallopian tube. These were the cases which made us look into pelvis and abdomen more closely. Surprisingly, they also had many of the laparoscopic lesions that we associated with TB abdomen in cases with sterility. Two things convinced us that we were on the right path by the sheer numbers which showed a coincidence (statistically significant) of having (1) a high ESR, done later as a double or triple blind study. (2) on going back and taking details of the history which showed they had many of the signs & symptoms connected with TB abdomen, which we were seeing in our sterility cases. This was found in more than 33% of the normal cases coming for tubectomy in the tribal population of Bihar. They also felt that repeated pregnancies had depleted their health. Was tuberculosis dormant or non-existent in them when they became pregnant? Did they acquire the disease later in life? Statistically, there was a definite connection between surgical interferences like D & C, cesarean section, and even forceps delivery and flare-up of TB. Corauval blocked fallapian tubes had this type of history, on obtaining closely scrutinized history.

Many of the other tests are cumbersome, expensive and require specialized instruments and technicians. They use deteriorating chemicals and reagents which may compromise their accuracy. The standardization criteria also differ in each laboratory. Controversial impressions and opinions of pathologists and clinicians are common. A typical example is of IgA, IgG and IgM. They are better done with peritoneal fluid than with serum.

We found that PCR with serum gave good results. But, in the past 2 years, we compared PCR with peritoneal fluid. This gave us more satisfaction and confirmed, for us, the value of ESR, which I feel is the best value for cost and ease of performance.

I feel you, my colleagues, should keep an open mind on diagnosis of abdominal tuberculosis. Good history correlated with symptoms and signs reveals a lot. I do not even want to dream of indulging in teaching you anything, but I only want to share with you what we have been seeing in our female sterility cases. I have been sharing some of

these findings at various fora abroad and in India. Many of my colleagues and students discuss it with respect and magnanimity towards me as "The Wadia Syndrome" for abdominal and pelvic tuberculosis, which I will relate under the headings of

- (1) History & Symptoms,
- (2) Clinical Examination & Signs,
- (3) Investigation & Routine Tests,
- (4) Laparoscopic Findings,
- (5) Hysteroscopic Picture,
- (6) Specific Tests, and
- (7) Principles of Management.

HISTORY & SYMPTOMS

- (1) Sterility (primary/after D&C for abortion/one child sterility specially after cesarean section)
- (2) Menstrual change (heavier bleeding with small fibrous uterus/scanty flow/amenorrhoea)
- (3) Painful period, half to one day before & half to one day after the onset of period
- (4) Feeling of tiredness, weakness, wanting to rest/sleep
- (5) Evening rise of fever
- (6) Loss of appetite and indigestion (constipation or diarrhea)
- (7) Sweating of palms and soles
- (8) Vague pain in abdomen
- (9) Dysparunia (introductory & deep seated), disinterest in sexual intercourse due to pain and tiredness
- (10) Menarche - very early or very late or even as primary amenorrhoea

CLINICAL EXAMINATION & SIGNS

- (1) Hypoplastic fibrous uterus (may be with heavy menstrual flow)
- (2) Retroverted uterus with restricted mobility or even fixed uterus
- (3) Narrow fornices (usually lateral) narrow vault/ or ring of fibrosis in upper vagina
- (4) Deviated uterus
- (5) Diffuse mass/bogginess/tenderness
- (6) Fibrosed interoitus
- (7) Doughy abdomen
- (8) Diabetic or prediabetic vulvitis & mondial vaginitis

- (9) Roughness on posterior wall of uterus mistaken for seedling fibroids
- (10) Cervical ulcer, more on anterior lip of cervix (appears to be malignant but does not bleed on touching)

INVESTIGATIONS & ROUTINE TESTS

- (1) ESR
- (2) Peritoneal fluid (transudate/exudate)
- (3) Endometrial biopsy or D&C with histopathology
- (4) Culture of endometrium & animal inoculation
- (5) Mantoux test (properly standardized)
- (6) X-ray chest & sputum for AFB
- (7) Biopsy of lymph glands
- (8) AFB in menstrual blood (concentrated with micro current)
- (9) Hysterosalpingogram
- (10) Ultrasound

LAPAROSCOPIC FINDINGS

- (1) High coloured copious peritoneal fluid (tending to become encysted)
- (2) Periuteritis (non glistening uterine surface), with lepra patches or a thrush appearance
- (3) Blue Uterus on injecting methylene blue
- (4) Perisalpingitis, salpingitis Isthmica Nodosa, beaded tubes, rosary appearance, thick tubes, hydrosalpinx
- (5) Tubercles, micro & macro caseation (on tube, pouch of Douglas, posterior part of broad ligament)
- (6) Flimsy adhesions in right iliac fossa, pouch of Douglas, left iliac fossa, and the liver area
- (7) Omental adhesions are fibrous and dense, if formed after surgery
- (8) Fibrosis in posterior part of broad ligament, mimicking endometriosis because of breaking of fibrosis typically by ante-verting the uterus
- (9) Smaller than normal size fibrous uterus
- (10) Synechiae observed by vaginal assistant during elevation of the uterus

HYSTEROSCOPIC PICTURE

- (1) Microcaseation
- (2) Hyperplasia of endometrium with scanty periods (not bleeding to touch with hysteroscope)

- (3) Exudation smeared in the uterine cavity
- (4) Funnel entrance to tubal ostium is distorted or completely lost
- (5) Non-breathing tubal ostium, focusing as a blocked tube
- (6) Canalization of ostial area releases flaky caseous material
- (7) Hysteroscopic biopsy of sinister part of endometrium gives more positive histopathological results
- (8) Irregular and ulcerated endocervical canal
- (9) Fleshy and hyperplastic cervical erosion not bleeding on touch, and placed anteriorly
- (10) Synechiae and fibrosis in the uterine cavity, specially precipitated after a curettage

SPECIFIC LABORATORY TESTS

- (1) ESR
- (2) Lymphocytosis
- (3) Histopathology of hysteroscopic aided biopsy (giant cells)
- (4) Kaolin Agglutination Test (KAT)
- (5) Animal inoculation of suspected endometrium
- (6) Tubercular antibodies & AFB in menstrual blood
- (7) Antibodies in blood (IgA, IgG, IgM)
- (8) Antibodies in peritoneal fluid
- (9) Specific antigen in peritoneal fluid
- (10) Polymerase chain reaction (PCR) of serum or peritoneal fluid

Before I end, I would like to give you some data collected over the last 3 decades. We have found that in India almost all the ectopic pregnancies are caused by tuberculosis. I also can share with you the cause of primary amenorrhoea. These young girls were subjected to a battery of tests making them nervous and psychological wrecks. In our referral practice, in my unit at the J.J. Hospital, we found that 74% cases of primary amenorrhoea had tuberculous endometritis as the cause, and this is when we get referred all sorts of congenital and endocrine cases which would actually be diluting our 74% figure. In our country, we should first think of tuberculosis before subjecting these girls to any expensive and invasive testing of endocrine or embryological, genetic, or congenital defects. My special thanks to the Chairman, and you, for giving me an encouraging hearing.

SEVEN YEAR FINDINGS OF SHORT-COURSE CHEMOTHERAPY IN 18 DISTRICTS IN INDIA UNDER DISTRICT TUBERCULOSIS PROGRAMME

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Summary: The ICMR undertook a study/project to find out the feasibility of introducing Short-course Chemotherapy (SCC) under the existing programme conditions and evaluate its acceptability. Sputum positive pulmonary tuberculosis patients aged 15 years or more who had not received more than two months of anti-tuberculosis chemotherapy, belonging to 18 districts spread over 9 states and one union territory of India, were treated with, one of the following regimens:

Regimen 1: Rifampicin, Isoniazid and Pyrazinamide for 2 months and Rifampicin and Isoniazid for the next 4 months, the drugs being given twice a week *under supervision*.

Regimen 2; Rifampicin, Isoniazid and Pyrazinamide dally for 2 months and Thioacetazone and Isoniazid for the next 6 months, drugs being *self-administered*.

Regimen 3: As to regimen 2 for 2 months and Rifampicin and Isoniazid for the next 4 months, the drugs being given twice-a-week *under supervision*.

In all, a population of 40 million was covered. Of the Peripheral Health Institutions where District Tuberculosis Programme had been implemented, 66% in 1985 and 93% in 1991 had Implemented SCC. Of the newly diagnosed patients, 83% were eligible for SCC and 62% of these were started on SCC. Of the remaining patients, with data available, the reasons for not starting, on SCC, related' in 58% and had organizational/administrative related aspects in 35%.

Of those who were started on SCC, 49% in regimen 1, 54% in regimen 2 and 61% in regimen 3 received 80% or more of chemotherapy. Concurrent cohort analysis of SCC and standard regimens showed that the overall treatment completion for SCC was fairly constant (51-55%), but ranged from 29% to 45% for the standard regimen.

Conclusion: It is is feasible to employ SCC Under the existing programme conditions. However, additional efforts have to be made to improve case-finding and case-holding further.

INTRODUCTION

The major constraint in the National Tuberculosis Programme in India is poor treatment completion with the conventional 12-18 month regimens^{1,2}. One of the main reasons for this poor treatment adherence is the prolonged treatment period. It is, therefore, logical to employ treatment regimens of shorter duration with an aim to improve the treatment adherence by patients. The efficacy of Short Course Chemotherapy (SCC) regimens, of 6-9 months' duration, containing powerful bactericidal and sterilising drugs, at least during the initial 2 months, has been established in the treatment of newly diagnosed sputum positive pulmonary tuberculosis and these regimens have been widely recommended^{3,4,5}. Further, the drug regimens employed in SCC rendered the vast majority of patients non-infectious in a short period. Even if a patient with initially drug-sensitive organisms defaults after 3 months of chemotherapy with a regimen containing Streptomycin plus Isoniazid

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plus Rifampicin plus Pyrazinamide daily, he stands a good chance of attaining sputum conversion (about 95% by 3 months)⁶, and remaining negative thereafter (about 80% up to 5 years of follow-up)⁷.

Considering these advantages, the Government of India introduced SCC as a pilot project under the existing District Tuberculosis Programme (DTP) in 18 districts spread all over India. The objective was to find out the feasibility of introducing SCC regimens under the existing programme conditions in all districts and to evaluate their acceptability.

MATERIAL AND METHODS

The project was undertaken between 1983 and 1991. The 18 districts where SCC was implemented were widely distributed all over India, involving 9 states and one union territory. There were 3 districts each in 4 states, 1 each in 5 states and one in a Union Territory. The population, according to the 1981 census, was below 1 million in 3 districts, 1-2 million in 5 districts, 2-3 million in 6 districts, 3-4 million in 3 districts and above 4 million in one district; the total population covered being about 40 million (Annexure).

Eligibility for Treatment with SCC regimens

Chest symptomatics* aged 15 years or more, belonging to the districts concerned, with at least one sputum smear found positive for acid-fast bacilli (AFB), who had not had more than 2 months of previous specific anti-tuberculosis chemotherapy and were attending the government health facilities on their own were considered eligible.

SCC regimens

The regimens prescribed were as follows:

Regimen 1: 2RHZ₂/4RH₂: A fully supervised 6-month intermittent regimen consisting of Rifampicin 600mg, Isoniazid 600mg and Pyrazinamide 2.0g for 2 months, followed by Rifampicin 600mg and Isoniazid 600mg for the next 4 months, all the doses

administered twice-weekly in the clinic under supervision.

Regimen 2: 2RHZ/6TH: A fully unsupervised daily 8-month regimen consisting of Rifampicin 450mg, Isoniazid 300mg and Pyrazinamide 1.5g for 2 months, followed by Thioacetazone 150mg and Isoniazid 300mg for the next 6 months, all the doses being collected by the patients twice-a-month for self administration

Regimen 3: 2RHZ/4RH₂: A partly unsupervised and partly supervised regimen consisting of Rifampicin 450mg, Isoniazid 300mg and Pyrazinamide 1.5g daily for 2 months, the drugs collected twice-a-month for self-administration, followed by Rifampicin 600 mg and Isoniazid 600 mg twice-weekly for the next 4 months, the drugs administered twice-a-week in the clinic under supervision, because patients tend to become irregular in the later months.

In addition, where facilities were available, Streptomycin 0.75g i.m. could be given in the first 2 months in all the 3 regimens**

Treatment policies

The 18 districts were divided into 3 groups of 6 each and allotted to one of the 3 policies described below: -

Policy A: Patients were to be treated with regimen 1 requiring twice-weekly attendance throughout. However, if the patient was not able to attend so often, regimen 2 was offered.

Policy B: Patients were to be treated with regimen 2 only.

Policy C: Patients were to be treated with regimen 3, but as in policy A, regimen 2 could be offered to patients who were unable to attend the clinic twice a week.

Management of Patients

Patients started on short course chemotherapy had to attend the treatment centre according to the

* Defined as patients with complaints of cough for 2 weeks or more, chest pain and/or fever for 1 month or more, or haemoptysis at any time.

** In practice, Streptomycin was given only to less than 1% of the patients.

regimen prescribed. For patients who did not attend on the due date for drug administration/collection, defaulter action such as a letter, home visit or a message was to be taken on the next day. For patients who did not turn up within 7 days of the first action, a second retrieval action (letter/home visit), was to be taken. Those who defaulted continuously for a period of one month were considered as "Lost" to SCC (patients who re-attended after after one month were managed on individual basis.)

One sputum smear examination for AFB was to be carried out at 3 months and another at the end of chemotherapy (6/8m). If the sputum examined at the end of treatment was found positive, a second specimen was to be examined. If this smear was also positive, treatment was to be continued with Thioacetazone 150 mg and Isoniazid 300 mg daily up to 9 months (i.e., for an additional 1 or 3 months) and another sputum examination was undertaken then. If that was also positive, the patient was to be referred to the District Tuberculosis Officer (DTO) for further management.

If a patient developed symptoms and/or signs of jaundice, Rifampicin and Pyrazinamide were to be terminated and Isoniazid withheld, and the patient put on standard chemotherapy consisting of EH/TH or SHtw after jaundice had subsided. For mild arthralgia, analgesics were to be prescribed; if it was incapacitating or pain persisted despite analgesics, Pyrazinamide was to be withheld and re-introduced when the pain subsided. If arthralgia recurred, the patient was to be referred to the DTO for further management. Gastro-intestinal upsets and other minor reactions were to be managed symptomatically.

Conduct of the Project and Role of Tuberculosis Research Centre (TRC)

The TRC was given the responsibility of implementation and monitoring of SCC in the 18 districts under the existing DTPs by the Government of India. Protocols and detailed work instructions were prepared by TRC and circulated to the Officers-in-charge of tuberculosis at the state level and the DTOs. The work instructions and guidelines were distributed to all the Peripheral Health Institutions (PHIs) of these districts through their respective DTOs. The DTOs and their teams were made

responsible for the implementation and conduct of the project. Rifampicin and Pyrazinamide were supplied by the Government of India (courtesy Swedish International Development Agency), according to the requirements, indicated twice a year by the DTOs. Certain modifications in the format of the monthly returns routinely submitted to the National Tuberculosis Institute (NTI), Bangalore, such as, number of PHIs implemented with SCC, dividing section on treatment into 3 parts to get information on sputum positive cases started on SCC or standard regimen and sputum negative cases started on standard treatment, patting an additional column to get information about the reasons for not starting eligible patients on SCC, etc. were made in consultation with the NTI, Bangalore. An additional statistician was posted to these 18 districts to monitor the programme, collect the required information and co-ordinate with the TRC.

The monthly and quarterly reports on tuberculosis and annual cohort reports were sent to the TRC by the DTOs. When reports were not received on time, reminders were sent to the concerned DTOs.

A team consisting of a medical officer, bacteriologist, statistician and medical social worker from TRC visited the District Tuberculosis Centres (DTCs) and PHIs and held discussions to identify problems, if any, and suggest remedial measures. The microscopy facilities were also inspected and corrective measures such as minor repairs of the microscopes were undertaken. A sample of positive and negative sputum slides was read by the TRC staff. Training programmes were conducted at the district level for medical and paramedical workers to get more personnel at the PHI level trained in the various aspects of the programme. Workshops were conducted at least once a year, initially at the TRC and later at a central location combining 3 or 4 districts for in-service training (courtesy, ICMR/WHO) of medical and paramedical workers involved in the programme.

Periodically, the DTOs and the state officers in-charge were briefed by the TRC about the performance of their districts and attempts were made to sort out any problems which had been identified. Thus, the role of the TRC, Madras was mainly in an advisory capacity to the programme

officers in addition to providing in-service training and monitoring.

FINDINGS

Documentation

The observations reported here are based on the information obtained from the monthly and quarterly returns on tuberculosis and the annual cohort reports from the various districts. These returns were received from all the districts every month, 57-77% received within one month and rest after reminders.

Implementation of SCC

Beginning in March 1983, with a district in Tamil Nadu, SCC was gradually introduced, and by

March 1985 all the 18 districts had been covered. Efforts were made to make SCC available in all the PHIs in each of the 18 districts as quickly as possible.

By 1985, the implementation of SCC in PHIs was 75% or more in 8 of the 18 districts and less than 50% in 7 districts (Table 1). By 1989, 14 districts had implemented SCC in 75% or more of the PHIs, including 9 with 100% and none had less than 50% implementation. By 1991, 15 districts had implemented SCC in 75% or more of the PHIs, including 10 districts with 100% and 3 districts with 90-99% implementation of the PHIs. In the remaining 3 districts, SCC was implemented in 73%, 50% and 55% of the PHIs. A visit was undertaken by TRC team to 2 districts where the implementation was low. It was observed that the major reasons for non-implementation were long

Table 1. SCC implementation in PHIs

No. of districts with SCC implemented according to year							
SCC implemented PHIs (%)	1985	1986	1987	1988	1989	1990	1991
100	6	5	4	5	9	9	10
90-99	1	1	2	2	2	2	3
75-89	1	1	0	1	3	4	2
50-74	3	3	6	8	4	3	3
<50	7	8	6	2	0	0	0

Note: The number of PHIs increased year to year in some districts, which could have resulted in a reduction in the percentage implemented

Table 2. Case finding activity and PHI contribution per district per year

Year	DTC sputa				PHI sputa			PHI contribution		
	Examined No. (a)	Positive No. (b)	Examined (%) ⁺	Positive (%) ⁺	Examined No. (c)	Positive No. (d)	Examined (%) ⁺	Positive (%) ⁺	Examined c/a+c (%)	Positive d/b+d (%)
1985	4629	531	100	100	10644	511	100-	100	70	49
1986	4426	561	96	106	12015	618	113	121	73	52
1987	4777	543	103	102	12267	567	115	111	72	51
1988	4967	561	107	106	12191	515	115	101	71	48
1989	4345	542	94	102	11940	650	112	127	73	55
1990	4027	530	87	100	12518	729	118	143	76	58
1991	4062	554	88	104	12297	812	116	159	75	59

⁺based on 1985 figure

distance and inaccessible PHIs. The overall implementation with SCC was 66% of the DTP-implemented PHIs in 1985 and 93% by 1991. And, as a proportion of the total PHIs, the implementation in respect of SCC was 54% in 1985 and 87% in 1991.

Case-finding activity

The case-finding activity in the districts was assessed by the total number of sputa examined and the sputum positive cases detected per year. Excluding 2 districts from where adequate information was not received for the initial 2-years period, the average sputum examination was 4629 per DTC in 1985 (Table 2). Considering 1985 as the baseline, there was no definite trend over the years as far as the DTCs were concerned (4629 in 1985 and 4062 in 1991). However, at the PHIs, the average sputum examination registered an increase from 10644 in 1985 to 12297 in 1991. Even though there was no increase in the sputum examinations at the DTC, the sputum positives detected remained fairly constant, the range being 530 to 561. The average number of sputum positive cases detected per year at the PHIs registered an increase from 511 in 1985 to 812 in 1991. The overall contribution of the PHIs towards sputum examinations was 70 and 75% of the total examinations and 49 and 59% with regards to sputum positive cases detected, respectively. Combining the DTCs and the PHIs, the increase in sputum examinations was 7% and in sputum positives detected 31%, between 1985 and 1991.

The total population of the 18 districts was 39.8 million, as per 1981 census. Considering the population aged 5 years or more to be around 85%, and the prevalence of sputum positive cases to be about 4 per 1000, and that about 50% of these cases attend a health centre and 80% of these cases can be detected by microscopy, the expected diagnosis of sputum positive cases was 54,128 per year, while the actual number diagnosed was 21,948 per year - an efficiency of 41%. However, there was a wide variation in case finding efficiency between the districts (range: 15% to 94%).

Condition of microscopes

Using a questionnaire, it was reported from 10 of the 18 districts that 250 microscopes were

defective. A TRC team detected 151 defective microscopes and undertook necessary repairs.

A total of 1010 sputum smear slides were collected during the supervisory visits to the districts and read at TRC later. It was found that there was 95% agreement between the readings, there being 4.5% under reading and 0.5% over reading of the smears in the districts.

Prescribed SCC

During the 7-year period, a total of 1,64,695 sputum positive cases were diagnosed in the 18 districts and 1,37,099 (83%) were eligible to be treated with SCC (Table 3). However, only 84,704 (62%) of the patients were started on SCC (66% in policy A, 52% in policy B and 67% in policy C districts). Of these, 75% of patients in policy A and 65% of patients in policy C districts were treated with regimen 2 (Annexure). Among the 6 policy A districts, excluding one district where only regimen 1 was implemented, 16% were treated with regimen 1. However, there was a wide variation between districts (1-50%).

Table 3. Policy-wise distribution of smear positive patients, eligible for SCC and started on SCC

Policy	Smear positives No. (a)	Eligible for SCC		Put on SCC	
		No. (b)	%of (a)	No. (b)	%of (b)
A	68185	58152	85	38252	66
B	52446	42270	81	21815	52
C	44064	36677	83	24637	67
Total	164695	137099	83	84704	62

Reasons for not starting SCC

The reason(s) for not starting SCC was/were available for 43% of 52395 patients (Table 4) and have been classified as reasons attributable to patients (58%), organisational/administrative (35%) causes and other reasons (7%). Of the reasons attributable to patients, 23% were living too far away, 15% were likely to migrate from the given address and 10% were too old or sick. Of the organisational/administrative reasons,

non-availability of SCC drugs and non-implementation of SCC in the PHIs accounted for 13% and 11%, respectively.

Table 4. Reason(s) given for not starting SCC

	Patients	
	No.	%
(a) Eligible but not put on SCC	52395	
(b) Reason available for not being put on SCC	22734	43(%of a)
A. Attributable to patients	13167	58*
Living too far away	5206	23
Likely to migrate	3486	15
Too old or sick	2237	10
Initial defaulter	451	2
Travel too expensive, non- availability of transport, } loss of wages etc. }	1787	8
B. Organisational/ Administrative Causes	7939	35
SCC drugs not available	2551	13
SCC not implemented	2551	11
Clinic hours not convenient	422	2
Patients admitted in hospital	261	1
Miscellaneous	1836	8
C. Others	1628	7

*: This percentage and all subsequent ones are based on (b).

Cohort analysis for treatment completion

Analyses of treatment completion were done based on the treatment cards returned to the DTCs. Of the 74,930 patients started on SCC in 17 districts, excluding 1 district where only limited information on a few patients was available, 64,729 patients (86%) were included in the cohort analysis. The proportion of patients included was 90% or more in 13 districts.

Treatment completion

In policy A districts, 52% of the 24,945 patients included in the cohort analysis had received 80% or more of their chemotherapy; the corresponding figures were 55% of 18,450 in Policy

B districts and 55% of 21334 in Policy C districts, the over all treatment completion being 54%. Detailed analyses showed that the treatment completion was 50% to 54% in policy A, 49% to 64% in policy B and 46% to 62% in policy C districts. In the 1990-91 cohort, the treatment completion was 50%, 64% and 62% for the 3 policies respectively (data not tabulated).

Since a proportion of patients in Policy A and C districts were treated with regimen 2, an analysis was undertaken to find out the treatment completion according to the regimen (Table 5). The proportion of patients receiving 80% or more of chemotherapy was 49% of 12929 patients (range 46-71%) treated with regimen 1 which was a fully supervised regimen, 54% of 44383 patients treated with regimen 2, a self-administered regimen (range 28-86%), and 61% of 7417 patients treated with regimen 3, a partially supervised regimen (range 39-79%). Considering the 20,346 patients who were started on regimens 1 and 3, the proportion of patients completing 80% or more of chemotherapy was 54%, similar to the 54% of 44383 patients started on regimen 2.

In regimen 1, 39% of patients had received 50% or less of chemotherapy, including 22% receiving 25% or less. The corresponding figures were 38% and 27% for regimen 2, and 33% and 17% for regimen 3.

The proportions of patients 'lost' from chemotherapy according to regimen were 45% with the fully supervised twice weekly regimen, 40% with the unsupervised regimen and 33% with the partially supervised regimen (data not tabulated).

Bacteriology at the end of chemotherapy

A sputum specimen was to be examined at the end of chemotherapy for all patients completing treatment. However, the coverage for sputum examination was 64% of patients on regimen 1, 80% on regimen 2 and 84% on regimen 3. Of those examined, 95%, 99% and 99% respectively were negative by smear (Table 5). Sputum smear results at the end of chemotherapy were available for 4 cohort periods for patients treated with standard chemotherapy. Of the 8847 patients eligible for

Table 5. Treatment completion rate and sputum smear status at the end of treatment, according to regimen

Regimen	Total patients# No.	Completed >80% Treatment		Patients available for sputum examination (c)	Patients available for sputum examination No. (d)	End of treatment			
		No. (b)	% (b/a)			Sputum examined		Sputum negative	
						No. (d/c)	% (e)	No. (e/d)	% (e/d)
(a)	(b)	(b/a)	(c)	(d)	(d/c)	(e)	(e/d)	(e/d)	
1. 2RHZ ₂ /4RH ₂									
No. of Patients	12929	6349	49	5334	3441	64	3276	95	-
Range	89-8984	63-4089	46-71	59-3300	5-1716	8-100	5-1590	93-100	
2. 2RHZ/6TH									
No. of Patients	44383	23944	54	22609	18065	80	17842	99	
Range	22-6371	19-4458	28-86	15-4232	14-4065	30-100	14-4039	95-100	
3. 2RHZ/4RH ₂									
No. of Patients	7417	4541	61	4374	3665	84	3643	99	
Range	49-2488	29-1696	39-79	22-1636	21-1425	75-96	21-1410	98-100	

From inception of SCC programme up to June 1991.

sputum examination at the end of chemotherapy, 4002 (45%) had sputum examination done and of these, 96% were negative by smear (data not tabulated).

Comparison of treatment completion among 4 cohorts of SCC and standard chemotherapy

Concurrent analyses were done for 4 cohort periods to compare the treatment completion rates between SCC and standard regimen. The overall treatment completion with SCC regimens for the 4 cohort periods ranged from 51% to 55% (Table 6). Considering the standard chemotherapy cohorts, the treatment completion rate increased from 29% in 1986-87 cohort to 41% in 1987-88 cohort, 45% in 1988-89 cohort and 40% in 1989-90 cohort.

Considering the proportions of patients 'lost' from treatment in SCC and standard regimen (data not tabulated), 18% and 20% of patients, respectively were lost after receiving the number of doses due for the first month of treatment, 35% and 34%, respectively, up to 3 months and 44% in each regimen up to 5 months.

Adverse reactions

Information on adverse reactions was not available in the periodic returns from all the districts. However, one district had reported less than 1% each of jaundice, vomiting and gastritis⁸. In addition, giddiness (1.6%) and arthralgia (1.7%) was also reported from the same district. Further, change of treatment for any reason (including adverse reactions, non-availability of SCC drugs and inability to attend frequently, etc.) was reported only in 4% of cases in regimens 1 and 3 and 2% in regimen 2.

DISCUSSION

The observations reported here cover a period of 7 years after introducing SCC in 18 districts spread all over India under the existing programme conditions. The SCC implementation was undertaken in a phased manner, and by March 1985, all the districts had implemented SCC. By 1985, the coverage for implementation was 66% of the PHIs which increased to 93% by 1991⁹.

Considering the case-finding activity, the

Table 6. Comparison of treatment completion between SCC and Standard Chemotherapy

Policy	1986-87*				1987-88				1988-89				1989-90			
	SCC		Standard		SCC		Standard		SCC		Standard		SCC		Standard	
	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#	No.	Comp- leted Treatment (%)#
A	3385	54	1902	28	2938	50	1740	38	2994	54	2087	34	4303	54	2265	31
B	2391	59	1885	31	2161	49	2177	46	2958	49	2264	52	3452	54	1952	48
C	2360	46	2336	27	2522	54	2537	40	3756	61	1947	49	4583	54	2029	45
Total	8136	53	2123	29	7621	51	6454	41	9708	55	6298	45	12338	54	6246	40

* July 1986 - June 1987 etc.; # > = 80% of Treatment.

overall efficiency was of the order of 41 %. This rate is similar to the national average of about 30-36%^{10,11} but substantially less than the expected potential of about 60-65%^{11,12}, which is very near the WHO target of 70%¹³.

Combining DTCs and PHIs, the total number of sputum examinations had registered an increase of 7% and in sputum positives of 31 % between 1985 and 1991. There was an increase in the number of sputum examinations by 16% at the PHIs and a decrease by 12% at the DTCs, a trend in the expected direction. The contribution of the PHIs during the 7-year period was in the range of 70-76% in respect of sputum examination and 48-59% with respect to detection of smear positive cases. The national figures during the same period were similar, being 70-72% and 49-53% respectively^{2,14-16}. Further, improvement is required in supplies given for sputum microscopy. The fact that a large number of the microscopes in the 18 districts needed repairs suggests the need for frequent supervision and service facilities. A check on the quality of sputum microscopy through random samples had shown 95% agreement between the readings at the district level and at TRC. Thus, the quality of the reading of sputum smears was found to be satisfactory. In addition, utilisation of volunteer workers like National Service Scheme (NSS) students, traditional birth attendants (Dais) and literate youth, in difficult terrains to improve detection of symptomatics is being evaluated at our Centre.

The proportion of eligible patients started on SCC was 62% in the present study. In a recent report from the NTI, Bangalore, it was observed that 49.4% of the smear positive cases diagnosed in 248 districts had been started on SCC regimens: of these, only 2.8% were treated with a supervised twice weekly regimen of 6-month duration⁹. In the present report, of the 6 districts with policy A, one district only had the fully supervised regimen implemented. In the remaining 5 districts, 16% were started on a fully supervised twice-weekly regimen. However, there was a wide variation (1 %-50%) between the 5 districts.

It was also observed that 38% of eligible patients were not started on SCC, even though they could be prescribed a regimen requiring only twice-a-month attendance for 8 months. The reasons for

not starting SCC were available only in 43% of the patients. Of these, 58% were attributable to the patients like living too far away, likely to migrate and too old or sick. It is possible to solve some of these problems by decentralising the treatment, utilising the sub-centres which cater to a relatively small population of 5000 where as the PHCs cater to a population of 30,000. The patients likely to migrate also could be given SCC with improvement in the implementation of SCC. Considering the administrative/organisational reasons, non-implementation of SCC and non-availability of drugs (either due to inadequate supply or failure to indent for the drugs on time) were the main problems faced. The monthly meetings of the DTO with the PHI staff could be utilised to introduce the SCC regimens and motivate the staff to implement SCC at the respective PHIs. It is also possible to take stock of the drug position at the PHIs during these meetings and, if necessary, redistribute the excess stock in some PHIs to tide over the drug shortage elsewhere. Timely indenting and streamlining of drug supply are also essential.

With respect to case-holding, during the 7-year period, approximately 54% completed 80% or more of treatment, figures similar to the 53% completing 75% or more of treatment reported by NTI⁹. Detailed analyses have shown that there was no difference in treatment completion rates between the different cohort periods. These completion rates are better than the 27-34% reported in the NTP with 12-month regimens^{1,2}. The completion rate with 12 month regimens for concurrent cohorts in these 18 districts was 29% in the 1986-87 cohort which increased to 40-45% in subsequent cohorts. It was found that the treatment completion was 54% in regimen 2 where patients had to attend twice a month, and 49% and 61% in regimens 1 and 3, respectively, where patients had to attend twice a week either throughout the 6-month period or for a 4-month period, respectively. The completion rates for the patients treated with the supervised regimen involving twice-weekly attendance either throughout or partially and for the unsupervised regimen in 12 districts, were similar. Thus, the frequency of clinic attendance does not appear to have had any influence on the treatment completion rates.

Considering the proportion of patients 'lost' from treatment, 18% in SCC and 20% in standard

chemotherapy were lost after receiving the doses due for the 1st month, 35 % and 34%, respectively, for up to 3 months and 44% in each for up to 5 months. Thus, it appears that the duration for which treatment is given exerts more influence on patient compliance than the drugs given.

In an attempt to find out the reasons for patients discontinuing treatment, visits were made in 2 districts to the homes of patients who had been 'lost' to treatment¹⁷. It was found that in an appreciable proportion of patients, the reasons, such as adverse reactions, inaccurate or inadequate address and abatement of symptoms are correctable. This Centre had evolved an inexpensive and efficient system of obtaining accurate addresses of patients by utilising an "address card system"¹⁸. This system was employed under programme conditions in one district and it was found that the system was acceptable and could improve the accuracy of addresses¹⁹. This is essential because the defaulter retrieval procedure in the programme depends largely on letter posting.

In earlier studies, one-time motivation at the start of treatment was found to be inadequate²⁰ but motivation of the patients together with their family members every month during the initial three months of treatment resulted in better drug collection²¹. A study at this Centre²² had also shown that there was a 10% increase in the compliance rate among patients motivated initially only and by 20% among those motivated at 0,1,2 and 5 months, compared to patients who were not subjected to motivation.

Treatment completion of 80% or more with SCC has been reported from other countries, adopting special measures to improve treatment adherence. Some of the measures used were home visit by a health worker in Botswana²³, a parish priest in the Philippines²⁴ and a nursing officer in Beijing²⁵, whereas in Tanzania²⁶, patients were hospitalised during the initial period of treatment. Application of any of these measures on a nationwide basis in India would require much more resources than are currently available. However, alternative approaches such as utilisation of the available community workers for retrieving patients is likely to improve case-holding without additional expenditure. This Centre is currently investigating different strategies, such as utilisation of

multipurpose workers (MPW), student volunteers of National Service Scheme (NSS), traditional birth attendants (Dais) at village level, drug supply through subcentres and patient-to-patient motivation in promoting patient compliance. The results of such studies will be useful in strategic planning of health care delivery.

A high proportion of patients for whom sputum examination was done at the end of treatment, namely 95-99% were smear negative. When a sample of sputum specimens from 2 districts was examined by culture at this Centre, 80% of 408 were negative in a district where the fully supervised regimen was prescribed and 92% of 876 in a district where the partially supervised regimen was prescribed²⁷. Studies are underway to estimate the relapse rates among patients put on SCC under DTP.

It was reported from this Centre that among a group of 2306 patients treated with SCC in the above districts with the fully supervised regimen, 42% had completed 80% or more of treatment²⁸. A one-time sputum specimen was collected (corresponding to 6-36 months after the start of treatment) and 79% of the patients who had received 80% or more of chemotherapy were negative by culture. It was also observed that even among patients who had received less than 50% of the drugs, 52% were culture negative. However, this Centre is undertaking another study to corroborate this finding by collecting periodic sputum specimens from the same district.

The following key issues are vital for the success of the programme: proper documentation and timely reporting², motivated and trained personnel at the periphery level^{10,29}, uninterrupted drug supply, good maintenance of microscopes and regular check of sputum microscopy, periodic evaluation and surveillance at all levels, in-service training for both technical and managerial personnel, and availability of functioning transport with adequate fuel supply to facilitate mobility of supervisory staff.

A study of the relative importance of the 3 components of the programme, namely, case-finding, case-holding and chemotherapy has been reported³⁰. In these 18 districts, the case-finding has been 41 %, the case-holding to be 54 % and the regimen used in the present project are of near

100 % efficacy (in clinical trials). In this situation, the overall impact of the programme could only be around 22%. There is, thus, a need to evolve strategies to improve case-finding and case-holding, the two deficient components of the programme.

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Annexure: Demographic data, case finding activity and application of SCC in 18 districts

District	State	Popula- tion (000000)	No. of Pffls		New smears <u>examined</u> No.	Positive		Eligi- ble for SCC No.	Pet on SCC		1st Reg* %
			under 1985	DTP 1991		No.	No.		No.	No.	
Policy A											
N. Arcot	Tamil Nadu	4.50	87	94	42863	2034	5	1990	1142	57	91**
Puri	Orissa	2.92	74	82	14390	594	4	511	377	74	50
Baroda	Gujarat	2.56	70	85	18657	2557	14	1866	1119	60	20
Thane	Maharashtra	3.35	84	94	31460	1780	6	1746	1380	79	1
Ujjain	Madhya Pradesh	1.12	30	54	9150	867	9	551	373	68	50
Dehra Dun	Uttar Pradesh	0.76	23	27	10359	975	9	810	570	70	2
Policy B											
Karnal	Haryana	1.32	20	29	10130	751	7	636	326	51	-
Kanpur	Uttar Pradesh	3.74	26	33	20282	1466	7	1032	353	34	-
Nagpur	Maharashtra	2.59	85	53@	27346	2184	8	2035	988	49	-
Raikot	Gujarat	2.09	29	75	10914	921	8	682	462	68	-
Raichur	Karnataka	1.78	26	73	13127	930	7	767	459	60	-
Sagar	Madhya Pradesh	1.32	38	48	7743	716	9	446	330	74	-
Policy C											
Pondicherry	Union Territory	0.44	52	58	19345	865	4	455	349	77	99
Vidisha	Madhya Pradesh	0.78	26	45	7009	561	8	469	379	81	23
Aurangabad	Maharashtra	2.43	40	50	13947	1276	9	1189	791	67	3
Varanasi	Uttar Pradesh	3.70	22	33	17174	914	5	697	464	67	69
Sabarkantha	Gujarat	1.50	41	69	19521	1392	7	1274	946	74	1
W. Godavari	Andhra Pradesh	2.87	37	61	16793	1165	7	1060	534	50	78

Figures given under these columns are mean values per year.

* Proportion prescribed the main regimen (in Policies A & C districts).

** 2nd regimen implemented in 1990

@ Due to administrative reasons, some PHIs were amalgamated.

PERSISTENT CHEST SYMPTOMS IN SMEAR POSITIVE PULMONARY TUBERCULOSIS PATIENTS TREATED WITH STANDARD AND SHORT COURSE CHEMOTHERAPY REGIMENS UNDER A DISTRICT TUBERCULOSIS PROGRAMME -- A FIVE YEAR FOLLOW-UP*

V.H. Balasangameshwara¹, P. Jagota² and R. Channabasavaiah³

Summary: In an earlier study about the fate of smear positive pulmonary tuberculosis patients five years after diagnosis in a District Tuberculosis Programme, information regarding persistent chest symptoms and history of subsequent treatment was also collected. The present report, gives the proportion of patients having persistent chest symptoms five years after diagnosis, according to present culture status, treatment adherence during primary treatment and the influence of subsequent treatment..

Chest symptoms persisted more among those now found culture positive compared to those now having negative culture {about 1/3rd of the culture negative patients were still attending health Institutions. Majority (about 50%) of such patients who had availed of government health facilities initially continued to take anti-tuberculosis treatment for persistent symptoms from government facilities.

Effective treatment, with standard regimens (SR) had reduced the proportion of patients with persistent chest symptoms and the situation was still better with SCC

In about 1/3rd of the now smear positive patients, the presence of persistent chest symptoms did not prompt the attending physicians to examine their sputum again for AEB, And they had not received specific subsequent treatment. However, subsequent treatment did not {reduce the proportion of patients having persistent chest symptoms. The practice of prescribing specific subsequent treatment,; therefore, should be based on the result of smear examination and not on symptoms in treated cases.

INTRODUCTION

It is a common practice to re prescribe anti-tuberculosis drugs for 'old cases' because of persistent chest symptoms. Sputum smear examinations are usually neither done at the end of primary treatment nor at the time of starting subsequent treatment. Even if they are done, they are not given due consideration at the time of subsequent treatment with anti-tuberculosis drugs.

In an earlier study¹ about the outcome of chemotherapy in patients with smear positive pulmonary tuberculosis five years after diagnosis, information regarding persistent chest symptoms and subsequent treatment taken was also collected. It was reported that 42.4% of patients placed on standard regimen (SR) were still having chest symptoms compared to 22.1% treated with short course chemotherapy (SCC). Cough, with or without other chest symptoms, was present in 36.4% of patients on SR compared to 19.5% on SCC. Cough constituted the predominant symptom (above 85%). In this report the two main groups i.e. one group of patients who had taken SR regimen and the other SCC as primary treatment were analysed according to the difference in the proportions having persistent chest symptoms, culture results at the end of five years, subsequent treatment taken and levels of treatment adherence during primary treatment.

METHOD

A cohort of smear positive pulmonary tuberculosis patients aged five years and above, diagnosed and treated with SR and SCC, as recommended in DTP manuals, during the calendar year 1985, at Lady Willingdon State Tuberculosis

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Centre (LWSTC), and residing within Bangalore city limits was the study material¹ for the main study. However, the treatment cards of those who had completed the treatment did not have the results of final follow-up sputum smear examination. The data¹ on the treatment cards were re-analysed for levels of primary treatment, and addresses were collected for contacting the patients in their homes to know their fate five years after primary treatment. The patients were traced out by the health visitors (HVs) of National Tuberculosis Institute (NTI) and LWSTC, who also collected the history of subsequent treatment, if taken. Two specimens of sputum were also collected from those contacted for direct smear and culture examination at NTI. From all those contacted, a social worker of NTI collected independently the information about presence of persisting symptoms.

DEFINITIONS

1. Primary treatment: anti-tuberculosis treatment prescribed at the time of initial diagnosis.
2. Chest symptoms: Cough of two weeks or more, with or without fever & chest pain of fifteen days' duration and haemoptysis.
3. Subsequent treatment: Any anti-tuberculosis treatment taken after the primary treatment.
4. Contacted: Patients traced at the address recorded on the treatment card (dead or alive).
5. Satisfactorily interviewed: patient found living and interviewed.

MATERIAL

In all, 1227 patients were registered for the study. Of them, 50 patients had not made even a single collection and were excluded. From the remaining, only 336 (29%) patients were satisfactorily interviewed. Of them, 219 (65%) did not have chest symptoms. Among 117 who gave history of chest symptoms, 101 had cough (86%) either alone or in combination with fever, chest pain or haemoptysis (Annexure I). The mean duration of cough was 2.1 and 1.4 months among SR and SCC patients respectively. The difference was not significant. Sufficient data were available for 302 patients and they form the material for this analysis. The reasons for the exclusion of 34 patients are: (i)

chest symptoms not stated (5), (ii) culture contaminated (4), (iii) subsequent treatment not known (16) and (iv) number of drug collections during primary treatment not known (9). Of the 34 patients excluded from analysis, 26 patients belonged to those treated with SR during primary treatment and 8 to SCC group. The age and sex distributions were similar among contacted and not contacted patients. Among those contacted, 216 (63%) patients had received subsequent treatment and among them 12.5%, 65.3% and 22.2% had received the subsequent treatment from LWSTC, other government facilities and private doctors respectively (Annexure II). This included 77 patients who were unable to say whether they had received anti-tuberculosis treatment subsequently. They have been excluded from analysis. Among the remaining 139 contacted patients who had received subsequent treatment, 30.2%, 59.7% and 10.1% had received SR, SCC and SR+SCC respectively (Annexure III). Of them, 138 have been taken for analysis.

RESULTS

1. Persistent chest symptoms and culture results among the contacted, relating to primary treatment, irrespective of subsequent treatment (Table 1)

Of the 302 patients, 194 (64.2%) had received SR as primary treatment and the remaining got SCC. It was found that (1) persistent symptoms were significantly more frequent among those treated with SR as primary treatment and found culture positive (63.6%) compared to the patients found culture negative (39.3%) ($P < 0.05$), (2) there was no difference in respect of persistent chest symptoms among those culture negative or positive but treated with SCC as primary treatment (20% among culture negative cases and three out of eight among culture positive patients), (3) persistent chest symptoms were significantly more frequent among culture negative SR treated patients (39.3%) compared to SCC culture negatives (20%) ($P < 0.05$), (4) there was no difference in persistent symptoms among those treated with SR or SCC as primary treatment who were culture positive (63.3% of those treated with SR and three out of eight treated with SCC), and (5) a majority (above 83%) had cough even five years after primary treatment, either alone or in combination with other chest symptoms.

Table 1. Persistent chest symptoms among the satisfactorily interviewed

Primary treatment	Present culture result	Number	Chest symptoms present			
			Number	Percent col.4/col.3	Cough alone or in combination	
					Number	Percent col.6/col.4
1	2	3	4	5	6	7
SR ¹	Neg.	150	59	39.3	49	83.1
	Pos.	44	28	63.6	26	92.9
	Total	194	87	44.8	75	86.2
SCC ²	Neg.	100	20	20.0	18	90.0
	Pos.	8	3	37.5	3	100.0
	Total	108	23	21.3	21	91.3

1. Excludes 26 patients: chest symptoms not stated (2), culture contaminated (2), primary drug collections not known (9) and subsequent treatment not known (13).

2. Excludes 8 patients: chest symptoms not stated (3), culture contaminated (2) and subsequent treatment not known (3).

2. Persistent chest symptoms and culture results according to subsequent treatment after primary treatment (Table 2)

Breakup of subsequent treatment into SR and SCC has not been done as this resulted in small

numbers. Persistent chest symptoms among those with SR as primary treatment who were not treated subsequently, were significantly higher among culture positives (69.2%) compared to culture negatives (33.3%) (P < 0.05). Number of those

Table 2. Persistent chest symptoms according to culture result and subsequent treatment

Primary treatment	Present culture result	Number	Subsequent treatment				
			Taken		Not taken		
			Chest symptoms present		Number	Chest symptoms present	
			Number	Percent		Number	Percent ²
1	2	3	4	5	6	7	8
SR	Neg.	84	37	44.0	66	22	33.3
	Pos.	31	19	61.3	13	9	69.2
	Total	115	56	48.7	79	31	39.2
SCC	Neg.	19	8	42.1	81	12	14.8
	Pos.	4	1	25.0	4	2	50.0
	Total	23	9	39.1	85	14	16.5

1 Percent of Col. 4/Col. 3

2 Percent of Col. 7/Col. 6

treated with SCC as primary treatment and with no subsequent treatment was small on account of few patients now culture positive. There was no significant difference in persistent chest symptoms among culture negative patients on SR or SCC for those who had taken subsequent treatment. Among the culture negative patients, persistent chest symptoms were significantly higher in SR patients who had not taken subsequent treatment (33.3%) compared to SCC (14.8%) patients ($P < 0.05$). In SR and SCC patients who had taken subsequent treatment there was no significant difference in persistent chest symptoms among the culture negatives (44% & 42.1%) compared to culture positives (61.3% & 1/4), respectively. Among the SCC culture negative patients persistent chest symptoms were significantly more among those who had taken subsequent treatment (42.1%) compared to those who did not (14.8%) There was no difference in persistent chest symptoms among the culture positive patients who had taken subsequent treatment (57.1%) compared with culture negative patients (43.7%).

3. Persistent chest symptoms and culture results according to adherence levels in primary treatment (Table 3)

Table 3 shows that among SR culture negative patients who had made <75% drug collections, 47% of those who had taken subsequent treatment had persistent chest symptoms, same as in those who had not taken subsequent treatment. For those who had made >75% drug collections, the respective proportions were 33.3% and 28.6%. Among the SR culture positive patients, the proportions of persistent chest symptoms who had made <75% and >75% drug collections in their primary treatment were 63.6% and 55.6% respectively among those who had taken subsequent treatment and 87.5% and 40.0% respectively among those who had not taken subsequent treatment. Therefore, in SR patients there was no significant difference according to either culture or subsequent treatment or level of treatment adherence regarding persistence of symptoms.

Table 3. Persistent chest symptoms according to adherence level in primary treatment

Primary treatment	Culture result	Primary treatment adherence (percentage collected out of due)	Subsequent treatment					
			Taken			Not taken		
			Total	Chest symptoms present		Total	Chest symptoms present	
				No.	%		No.	%
SR	Neg.	<75%	66	31	47.0	17	8	47.1
		>75%	18	6	33.3	49	14	28.6
		Total	84	37	44.0	66	22	33.3
	Pos.	<75%	22	14	63.6	8	7	87.5
		>75%	9	5	55.6	5	2	40.0
		Total	31	19	61.3	13	9	69.2
SCC	Neg.	<75%	11	4	36.4	9	0	0.0
		>75%	8	4	50.0	72	12	16.7
		Total	19	8	42.1	81	12	14.8
	Pos.	<75%	2	1	50.0	1	0	0.0
		>75%	2	0	0	3	2	66.7
		Total	4	1	25.0	4	2	50.0

Although number of patients is rather small, it appears that persistent chest symptoms were generally less common in patients treated with >75% of SCC as primary treatment and found culture negative with or without subsequent treatment compared to similar patients treated with >75% of SR treatment. The numbers of SCC patients found culture positive at the end of five years were too small to analyse. Among SR patients, who had not received subsequent treatment, persistent chest symptoms were significantly less among patients found culture negative with >75 % level of adherence (14 (28.6%) out of 49) compared to culture positive patients with <75% treatment (7 (87.5%) out of 8).

DISCUSSION

In the present analysis, the proportions of patients, treated in a DTP, having persistent chest symptoms five years after diagnosis according to levels of adherence during primary treatment and the present culture status were studied. The influence of subsequent treatment taken was also analysed. In the absence of information on culture status at the end of primary treatment, the effect of subsequent treatment in reducing chest symptoms in those who were treatment failures or relapses was not possible to analyse.

The results of the analysis showed that persistent chest symptoms were more frequent among those found culture positive after five years compared to those having negative culture status. This is as could be expected. Also, the expectations are that a majority of those who take satisfactory treatment (>75%) get cured and may not have persistent chest symptoms compared to those who take unsatisfactory treatment (<75%). Thus, in our study, among those who did not give history of subsequent treatment, the patients with >75 % primary treatment and culture negative status at the end of five years, are expected to be those who had been cured because of primary treatment. And those with <75% primary treatment and found to be culture positive at the end of five years, were to be those who had not been cured with primary treatment². It was found that persistent chest symptoms were significantly more in the latter group compared to the former in so far as SR as primary treatment was concerned. Among the culture negative patients, however, who had <75% level of treatment and had not taken subsequent treatment,

those who had taken SCC as primary treatment had significantly less chest symptoms compared to those on SR. This appears to correlate with the finding that the proportion of cases becoming culture negative with <75% of SCC is more than those with the same level of SR².

As regards the cases who were culture positive at the end of 5 years, the number of patients in the SCC group being small, the same type of analysis was not possible. Among the patients who received subsequent treatment, in the absence of information on sputum status at the end of primary treatment, it is difficult to say whether the patients became culture negative because of subsequent treatment. Though the patients who got subsequent treatment had a more favourable outcome¹, it did not help in reducing the persisting chest symptoms. The finding that significantly more patients had persistent chest symptoms even among culture negative patients may be due to over-treatment or bronchial sequelae of primary treatment. However, it can be seen that 31.6% and 14.8% of the now culture negative SR and SCC patients, respectively, had persisting symptoms obliging them to visit health institutions for relief of their suffering. The practice of prescribing subsequent anti-tuberculosis treatment should, therefore, be based on sputum smear examination. In the absence of a positive smear result, even a more serious chest symptom like haemoptysis should not be the reason for starting anti-tuberculosis treatment. It is known that haemoptysis occurs in some treated pulmonary tuberculosis patients due to resulting bronchiectasis³, which is also the reason for cough.

In such patients, the correlation between smear and culture examinations is fairly high¹. Those requiring subsequent anti-tuberculosis treatment could be identified, and unnecessary subsequent treatment avoided, by performing a smear examination in 'old cases' reporting with chest symptoms. Medical practitioners generally do not appear to accept sputum smear microscopy, as a follow-up examination because though cough was present in about 35.5% of the now culture positive patients, they had not been given subsequent treatment by the attending physicians (Table 2). The district tuberculosis programme, however, provides for restarting treatment of pulmonary tuberculosis patients only if they are

smear positive. And it is, encouraging to note that about 80% of the patients who had received subsequent treatment did so from government facilities.

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Annexure I

Chest symptoms among satisfactorily interviewed

Primary treatment	Chest symptoms					
	Absent	Cough alone	Cough with others	Others without cough	Not known	Total
	No.	No.	No.	No.	No.	No.
SR	125	38	41	13	3	220
ScC	88	8	14	3	3	116
Total	213	46	55	16	6	336 ^a

^a Included for analysis : 302

Annexure II

Source of subsequent treatment among satisfactorily interviewed

Subsequent treatment	Primary treatment					
	SR		scC		Total	
	No.	%	No.	%	No.	%
LWSTC	18	9.7	9	30.0	27	12.5
Other Government facilities	125	67.2	16	53.3	141	65.3
Private physician	43	23.1	5	16.7	48	22.2
Total	186	100.0	30	100.0	216 ^c	100.0

^c Included for analysis : 138

Annexure III

Type of subsequent treatment among those satisfactorily interviewed, according to primary treatment

Subsequent treatment	Primary treatment					
	SR		scC		Total	
	No.	%	No.	%	No.	%
SR	37	31.4	5	23.8	42	30.2
ScC	72	61.0	11	52.4	83	58.7
SR+SCC	9	7.6	5	23.8	14	10.1
Sub-total	118	100.0	21	100.0	139 ^b	100.0
Not known	68		9		77	
Total	186		30		216	

^b Included for analysis : 138

Smear and culture results of satisfactorily interviewed patients

Sputum examination		Culture result				
		Pos.	Neg.	Sub-total	Contaminated	Total
Smear result	Pos.	39	8	47	0	47
	Neg.	30	265	285	4	289
	Total	59	273	32	4	336

Accuracy of smear examination = $(39+265)/332=91.6\%$

A HIGHLY SPECIFIC POLYMERASE CHAIN REACTION TEST FOR DETECTION OF *MYCOBACTERIUM TUBERCULOSIS**

Gururaj V. Kadival, C.D. D'Souza, S.P. Kulkarni and A.M. Samuel**

Summary; A Polymerase Chain Reaction for the amplification of a 340 bp sequence of the 38 kDa protein gene of *Mycobacterium tuberculosis* has been developed. This has a sensitivity of 10⁶, both by agarose gel electrophoresis and Southern Blot hybridisation, which is equivalent to 2-3 organisms. It is highly specific for *M. tuberculosis* and excludes even *M. tuberculosis* H 37Ra and *Mycobacterium bovis* BCG, AFB positive sputum specimens from patients with pulmonary tuberculosis gave positive results by this PCR. Specificity of this PCR in clinical samples was 96%.

tuberculosis H₃₇Ra, *M. bovis* BCG, *M. smegmatis*, *M. Phlei*, *M. intracellulare*, *M. avium*, *M. microti*, *M. scrofulaceum*, *M. vaccae*, *M. ulcerans*, *M. Kansasii*, *M. flavescens*, *Corynebacterium diphtheriae*, *C. murisepticum*, *Nocardia*, *Streptomyces albus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichiacoli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae* and *Salmonella typhi* were used for studying the specificity of PCR. The above strains were cultured in liquid media and DNA was extracted by conventional methods.

Oligonucleotide primers and probes: Primers for the amplification of the 340 bp region of the 38 kDa protein gene designated as KD1 (5' CCA AGC AAG ATC CCG AGG GCT 3') and KD2 (5' TTG ATG ATC GGG TAG CCG TCC 3') and an internal probe KD3 (5' TGC GCC GAG ACA CCG GGC TGC GTG GCC TAT 3') were custom synthesized at the National Chemical Laboratory, Pune, India.

INTRODUCTION

Diagnosis of tuberculosis by conventional methods such as microscopy and culture has inadequate sensitivity and specificity. While microscopy needs 10⁵ organisms/ml for a positive result, culture takes 3-6 weeks. Early diagnosis of tuberculosis is essential for control of tuberculosis. Many reports have appeared on the use of Polymerase chain reaction (PCR) for early diagnosis of tuberculosis¹⁻¹⁰. For PCR, majority of authors use IS6110, an insertion sequence, as the target for amplification, as *M. tuberculosis* is reported to contain multiple copies of this sequence^{3,6,9,11}. There are, however, reports indicating that strains from India¹² lack IS6110. Hence, it is essential to identify other sequences for use as target for amplification. In the present study, we amplified a 340bp sequence of the 38 kDa protein gene as the target sequence, as this gene sequence has been shown to be specific for *M. tuberculosis*.

MATERIAL AND METHODS

Bacterial Strains: *M. tuberculosis* H₃₇Rv, *M.*

PCR

a. 38 kDa protein gene: The PCR mix consisted of 10 mM Tris-HCl pH 8.3, 50mM NaCl, 1.5 mM MgCl₂, 0.01% gelatin, 0.2mM of each dNTP's, 0.5 uM of each primer KD1 and KD2 and 2.5 U of Taq DNA polymerase (Perkin Elmer, Cetus) per 100 ul reaction volume. The above mix was freshly prepared every time without Taq DNA polymerase. At the time of the test, 70 ul of mineral oil was added to each tube before 10 ul of DNA, extracted from mycobacteria or sputum specimens was added. These were preheated to 95°C for 5 min., to ensure complete denaturation of the template. Taq DNA polymerase was then added and PCR performed for 40 cycles of 1 min. at 94°C for denaturation, 1 min at 64°C for annealing of primer and 1 min. at 72°C

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for extension of the target sequence (Temp. Cyclor II, Coy Corporation USA)

b. *Detection of amplified DNA*: PCR products were analysed by electrophoresis on 2% agarose gel and stained with Ethidium bromide. To confirm the identity of the amplicon, Dot Blot hybridisation using a 32p labelled internal probe KD3 sequence was performed. The 5'end labelling of the probe was done using a kit and 32p]ATP supplied, ed by BRIT, Bombay, India.

PCR for clinical specimens: Sputum specimens from patients with pulmonary tuberculosis and other diseases of the lung, as controls, were collected in sterile McCartney bottles containing DTT. These were incubated at 95°C for 10 min., blind coded and stored at -20° until processed. A 750 ul aliquot of the sputum specimen was centrifuged at 12000 x g, and the pellet resuspended in 90 ul of TE buffer. Then 10 u l of digestion buffer containing proteinase K was added and incubated at 60°C for 18 h. Further incubation at 100°C for 15 min. was carried out to release the DNA and inactivate proteinase K. DNA was extracted using the chloroform method described by Wilson et al¹⁰, and 10 ul of the extracted sample was used for PCR.

Routine AFB staining and cultures were also carried out on all sputum specimens

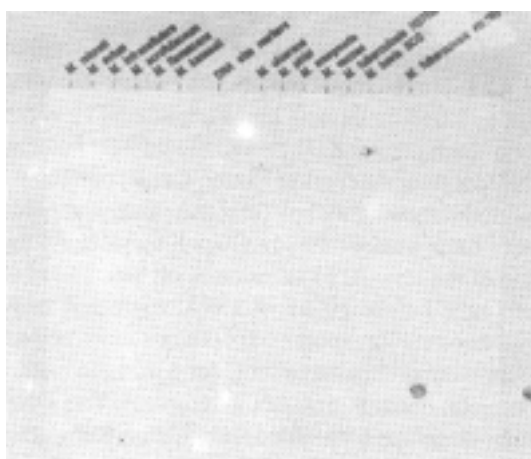
RESULTS

Amplification for 340 bp of 38 kDa protein gene

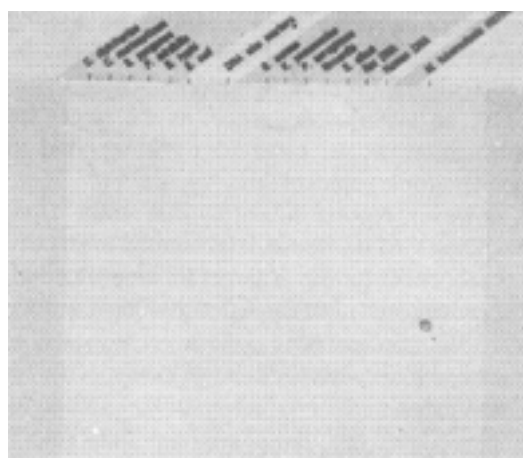
Sensitivity of PCR: Using primers KD1 and KD2 for the amplification of the 340 bp sequence of the 38 kDa protein gene, the amplification product could be visualised after electrophoresis and staining by Ethidium bromide as well as Dot Blot hybridisation. All concentrations upto 10fg of *M. tuberculosis* genomic DNA as target, which corresponds to 2-3 mycobactena, could be visualised.

Specificity of PCR: The specificity of primers KD1 and KD2 was tested by carrying out amplification with purified genomic DNA from 13 different mycobacterial species, 11 bacterial species, human and rat leucocytes. The 340 bp amplicon was found only with *M. tuberculosis* and not with any other mycobacterium including *M. bovis* BCG and *M. tuberculosis* H₃₇Ra (Fig. 1)

PCR with Sputum Specimens: DNA extracted from sputum specimens was tested in triplicate, one of which was spiked with 10fg of pure *M. tuberculosis* DNA. A specimen was considered negative if it failed to show amplicons in two determinations while the spiked sample was positive. It was



Panel A



Panel B

Figure 1. Specificity of primers KD1 and KD2 in PCR amplification with mycobacterial and other bacterial DNA. Analysis by agarose gel electrophoresis (Panel A), and Southern blot hybridisation with the radiolabelled internal probe KD3 (Panel B). One nanogram of DNA from different bacteria was used in the PCR. Amplification was highly specific to *M. tuberculosis* H₃₇RV.

considered positive if all the 3 showed amplification. However, if all the three including the spiked sample were negative, it was considered that there were interfering substances causing inhibition of the reaction.

Twenty six control specimens which had originated from the Respiratory Unit of a general hospital and a cancer hospital were similarly tested, of which one was positive for the 38 kDa sequence. Ten samples obtained from patients with pulmonary tuberculosis and sputum positive for AFB were also positive by PCR.

DISCUSSION

PCR, a recent biotechnology development is extensively utilised in the diagnosis of infectious diseases. A number of investigators have attempted to use this rapid technique for the diagnosis of tuberculosis. Earlier attempts used sequences from protein genes as target such as the heat shock proteins. However, isolation of the insertion element IS6110 (Thierry et al¹³) also designated as IS 986 (McAdam et al¹⁴), a member of the IS3 family of insertion elements led to the extensive use of this sequence as a target for amplification. The principal reason for using IS6110 as a target was that multiple copies (up to 19) of this were present on the *M. tuberculosis* genome¹⁵ and higher sensitivity could thus be obtained. Recently, it has been shown that there are *M. tuberculosis* strains originating from India¹² which do not contain IS6110. Thus, a need has arisen to identify alternative sequences which may be present as single copy genes but exhibit the same degree of sensitivity and specificity. In our opinion, functional protein genes offer the best advantage as targets for amplification.

The 38 kDa protein has been shown to be serospecific to *M. tuberculosis* complex group of organisms^{16,17}. It has also been shown to be a transport-protein essential for phosphate transportation into the cell and secretion of this protein is known to be enhanced on phosphate starvation¹⁸. Thus, the 38 kDa protein gene appears to be an ideal target for amplification.

A sensitivity of 10 fg of target, which is equivalent to 2-3 organisms was obtained. Specificity

of the PCR was tested by using, as target, the DNA obtained from various atypical mycobacteria, bacterial species and human and rat DNA. The fact that no amplification of a 340 bp sequence was observed with any of these, including *M. bovis* BCG and *M. tuberculosis* H₃₇Ra, indicates the exclusive nature of this sequence under the PCR conditions adopted.

Sputum specimens from patients with pulmonary tuberculosis and other diseases were also studied. Care was taken to differentiate between true negative and false negative determinations by spiking a sample each with *M. tuberculosis* genomic DNA. Sensitivity in AFB positive specimens was quite good and only 1 of 26 controls gave a positive PCR. Thus, the test has a specificity of 96%. Yuen et al¹⁹ have reported on the amplification of a 239 bp sequence of the 38 kDa protein gene which gave 8% false negative results if a single specimen from each patient was used. However, if 3 specimens from each patient were analysed, 100% positive results were obtained. Thus, the PCR technology is rapid, sensitive and ready to move out from the research laboratory to clinical use. For its successful application, however, simpler procedures for extraction of DNA and detection of amplicon are needed.

In conclusion, we have demonstrated that amplification of the 340 bp sequence of 38 kDa protein gene is highly specific to *M. tuberculosis* and being a functional gene, it is an ideal target for amplification for clinical use.

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DRUG SENSITIVITY AND VIRULENCE OF *M. TUBERCULOSIS* GROWN IN THE PRESENCE OF CARBON DIOXIDE*

M.M. Chauhan¹ and V.K. Challu²

Summary: In order to study the virulence and sensitivity patterns of *M. tuberculosis* grown in an atmosphere with (A) and without (B) 10% CO₂, 219 isolates were examined.

Of the total isolates, 98(44.7%) were found sensitive to all drugs and the remaining 121 (55.3%) resistant to one or more drugs. Method A was superior to method B. For INH sensitive strains subjected to virulence study, method A was superior to method B and the percentages of low and high virulence were 73.8 and 26.2 for method A compared to 45.7 and 54.3 for method B respectively. Thus the presence of 10% CO₂

Enhances the growth of sensitive bacilli and facilitates the detection of low virulence isolates sensitive to INH.

INTRODUCTION

Although the causative agent of tuberculosis was identified over a century ago, knowledge about its fundamental physiological capabilities, genetics, drug resistance and specific virulence determinates, especially mechanisms of pathogenicity under increased Carbon Dioxide (CO₂) tension is still almost non-existent.

Although CO₂ is not essential for initiating primary growth on egg medium (LJ medium), studies have shown that CO₂ stimulates greater and faster growth¹². In an earlier study¹, we had shown that CO₂ increased the yield of *M. tuberculosis* in primary culture on LJ medium. The present study was undertaken to assess drug sensitivity and

virulence of *M. tuberculosis* when grown in the presence of 10% CO₂

OBJECT

The objective was to study

The growth of sensitive and resistant strains of *M. Tuberculosis* under 10% CO₂

The low and high virulence status of strains grown in the presence of 10% CO₂.

MATERIAL & METHODS

One thousand and five clinical specimens received for isolation of mycobacteria from the various ongoing studies of the National Tuberculosis Institute, Bangalore, during the period February to May, 1990 were included in the study.

All the specimens were subjected to smear examination by Ziehl-Neelsen's (ZN) method and culture by modified Petroff's method⁵. The sediment was inoculated on four slopes of Lowenstein Jensen's (LJ) medium. Two randomly selected slopes of LJ medium were incubated in a CO₂ incubator in a slanting position with caps loose for the first twelve days. The caps were later tightened to prevent dehydration. CO₂ was maintained at 10% concentration and humidity at 82% to 87% (Method A). The remaining two slopes of each specimen were incubated at 37°C without CO₂ (Method B). Positive cultures were subjected to the identification and sensitivity tests as per our routine procedure⁵.

All the INH sensitive cultures were subjected to virulence assay and calculation of the root-index of virulence (RIV) according to the method

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described by Mitchison et al⁶. Briefly, 1.0 mg of dry cells harvested from a three weeks old culture was injected intramuscularly into NTI bred albino guinea pigs. The animals were killed after six weeks to assess the extent of gross disease in different organs like lymph node, liver and spleen. Pairs of guinea pigs were randomly allocated for injection of coded isolates and the persons scoring the gross findings were not aware of the type of isolate (i.e., whether grown under method A or B) having been injected to the animal. The categorization of low or high virulence isolates was done as described by Ramakrishna et al⁷.

RESULTS

Out of 1,005 specimens subjected to culture, 219 (21.9%) were culture positive. Of the 219 cultures, 98 isolates were INH sensitive and 121 resistant to one or more drugs (Table I).

Comparison of growth with CO₂ and without CO₂ among resistant cultures is represented in Table 4. The results were not significantly different.

The virulence status of INH sensitive cultures is indicated in Table 5. Out of 61 INH sensitive cultures grown only in 10% CO₂, 45 (73.8%) and 16 (26.2%) were of low and high virulence respectively, differing from that by methods, i.e., 16 (45.7%) and 19 (54.3%) of low and high virulence respectively. This is statistically significant ($\chi^2 = 48.91$, $P < 0.001$).

DISCUSSION

In our earlier study¹, we had shown that CO₂ markedly increased the yield of *M. tuberculosis* in primary cultures grown on LJ medium. In this report, the effect on growth by method A (with CO₂)

Table 1. Drug Sensitivity Status of Positive Cultures

Result	Positive Cultures Total 219		Positive Growth			
			With CO ₂		Without CO ₂	
	No.	%	No	%*	No.	%*
1	2	3	4	5	6	7
Sensitive to all Drugs	98	44.7	92@	91.0	36@	35.6
Resistant to one or more Drugs	121	55.3	94	77.7	93	76.9

*Percent of Col.2

@ Difference in totals is due to removal of contaminations

Of the 98 INH sensitive cultures, 60 had grown in the presence of CO₂, 5 without CO₂ and 33 both with and without CO₂. Out of 118 resistant isolates, 5 and 2 were grown in the presence of CO₂ and without CO₂ respectively. Table 2 shows that method A differed significantly from method B in respect of drug sensitive isolates ($\chi^2 = 88.99$, $P < 0.001$).

Table 3 also shows that method A differed significantly from method B in respect of drug sensitive strains, i.e., culture positivity was 93.9% in method A and 35.7% in method B ($t = 10.57$, $P < 0.01$).

Table 2. Effect of CO₂ on the Growth of Drug Sensitive and Resistant Isolates

Growth	Sensitivity Status		Total
	Sensitive to all drugs	Resistant to one or more drugs	
With only CO ₂	60	5	65
Without CO ₂	5	2	7
With and without CO ₂	33	111	144
Total	98	118	216

$\chi^2 = 88.99$ for 2 D.F. ($P < 0.001$)

Table 3. Comparison of Two Methods for Cultures Sensitive to all Drugs

Method	Pos.	Neg.	Contaminated*	Total
	No.	No.	No.	No.
With CO ₂	92	5	1	98
Without CO ₂	35	61	2	98

* = Excluded from total
t=10.57, P<0.01

Table 4. Effect of CO₂ on the Growth of Drug Resistant Cultures

Method of culture	"Resistant to INH only		Resistant to more than one		Resistant to all drugs		Total
	No.	%	No.	%	No.	%	
With CO ₂	94	81.1	16	13.8	6	5.1	116
Without CO ₂	93	81.6	15	13.2	6	5.2	114

Statistically there was no significant difference in growth because of CO₂ for drug resistant cultures

Table 5. Virulence Status of INH Sensitive Cultures

Method of culture	Virulence status				Total
	Low		High*		
	No.	%	No.	%	No.
With CO ₂ only	45	73.8	16	26.2	61
Without CO ₂	16	45.7	19	54.3	35
Total	61	63.5	35	36.4	96

* High virulence - RIV >0.9
X² = 48.9137 for D.F.2(P = 0.001)

and method B (without CO₂) is compared according to sensitivity status of the isolates. Method A significantly enhanced the growth of drug sensitive isolates compared to method B.

It is generally believed that CO₂ enhances the growth of drug resistant rather than sensitive

bacilli. The study revealed that the yield of resistant bacilli in both the methods was equal. But method A markedly increased the yield of cultures sensitive to all drugs.

About virulence of *M.tuberculosis*, Raffel and Clifton⁸ found that virulent strains of *M. tuberculosis* were more tolerant of low oxygen tension than avirulent ones. They hypothesized that virulence of *M. tuberculosis* is a function of its ability to respire and grow at lower oxygen tension, present in host tissue, and hence ability to produce active tissue damage. But, in our study higher CO₂ content in environment enhanced the growth of low virulent INH sensitive *M. tuberculosis* bacilli.

Also, it is believed that CO₂ enhances the growth of atypical (MOTT) mycobacteria, specially *M.bovis*, but we got no more than three isolates of atypical mycobacteria and no isolation of *M.bovis*. Therefore, the influence of CO₂ on the metabolism, physiological and biochemical activities of low and high virulence *M. tuberculosis* needs to be further studied.

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SERODIAGNOSIS OF PULMONARY TUBERCULOSIS AND EVALUATION OF TWO ELISA KITS*

Sujatha Chandrasekaran¹, M.M. Chauhan² & N. Parimab³

Summary: An investigation was carried out to assess the value of ELISA test in the serodiagnosis of pulmonary tuberculosis and the effectiveness of two ELISA test kits, using A 60 and Kp90 antigens respectively. Sputum culture was performed to confirm the diagnoses. Serum dilution of 1:100 was used and Ig G antibodies to A 60 and Ig antibodies to KP 90 were looked for. A total of 317 patients were studied. The cut-off point (mean+SD) was taken from healthy controls. The sensitivity, specificity and accuracy of KP 90 ELISA were 49.7%, 84.0% and 61.5% and those of A 60 ELISA were 48.3%, 92.0% and 71.3% respectively.

It is considered that in high prevalence conditions, serological tests for tuberculosis based on antibody detection should be used and interpreted with extreme caution. Their results should definitely score over sputum microscopy results in order to be widely applied.

INTRODUCTION

There are no two opinions about the prime role of sputum microscopy in the diagnosis of pulmonary tuberculosis. It is the non-availability of an equally specific and rapid diagnostic test for smear-negative cases and extrapulmonary tuberculosis that necessitates the search for other diagnostic tools.

The introduction of Enzyme Linked Immunosorbent Assay (ELISA) for rapid serological diagnosis has been a major developmental laboratory medicine. In tuberculosis also, ELISA test has been tried using different antigens such as antigen 5, phenolic glycoUrid, PPD, etc., mainly keeping in

mind the limitations of sputum microscopy and culture¹. A number of ELISA kits have recently been marketed in India, for use in diagnosis of tuberculosis. One of them, Anelisa Ig G, uses antigen A60 derived from *M. bovis* BCG, and another one, Kreatech Ig A employs antigen KP90 derived from *M. tuberculosis*. It was planned to conduct this study, in order to find out their utility in serodiagnosis of tuberculosis under Indian conditions.

OBJECTIVES

To evaluate two tuberculosis ELISA kits, Anelisa Ig G (A60) and Kreatech Ig A (KP90), in terms of their sensitivity, specificity, accuracy, and predictive value in respect of positive diagnosis.

MATERIAL AND METHODS

Newly diagnosed tuberculosis patients attending the Lady Willingdon State Tuberculosis Centre, S.D.S. Sanatorium and patients having non-tuberculous chest disease from M.S. Ramaiah Medical College Hospital, Bangalore, were taken into the study. Normal healthy controls were the blood donors from Jayadeva Institute of Cardiology, Bangalore. Serum specimens were obtained from all of them and stored at -20°C for about a week till ELISA tests were performed. Sputum specimens were also collected from all, except the healthy controls and subjected to AFB microscopy and culture for *M. tuberculosis*, using modified Petroff's method.

The study population was classified into four groups:

Group 1: Healthy subjects (105)

Group 2: Patients with non-tuberculous lung disease

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(lung abscess, chronic bronchitis, bronchial asthma, etc); all smear and culture negative (63)

Group 3: Newly diagnosed pulmonary tuberculosis patients; all smear negative and culture positive (S-C+). (These X-ray positive patients were provisionally included till confirmed by culture) (39)

Group 4: Newly diagnosed smear positive and culture positive cases of pulmonary tuberculosis (S+C+) (110).

All the specimens were coded and the codes were broken after all the results had been obtained.

ELISA Test Procedure

Serum specimens were diluted to 1:100, distributed into microtitre plate wells, coated with antigen and incubated for one hour at 37°C. After a washing cycle of five times, peroxidase labelled antihuman-immunoglobulin (Ig G/Ig A as the case may be) was distributed and incubated at 37°C for one hour. After another washing cycle, TMB solution was added in the dark and the plates were incubated at room temperature for 30 minutes. The reaction was stopped with H₂SO₄ and the optical density (OD) was measured at 450 nm in an ELISA Reader.

Analysis

Culture results were considered as the 'gold'

$$\text{Sensitivity} = \frac{\text{True Positives (TP)}}{\text{True Positives (TP)} + \text{False Negatives (FN)}} \times 100$$

$$\text{Specificity} = \frac{\text{True Negatives (TN)}}{\text{False positives (FP)} + \text{True Negatives (TN)}} \times 100$$

$$\text{Accuracy (Efficiency)} = \frac{\text{True Positives (TP)} + \text{True Negatives (TN)}}{\text{True Positives (TP)} + \text{True Negatives (TN)} + \text{False positives (FP)} + \text{False Negatives (FN)}} \times 100$$

$$\text{Predictive Value of Positives} = \frac{\text{True Positives (TP)}}{\text{True positives (TP)} + \text{False Positives (FP)}} \times 100$$

The mean titre of control group was compared with those of test groups and significance was tested by using 't' test. standard" and the following values were calculated:

RESULTS

The frequency distribution of optical densities in different study groups is given in Tables 1(a) and (b). In both the ELISA tests, the control groups do not show very high titres as do the diseased groups, but there is considerable overlapping of values in the middle range (0.600 to 1.799).

Table 1 (a). Frequency Distribution of Optical Densities in Patients and Controls ELISA with KP90

O.D. Values	Normals Group 1	NT Group 2	S-C+ Group 3	S+C+ Group 4
<0	9	0	2	0
0-0.3	38	10	5	15
0.3-0.6	26	10	6	18
0.6-0.9	13	8	7	21
0.9-1.2	10	9	1	8
1.2-1.5	6	10	6	16
1.5-1.8	1	4	5	10
1.8-2.1	1	3	3	3
2.1-2.4	2	3	2	6
2.4-2.7	0	4	2	8
2.7-3	0	0	2	3

Table 1 (b). Frequency Distribution of Optical Densities in Patients and Controls ELISA with A60

O.D. Values	Normals Group 1	NT Group 2	S-C+ Group 3	S+C+ Group 4
<0	9	0	2	0
0-0.3	38	18	7	10
0.3-0.6	24	26	6	15
0.6-0.9	24	9	9	23
0.9-1.2	2	5	8	24
1.2-1.5	4	1	5	21
1.5-1.8	1	2	2	7
1.8-2.1	0	1	0	2
2.1-2.4	1	1	0	6
2.4-2.7	2	0	0	2
2.7-3	0	0	0	0

In the patients with proven tuberculosis, the mean OD values were 1.228 ± 0.768 and 1.098 ± 0.787 with KP90 ELISA. These values are significantly higher than the mean OD values in the healthy controls (0.488 ± 0.480) given in Table 2. With A60 ELISA also, a similar observation was

made, indicating that there is a significant rise in antibody levels during the disease process.

Table 2. Optical Density Values in Different Groups According to ELISA Kit used

Group	No. of patients	KP90 ELISA		A60 ELISA	
		Mean		Mean	
		OD	SD	OD	SD
1	105	0.488	0.480	0.463	0.510
2	63	1.013	0.727	0.563	0.440
3	39	1.228	0.768	0.754	0.496
4	110	1.098	0.787	1.034	0.564

The cut-off point (mean + 1 SD), relative to the mean observed in the healthy controls approximated also to that recommended by the manufacturers. Thus, with this cut-off, it was seen that 16.2% of the normals, 47.6% of the non-tuberculous patients, 53.9% of the smear negative culture positives and 48.2% of the smear and culture positives were declared positive, using the KP90 test. A lower rate was seen among controls with the A60 ELISA indicating a higher specificity (Table 3). Taking culture as the standard, the specificity was 84% using KP90 and 92% using A60. The sensitivity, accuracy and positive predictive values were 49.7%, 61.5% and 56.1% with KP90 and 48.3% 71.3% and 75% respectively with A60 (Table 4).

Table 3. ELISA Seropositives Among Study Groups According to Kit Used

Group % Positive	KP90 ELISA		A60 ELISA	
	OD	SD	OD	SD
Normals	16.2	8.5		
Non-tuberculous lung disease	47.6	7.9		
Smear negative, culture pos.	53.9	38.5		
Smear positive, culture pos.	48.2	51.8		

DISCUSSION

It is generally accepted that infection with *M. tuberculosis* induces an antibody response which can be detected and measured. But the antibody

Table 4. Characteristics of Two ELISA Assays

	KP90	A60
Sensitivity	49.7%	48.3%
Specificity	84.0%	92.0%
Accuracy	61.5%	71.3%
Positive predictive Value	56.1%	75.0%

activity may not correlate with the severity of the disease², as has been seen in the present study also. It has been suggested that this could be due to: (a) the formation of immune complexes resulting in a reduction of specific antibody level, or (b) chronic stimulation of antibody production, leading to synthesis of progressively low avidity antibody. The present study also found low levels of antibodies in many smear positives, thus affecting the sensitivity of the assay. Unfortunately, it is difficult to evaluate the test in the bacteriologically negative patients in whom there is a low antigen load, because of the non-availability of the "gold standard" i.e., culture confirmation.

A significant overlap of antibody levels between patient and control groups has been observed in the present study. A similar overlap, to the extent of 20-25% was reported by other authors³¹⁴. In a high prevalence country such as ours, this finding could be ascribed to circulating antibodies due to sub-clinical specific infection or infection with environmental mycobacteria.

Reports from elsewhere using A60 antigen have also shown similar low values, i.e., sensitivity of 48-52%, specificity of 71%, and 50% positive predictive value^{5,6}. If (a) so many (8.5% to 16%) healthy persons have antibody levels overlapping with those of patients, and (b) almost 50% of the smear positives show low antibody levels, there can be no utility of these serodiagnostic tests in the diagnosis of pulmonary tuberculosis. In the programme, in fact, there is no need for any serological test because diagnosis is by smear examination. In the case of smear negatives, till an extensive evaluation of antibody tests has been made taking into account all the aspects of the disease, these tests should be interpreted with utmost caution.

ACKNOWLEDGEMENTS

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Abstract of the Presidential Address of Dr. C. Srinivasa Rao delivered at the 50th National Conference on Tuberculosis & Chest Diseases held at Thiruvananthapuram from 6th to 9th December, 1995

During the past 50 years of its existence, the Tuberculosis Association of India (TAI) has been able to give meaningful objectives to the control of tuberculosis which, however, still remains one of the major causes of morbidity and mortality. The morbidity from tuberculosis in the country has remained constant over the years. Multiple drug resistance and HIV infection have added frightening dimensions to the tuberculosis problem, rendering it a 'global emergency', as declared by the WHO.

The NTP was planned to be delivered through the existing health services network and has been considered, all over the world, as the ideal blue print for TB control. Unfortunately, it has not been possible to attain the objectives due to, among other factors, population explosion, lack of trained manpower, budgetary constraints, erratic drug supply, etc. A new revised strategy has been evolved by Government of India, supported by some international agencies which have come forward to augment the resources. This revised strategy involves directly supervised drug taking under short course therapy (DOTS) by the patient. DOTS has been introduced in 10 cities and 5 states and is aimed at ensuring cent per cent drug taking by the patient, at least during the intensive phase. Sputum conversion is 95-97% but certain difficulties are likely to arise, specially in the rural areas. Encouraging results have so far been obtained in pilot areas.

Since the area covered by a DTO is large,

it may not be possible to ensure total success of revised strategy in this programme. Additional inputs by voluntary organisations and private practitioners are necessary. The Indian Medical Association should be approached to work in liaison with the TAI to supplement governmental efforts.

Proper training of doctors involved is very important but facilities for postgraduate training fall far short of Indian Medical Council standards. In spite of that, a few training institutions have been recognised and their students often lack confidence. Urgent steps have to be taken to rectify the situation. Each region could have one or two first class postgraduate colleges.

HIV infection and AIDS have added a serious threat, as 60-80% of the AIDS cases have been reported to develop tuberculosis. In fact, TB has become an indicator for presence of AIDS.

Involvement of the community through voluntary organisations is a key factor in the programme and the recommendations of the Suraj Kund Workshop and the Workshop on Revised Strategy should be implemented. A computer should be made available at each State TB Centre. Private practice by TB medical officers should be banned. A properly structured career graph should be made for these doctors. Paramedical staff should be increased. There should be more operational research.

SUMMARIES OF THE PAPERS PRESENTED AT THE GOLDEN JUBILEE NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES HELD AT THIRUVANANTHAPURAM FROM 6TH TO 9TH DECEMBER, 1995

CLINICAL TRIAL OF 4 MONTH CHEMOTHERAPY REGIMENS IN THE TREATMENT OF TUBERCULOUS PLEURAL EFFUSION

Ashok Janmeja, Baldev Raj and Narinder Kumar Jhamb

Fifty proven (through pleural biopsy) new adult cases of tuberculous pleural effusion were selected from the OPD of Medical College, Rohtak during January to June 1994. Cases with lung disease, with or without positive sputum, or other concomitant diseases were excluded. AFB could not be found in the pleural aspirate of any of the selected cases and culture facilities were not available. Mantoux test was ≥ 10 mm in 44 cases.

They were all treated with two 4 month SCC regimens. Twenty cases received 2 SJiRZ/2 HR and 30 cases 2 EHRZ/2HR. More patients preferred the regimen which did not have injectable drug. Both the regimens were administered on a domiciliary

basis. Only 3 patients were lost, 2 after 15 days and 1 after 2 months. Two cases subsequently developed drug induced hepatitis and had to be excluded. The rest (90%) completed their treatment satisfactorily. Pleural aspiration was done as and when required.

All the cases became asymptomatic, except 5 who continued to complain of mild chest pain at the end of treatment and even during follow up. Both the regimens were well tolerated. During the quarterly follow up for one year after completion of treatment, only 3 more cases were lost. There was no recurrence of disease in the remaining 42 cases.

INFLUENCE OF INITIAL DRUG RESISTANCE ON RESPONSE TO SHORT COURSE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

B.R. Maldhure, R.P. Munje, S.P. Zodpey and A.B. Fuladi

A study was carried out at TB Control and Training Centre, Govt. Medical College and Hospital, Nagpur, during the period July 1986 to December 1994 to estimate the prevalence of initial drug resistance to H, S, R and to find out its effect singly or in combination on response to S.C.C. as compared to drug sensitive cases of pulmonary tuberculosis.

Patients aged 15 years and above who were smear positive for AFB (two samples) and had not taken anti-TB treatment in the past were included in study. Sputum sample for AFB culture was taken and those reported positive were subjected to drug resistance tests. Drug resistant cases were matched with drug sensitive controls for age, sex, socio-economic status, extent of disease and S.C.C. regimen - R₁: 2HRZ+6TH/EH, R₂: 2SHRZ+6TH/EH R₃: 2EHRZ+6TH/EH, and results were

analysed by applying statistical tests.

The overall prevalence of drug resistance was estimated to be 25.63% (413/1611); for H it was 24.39%, S-13.40%, R-0/80 and for SH-11/85. Significantly higher levels of unfavourable results were obtained in resistant cases (15.31%) than sensitive controls (5.10%), $P < 0.05$. failure/relapse % were less in regimens R₂ and R₃ with S or E in intensive phase in addition to HRZ. But this gain was not statistically significant ($P > 0.05$).

Among single drug resistant cases, H resistance caused failure/relapse in 13.33% of patients and S resistance in 6.66% of patients. Failure/relapse rates were high in those resistant to two (17.34%) or three drugs (100%). Rifampicin resistance observed in combination with other drugs caused failure in 71.42% of patients.

TOWARDS REVISED NTP - A STUDY IN MADRAS**K. Jagannath**

Ten divisions in the Saidapet Zone of Madras city (population 0.25 million) were selected for carrying out a strategy of case-detection followed by treatment with SCC among the entire urban population. For this, 150 workers of the Indian Population Project-V were given intensive training in door-to-door enumeration and symptomatology questioning and 10 qualified microscopists were contracted and trained as multi-purpose tuberculosis workers. These MPWs delivered supervised treatment with 2 EHRZ/4 H₃R₃ to sputum positives or those with radiologically extensive disease and 2 HRZ/4 H₃R₃ to sputum negative cases. X-rays of

the symptomatics and for follow up of cases were taken by mobile MMR unit.

In all, 12,758 symptomatics (7.94%) were registered, but only 8,197 were available for various examinations; 83 were sputum positive (1% among symptomatics and 0.05% in population) and, 632 were radiologically positive. Of the 83 cases, 58 were fully sensitive while 25 had resistance to one or more drugs. Of the 25 cases with initial drug resistance, 13 gave satisfactory response while 12 were treatment failures. Over all, among 83 sputum positive cases, 85.5% attained sputum conversion and in 14.5% treatment failed.

DRUG SENSITIVITY AND VIRULENCE OF *M. TUBERCULOSIS* GROWN IN THE PRESENCE OF CARBON DIOXIDE**M.M. Chauhan and V.K. Challu***(Paper is being published in full)***IMPACT OF PREVIOUS CHEMOTHERAPY ON CULTURE OF *MYCOBACTERIUM TUBERCULOSIS* FROM SPUTA OF FRESHLY DIAGNOSED SMEAR POSITIVE CASES OF PULMONARY TUBERCULOSIS****J. Jena, B.N. Panda, S.K. Nema and A.K. Mishra***(Paper will be published in full in a subsequent issue)***A HIGHLY SPECIFIC POLYMERASE CHAIN REACTION TEST FOR DETECTION OF *MYCOBACTERIUM TUBERCULOSIS*****Gururaj V. Kadival, C.D. D'Souza, S.P. Kulkarni and A.M. Samuel***(Paper is being published in full)***RESPONSE OF HIV SEROPOSITIVE PATIENTS WITH TUBERCULOUS DISEASE TO SHORT COURSE CHEMOTHERAPY (SCC)****B.N. Panda, S.C. Tewari, P.N. Arora, J. Jena, S.K. Nema and R. Jayaswal***(Paper will be published in full in a subsequent issue)***DETERMINATION OF THE CAUSES OF MORTALITY IN TUBERCULOSIS AND RESPIRATORY DISEASES WITH HIV INFECTION****V.K. Arora, S. Vinod Kumar and A. Tumbanathan**

Thirty-six patients with HIV infection who had died during the period April, 1991 to September,

1995 were taken up for study to determine the aetiological factors leading to their death. Nineteen patients had associated tuberculous disease whereas 10 patients had non-tuberculous aetiology. The

median survival time of disseminated tuberculosis was 9 days, whereas it was 11 months for non-disseminated tuberculosis. Median survival time in non-tuberculous cases was 3 days (range 2-11 days).

ECG CHANGES IN SPONTANEOUS PNEUMOTHORAX

B. Raj, S. Tandon, A.K. Sood and Kamal Arora

Twenty patients under 40 years of age, who suffered spontaneous pneumothorax, were subjected to electrocardiography on diagnosis, and after complete re-expansion of the lung. It was seen that after re-expansion, the ECG pattern showed some

changes from the original, especially improvement of QRS voltage in left sided cases, and Changes in the axis in almost all the cases. P. pulmonale, where originally present, also reverted to normal, as did T wave inversion.

MULTI DRUG RESISTANT TUBERCULOSIS IN TAMIL NADU

R. Vasanthakumari and K. Jagannath

In all, 782 sputum specimens (from Govt. TB Sanatoria at Nagercoil (172), Somanathapuram (134), Vellore (172) and the Institute of Thoracic Medicine, Madras (304), were cultured, of which 168 (21.5%) were found culture positive. Of the sanatoria sourced cultures, 162 (100%) were subjected to sensitivity testing for H, R, S, E and Z.

Sixty cultures (37%) were found to be fully sensitive, while 63% were resistant to one or more drugs. Of the 102 resistant strains, 38 were resistant to a single drug (23%), 64 resistant to multiple drugs (40%) while 33 (20%) were resistant to H and R (MDR-TB). History of contact and previous treatment received was obtained in the resistant cases.

MULTI DRUG RESISTANT TUBERCULOSIS AS SEEN IN A NATIONAL REFERENCE LABORATORY

Sujatha Chandrasekaran

During the period 1989 to 1994, sputum specimens of 3,965 pulmonary tuberculosis patients were referred to National Tuberculosis Institute, Bangalore (NTI) for culture and drug sensitivity tests. Two thousand and forty cultures were positive for *M. tuberculosis*. These patients were divided into three categories, viz. (1) previously treated patients; (2) new patients; and (3) those in whom history of previous anti-tuberculosis therapy was unknown. It was seen that 918 of 1,128 previously treated patients harboured resistant

bacilli, of which 61.7% were resistant to INH and Rifampicin. Of 380 new patients, 100 (26.3%) had resistant bacilli, 8.68% of which were HR resistant. This situation by no means reflects the situation in the community or under NTP because of the high level of selection involved. However, because of the close association of multi-drug resistance with previous chemotherapy, issues such as improving cure rate in the programme, safety guidelines, infection control in referral laboratories and sanatoria, need to be addressed.

MULTIPLE DRUG RESISTANT TUBERCULOSIS: INTERVENTIONS AND STRATEGIES AT AMARGADH

A.L. Anand

All cases of pulmonary tuberculosis diagnosed as having multi drug resistance (MDR TB) at the Amargadh Tuberculosis Research Centre during

1985 to 1994 were retrospectively reviewed. While resistance to Rifampicin (R) and Isoniazid (H) *in vitro* could be measured more reliably and

consistently, that to Pyrazinamide, Streptomycin and Ethambutol was more difficult to measure. Resistance to R, H and at least one more drug was considered as MDR TB.

One hundred such cases were managed with reserve drugs, with or without suitable surgical

procedures. The comparatively poor results obtained with costly drug regimens used, sometimes combined with aggressive surgery, underline the need for more rational and stronger primary treatment of tuberculosis to avoid emergence of MDRTB.

ROLE OF INTRACATH IN ACUTE PRIMARY SPONTANEOUS PNEUMOTHORAX

E. Ravindra Reddy, K. Venu, P. Navneeth Sagar Reddy and C. Eshwar Prasad

During January 1993 to October 1995, 25 cases of acute primary spontaneous pneumothorax were treated with 14G Venflon intracath underwater seal drainage. The lung expanded completely in all

the cases within 24 to 48 hours. It is a simple, safe, economical, less traumatic, time saving and rewarding bed side procedure. It can be done as first line life saving procedure even in remote places.

TRANSCATHETER BRONCHIAL ARTERY EMBOLIZATION IN THE MANAGEMENT OF MASSIVE HAEMOPTYSIS

Liesel D'Silva, P.M. Basheer Muhammed and K.C. Mohanty

(Paper will be published in full in a subsequent issue)

SERODIAGNOSIS OF PULMONARY TUBERCULOSIS AND EVALUATION OF TWO ELISA KITS

Sujatha Chandrasekaran, M.M. Chauhan and N. Parimala

(Paper is being published in full)

DIAGNOSIS OF SPUTUM NEGATIVE PULMONARY TUBERCULOSIS BY TRANSTHORACIC FINE NEEDLE ASPIRATION

B.R. Maldhure, S.P. Papinwar and S.P. Zodpey

Sixty two patients in whom there was suggestive X-ray evidence of pulmonary tuberculosis but sputum was smear negative at least twice were offered sputum culture and transthoracic fine needle aspiration (TFNA) examinations to evaluate their respective role in clinching the diagnosis. TFNA was done both unguided and under ultrasonic guidance.

Sputum was found AFB positive by culture in 8 (12.9%) patients. TFNA aspirates were smear/

culture AFB positive in 27 (43.5%) cases; had suggestive tuberculous cytology in 18 (29.0%), suggestive non-tuberculous cytology in 3 (4.8%) and were inconclusive in 14 (22.7%) cases.

Associated complications were pneumothorax and haemoptysis but these were self limiting and needed no active management. TFNA could be accepted as an additional tool for differential diagnosis of smear negative pulmonary tuberculosis.

ELISA FOR SERODIAGNOSIS OF TUBERCULOSIS**B.L. Bhardwaj, Kanchan Saint, Jagdish Chander and G.S. Mann**

The study aims at evaluating the sensitivity and specificity of Enzyme Linked Immunosorbent Assay (ELISA) in the diagnosis of tuberculosis by way of detecting mycobacterial antibodies using 38 kDa antigen. Sera were collected from 104 smear negative cases suspected to be suffering from pulmonary tuberculosis, or extra pulmonary tuberculosis along with 10 sputum positive cases

and 20 age and sex matched healthy controls. Overall sensitivity of the test was 76.92% and specificity was 90%. The present study recommends that ELISA could be used as an adjunct to other methods of diagnosis of tuberculosis, particularly for extrapulmonary and sputum negative pulmonary tuberculosis.

RELAPSE PREDICTING FACTORS IN TUBERCULOSIS AFTER SUPERVISED SHORT TERM CHEMOTHERAPY**S.P. Rai, B.N. Panda, R.S. Pahus and K.E. Rajan**

At the various tuberculosis hospitals of the armed forces, tuberculosis patients are given sanatorium treatment (supervised) with 2 SHRZ 4RH. After successful completion of treatment, they are followed up clinically, radiologically and bacteriologically every 3 months during the first 6 months, every 6 months during next 18 months and yearly for next 3 years, to detect relapse.

During October 1991 to December 1993, 35 cases admitted with relapse were reviewed retrospectively for factors which might have contributed to relapse. Extent of residual lung lesions, delayed sputum conversion, initial extent of lung lesions, smoking and surgical intervention with inadequate pre-and post-operative anti-tuberculosis treatment were considered to have possibly contributed to the relapse.

CHEST SYMPTOMS IN SMEAR POSITIVE PULMONARY TUBERCULOSIS PATIENTS TREATED WITH STANDARD AND SHORT COURSE CHEMOTHERAPY REGIMENS UNDER A DISTRICT TUBERCULOSIS PROGRAMME - A FIVE YEAR FOLLOW-UP**V.H. Balasangameshwara, P. Jagota and R. Channabasavaiah**

(Paper is being published in full)

REVISED NTP: CURRENT STATUS OF PILOT PROJECT

The Government of India, WHO and World Bank together reviewed the NTP in 1992. Based on the findings of that review a revised strategy for NTP was evolved. The main pillars of the revised strategy are: (i) achievement of not less than 85% cure rate amongst infectious cases of tuberculosis and (ii) detecting 70% of the estimated case - load through quality sputum microscopy. The revised strategy has been introduced in the country as a Pilot Project since 1993. The following 3 phases have been planned so far:

Pilot Phase I - (in 5 areas covering 2.35 million population)

State/City	Project Area	Population
Delhi	Gulabi Bagh	1.00 million
Mumbai	H/West Ward	0.35 million
Calcutta	Tangra Topsia	0.30 million
Bangalore	Shanti Nagar	0.25 million
Gujarat	Mehsana District (Patan & Chanasma Taluks)	0.45 million
Total		2.35 million

This phase has shown that the new strategy is feasible and acceptable to project staff and patients. Average cure rate achieved in the first cohort was 83%, and the proportion of sputum smear positive cases rose to 50% of all the cases found.

Pilot Phase II - (extended to 16 more areas covering a total population of 15.83 million)

State	Districts*	Population
Gujarat	Mehsana	1.50 million
West Bengal	Murshidabad	0.20 million
Himachal Pradesh	Hooghly	0.80 million
Bihar	Hamirpur	0.40 million
Kerala	Vaishali	0.30 million
Maharashtra	Pathanamthitta	1.10 million
	Raigad	1.98 million
Total		6.28 million

*District	Taluks covered
Mehsana	Pattan, Chanasma, Harij, Sami,
Murshidabad	Sidhopur, Mehsana Sagardigi block

State	Districts	Population
Hooghly	Chandannagar sub-division	
Hamirpur	Entire district	
Vaishali	Lalgunj, Sadar block	
Pathanamthitta	Entire district	
Raigad	Entire district	
City	Area	Population
Delhi	Gulabi Bagh	1.00 million
	L.R.S. TB Institute	0.70 million
Mumbai	Munshi Chest Clinic area	1.50 million
Calcutta	Tangra	1.50 million
Bangalore	(Urban) Shanti Nagar Range	0.25 million
Hyderabad	Wards 6,7,8, (Hyd.) & Wards 12 (See.)	1.00 million
Madras	Wards 32 to 49 of Zone - n	0.40 million
Pune	Entire City	1.60 million
Lucknow	Lai Bagh area	0.50 million
Bhopal	Itawara area	0.20 million
Jaipur	Entire City	1.40 million
Total		9.55 million
Grand Total		15.83 Million

This phase has reached an advanced stage and the initial results show around 80% cure rate in the aggregate.

Pilot Phase - III - (It is envisaged to extend the project area to 15 states covering a total population of 271.21 million)

State	Number of Districts proposed to be covered and their population during Phase-II	Population
West Bengal	18	74.24 million
Himachal Pradesh	12	5.68 million
Bihar	7	21.17 million
Kerala	14	31.19 million
Gujarat	19	45.14 million
Maharashtra	3	17.64 million
Manipur	1	1.00 million
Uttar Pradesh	4	9.64 million
Tamil Nadu	6	16.86 million
Madhya Pradesh	5	5.50 million
Andhra Pradesh	1	3.35 million
Karnataka	7	19.81 million
Rajasthan	3	8.63 million
Delhi	1*	10.00 million
Assam	1	1.16 million
Total	102	271.21 million

* 14 project areas

IN MY OPINION •••

At a time when the health services of the country and its National Tuberculosis Programme are in such a sad state, it is worthwhile to ‘remember’ that the concerned authorities seem to have ‘forgotten’ some of the key issues that are associated with this condition. This “forgetting” is not due to absentmindedness; it is an active process to justify something different, particularly when there are doubts about their scientific validity. Only three of the forgotten issues will be taken up within this limited space.

The first two decades after Independence saw a virtual efflorescence in public health research, practice, education and training. In the field of tuberculosis, for instance, the research findings concerning equal efficacy of home treatment and lack of protective value of the BCG vaccine, at least among adults, brought about fundamental changes in dealing with tuberculosis as a public health problem all over the world. The series of researches that led to the formulation of the NTP was taken up as the basic approach by the WHO Expert Committee of 1964 for recommending tuberculosis programmes. The second forgotten issue concerns drastic changes in the organisation and management of the health services in the country in the wake of the division of the then Ministry of Health into separate departments of health and family planning, in 1967, with the generalist administrators (IAS) acquiring much more

dominant positions in the fields of health and family planning. The third ‘forgotten’ issue relates to the withering away of the cadre of Indian Medical Service, without replacing it with an alternative one, as happened when the ICS cadre was replaced by the IAS. This led to a sharp deterioration in the quality of the health administration in the country. Concurrently, there was also a steep decline in the quality of medical education and other programmes for education and training of health workers, which correspondingly affected the stature of the medical profession as a whole. How many professors of preventive and social medicine and professors of tuberculosis in medical colleges, for instance, are even familiar with the basic components of the NTP, what to speak of its research foundations?

I would contend that it is this type of forgetfulness which is responsible for the present predicament of the health services and the NTP. This can also explain why the authorities concerned are so enthusiastic about the World Bank supported proposal for a Revised National Tuberculosis Control Programme (RNTCP) even though there are several shortcomings in its conceptualisation, planning and programming. One simply has to ‘forget’ about the scientific bases of the NTP if one has to get along with the RNTCP.

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Sir,

I have read with interest the article by Uplekar et al. "Tuberculosis management in Private Practice and its Implications" - published in the Jan., 1996 issue of the IJT. All the observations made by the authors about GPs are valid, by and large. We must analyze the factors responsible for this dismal situation, especially when we all agree that GP has a key role to play in the care of TB patients.

- (1) Professional education must continue throughout a doctor's working life (CME). It is very difficult to maintain the quality of one's practice twenty to thirty years after graduation without undergoing some continual training. There is no incentive for our GPs to undergo such a training. In our country, funding constraints, the heavy clinical work-load and sheer inertia are important deterrents to CME. Our medical policy makers must evolve some *via media* by which recertification at every 5 to 10 years' interval is made compulsory for every GP
- (2) For playing his role effectively, a GP should follow all the guidelines for proper management of tuberculosis. Hardly any planned efforts have been made by our policy makers to achieve this goal. The refresher courses being organised under the auspices of TAI and its state affiliates have attracted satisfactory attendance but have not shown significant impact on GPs' performance, as is evident from Uplekar's study. A reason for poor performance could be that while planning such courses, we have ignored the fact that the CME requirements for consultants in hospitals, primary health centres and private clinics in urban and rural areas are different. There is urgent need for planning long-term education strategies for these different groups. Such programmes should be focused, interactive, and use hands-on-training and clinic settings, when appropriate GPs'

problems, requirements and suggestions should be sought and given due weightage,

- (3) At present, a majority of our GPs are fed biased information by different pharmaceutical companies in a way as to promote their own products. The chaos created by different companies by bringing out different "kits and combinations" and promoting different regimens and dosages have further worsened the already limited and inadequate knowledge of today's GP. With companies complaining about the cost of research and the necessity of years of clinical trials, the possibility of newer or better drugs appears to be remote. So, what is actually being done by these companies is very similar to supplying the same old wine in new bottles. A planned effort is urgently needed to check this "exploitation" of GPs.
- (4) No doubt, the Consumer Protection Act has improved the prospect of rational drug prescriptions by the professionals. But what about the non-professionals who are playing with the lives of the people? With these non-professionals having a 'roaring business', without any check or legislation, the poor GP sees no logic in making any effort to update his knowledge or achieving his career development needs. Some one has to check these non-professionals with the help of legislation or otherwise.

Studies like the one by Uplekar et al have found major and recurring inadequacies in physician practices in TB management. These failures have resulted in delayed diagnosis, increased risk of disease transmission, inappropriate treatment and the development of multidrug resistance. We know our deficiencies. We know some of the reasons for the deficiencies. What we need to know is how to remove these deficiencies.

**Rajinder Singh Bedi
Patiala**

Enhancement of Annual Subscription

In view of the substantial increase in the cost of production of the *Indian Journal of Tuberculosis*, the Finance & Executive Committees of the Tuberculosis Association of India have decided to enhance the annual subscription of the *Indian Journal of Tuberculosis* from Rs. 2007- to Rs. 2507- from the January 1997 issue. All subscribers are requested to kindly remit their annual subscription for the Journal for the year 1997 in November/December 1996 together with the form which will appear in the October 1996 issue. The overseas subscription rates remain unchanged.

51st National Conference on Tuberculosis & Chest Diseases

The 51st National Conference on Tuberculosis and Chest Diseases under the auspices of the Tuberculosis Association of India and the Karnataka State TB Association will be held at J.N. Tata Memorial Auditorium, Indian Institute of Sciences, Bangalore from 3rd to 6th November, 1996. Those who wish to attend the Conference can obtain the Registration Form from the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi - 110001.

Anti-TB Week

The Tuberculosis Association of Haryana and the District Tuberculosis Associations in Haryana observed the 'Anti-TB Week' recently. During this week, they held group meetings of the people to create awareness among them about all aspects of tuberculosis. During these meetings, they also distributed health education pamphlets to the people.

The Tuberculosis Association of Andhra Pradesh celebrated the Anti-TB Day and Anti-TB Week in the various District TB Associations in the State, from 17th to 23rd February, 1996. During the week, public meetings, camps, BCG vaccination for children, intensive mass health education programmes, film shows, exhibitions, and radio talks were organised.

Refresher Courses on Tuberculosis & Chest Diseases

Under the joint auspices of the Tuberculosis Association of Andhra Pradesh and TB Association of Ranga Reddy district, a refresher course on tuberculosis was held on 3rd April, 1996, at Hyderabad. The Course was inaugurated by Dr. S. Adinarayana Reddy, District Medical and Health Officer, Ranga Reddy District, and presided over by Dr. C. Srinivasa Rao, former Honorary General Secretary of the TB Association of Andhra Pradesh. Drs. I. Ranga Rao, B. Ishweriah, N. Kumar Rao and O.A. Sarma gave lectures on "Diagnosis of Tuberculosis", "National TB Control Programme and the Role of PHI Medical Officers", "Revised National TB Programme" and "Chemotherapy of Tuberculosis" respectively. About 50 doctors attended the refresher course.

National Congress on Diseases of the Chest

The International Academy of Chest Physicians and Surgeons of the American College of Chest Physicians (South India Chapter) will be holding a National Congress on Diseases of the Chest in Madras from February 26-28, 1997. For further details, kindly contact Dr. V.K. Vijayan, Organising Chairman, National Congress on Diseases of the Chest 1997, Cardio-Pulmonary Medicine Unit, TB Research Centre, Chetput, Madras-600031.

Honour Conferred on Dr. Karel Styblo

It is unlikely there is any tuberculosis worker in the world who is not familiar with the name of Dr. Karel Styblo, or has not used his formula for calculating Annual Risk of Infection (ART). Some may have met him personally, or even had the pleasure of having worked with him.

On 24 March 1996, on the World Tuberculosis Day, Dr. Karel Styblo was conferred the highest honour in the Netherlands, the 'Ridder in de Orde Van de Nederlandse Leew (Knight of the order of the lion of the Netherlands)' by Her Royal Highness, the Queen of Netherlands, for his services to tuberculosis control.

IUATLD Working Groups

In order to make it possible for members with special interests to maintain an active involvement in the fight against tuberculosis and lung disease, the IUATLD has constituted several working groups and given them clear and precise objectives and organisational patterns to make their contributions. And, thus, tried to improve the tuberculosis situation globally. These Working Groups have replaced the erstwhile Scientific Committees. Details about how a Working Group can be established, the objectives defined and the organisations set up, etc. can be obtained from the IUATLD office at 68 Boulevard Saint Michel, 75006 Paris, France. The following Working Groups have already been established:

Global Anti-tuberculosis Drug Resistance Surveillance; Guidelines for Tuberculosis Laboratory Safety; Emergence of New Mycobacterial Pathogens; Clinical Trials in Tuberculosis Treatment; Treatment Regimens for HIV Infected Tuberculosis Patients; Treatment Regimens for Chronic Tuberculosis Patients; Supply and Quality Assurance of Tuberculosis Medications; Prevention of the Development of Drug Resistant Tuberculosis; Diagnostic Criteria for Paediatric Tuberculosis; Tuberculosis in Animals; Health Effects of Pollution from Mobile Sources in Europe; Management of Pneumonia and Asthma in Low Income Countries; Database on Research in Acute Respiratory Infections, Research Training Course; Educating Medical Students about Tobacco; Tobacco Prevention Guidelines for National Associations; Nursing Models; Primary Health Care and Tuberculosis Control, Contacts Tracing and Treatment Follow up for Tuberculosis Patients.

SAARC Tuberculosis Centre, Kathmandu, Nepal

A Workshop was held during October, 1995, at SAARC Tuberculosis Centre (STC) for preparation of health education material suitable for conditions prevailing in the SAARC countries. The workshop made the following recommendations:

- 1: Health education and community involvement must be accorded a high priority in National Tuberculosis Programme.
2. A senior level officer should be identified for IEC (TB) in the central level health education organisation.
3. Earmarked funds should be provided for IEC activities and training of personnel for it.
4. Sufficient time for telecasting/broadcasting tuberculosis IEC (at least thrice a week on prime time) should be provided.
5. STC should develop its capacity to train senior level IEC officers deputed by member countries.
6. Each member country should evolve a standardized IEC strategy suitable for that country.
7. A "SAARC TB Day" could be observed.
8. The existing SAVE (SAARC Audio-Visual Exchange) programme should be used for IEC (TB)
9. STC should organise periodic inter-country visits within the region to observe IEC
10. STC should organise a follow-up workshop to review the action taken.

OBITUARY

With great sorrow, we have to record the sad and untimely demise of the former Director of New Delhi TB Centre, Dr. B.B. Surpal, MD, on 30th May 1996. Having joined the New Delhi TB Centre in 1970, as Clinical Assistant, the late Dr. B.B. Surpal rose to become its Director in charge on 3.1.94, which position he held till his retirement on 31.8.94.

The Association mourns his loss and conveys its deepest heartfelt condolences to the bereaved family. May his soul rest in peace.

General

1. All correspondence relating to the Indian Journal of Tuberculosis (IJT) may please be addressed to:

The Editor, Indian Journal of Tuberculosis, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110001.

2. The four issues of IJT, appearing every year in January, April, July and October, contain original articles on all aspects of tuberculosis and non-tuberculous respiratory diseases, case reports, reviews and leading articles (see item 6) as well as abstracts of articles/matter published in other scientific journals and books dealing with same subjects. Besides, each issue has an Editorial, sections on Contemporary Issues and Continuing Medical Education, News and Notes as well as Forum wherein readers can express opinion on the published articles or ask questions on the subjects covered by the Journal.

3. Three copies of the article (including diagrams and photographs) typed on one side of the paper with double spacing and wide margins should be submitted.

4. It is understood and accepted that the submitted matter would be editorially revised to make it suitable for publication. The decision of the Editor regarding acceptance or revision can not be contested. However, every effort is made to communicate the reason or deficiencies to the author in order to associate him with the steps to improve the article.

5. All the received articles are serially registered and usually published in the order of registration. However, the date of registration will be after the completion of the basic formalities, if the authors have overlooked these guidelines. The articles registered are reviewed by the IJT Editorial Board to judge suitability for publication and to give suggestions for improvement.

6. Original articles deal with planned studies that have been duly completed and convey definite conclusions from the data presented in the text. However, preliminary communication from research

still in progress could be submitted, exceptionally, if the topic is important and the interim results could be of interest. Case reports present problems of unusual clinical interest which have been systematically and fully investigated and where a firm diagnosis has been established with reasonable certainty or the result of therapeutic management is of great significance. Review Articles are those specially requested from persons who have acknowledged competence in given subjects. These are useful for updating knowledge. Leading articles are contributed by those who have expertise in selected aspects of a subject.

Foruta provides a platform to readers for expressing opinion and a channel of communication with the Journal and its other readers. It could be used for making suggestion, scientific critique on published articles or for reaching independent conclusions, asking questions, on the subject covered by the Journal and for providing supplementary information either confirming or contradicting the conclusions reached in the articles.

7. Twenty five reprints of each published article are supplied free of cost to the author whose address is indicated for correspondence. More reprints are, exceptionally, supplied if the order is placed at the time of acceptance of the article. The cost of the order will be intimated and must be paid for in advance of the publication of the article.

FORMAT AND PROCEDURE

8. All submitted articles shall have a definite format. Each article should comprise sections, *ad seriatim*, on Summary, Introduction, Material and Methods, Results, Discussion, Acknowledgements (if necessary) and References. Additional sections could be interposed. In Case Reports the sections on Material and Methods and Results are replaced by the section 'Clinical Record' and all other sections are appropriately shortened.

Care should be exercised in making the language grammatically correct and free flowing, ensuring that all pertinent information has been included, irrelevant details omitted and repetitions, especially from section to section, avoided. Tables and figures must be self explanatory and their number kept to the minimum. It is not usually

necessary to present the same information both in a table as well as a diagram: the more effective of the two presentations has, therefore, to be chosen. Tables must be numbered, have a descriptive legend on the top, minimum essential data in the body and necessary explanatory notes at the bottom. Tables (and diagrams) should be made on separate sheets of paper, with their place in the text indicated clearly and attached at the end of the article. Drawings are best made with black India Ink and of a size larger than required in the text. Legends for the photographs should be typed separately with appropriate indication regarding the photograph to which a legend pertains. Photographs (black and white prints) should be clear, glossy and unmounted. The attached sheets should carry the title of the paper and name of the author in pencil on the backside. Photographs, inscribed in pencil at the back, should be put in an envelope and properly labelled on the outside and attached to the article last.

It is understood that the planning of the study submitted for publication as well as the analysis of the data, presentation in the text and the reaching of conclusions have been done in consultation with a statistician.

9. After the title of the article, the name of the principal author should be followed by names of other authors.

10. The position held by each author in any institution is indicated only in the footnote against Arabic numerals indicated on the top of each name. This information is followed by any special annotation such as title of oration, or, say, paper presented at a scientific conference, etc. Lastly, the name and address of the author to whom correspondence regarding the article has to be sent should be indicated.

11. In respect of preliminary communications, the nature of the paper must be clearly indicated so that editorial processing could be specially expedited.

12. References cited in the text and at the end

should conform to the procedure recommended by the International Steering Committee of Medical Editors. Therefore, special care must be taken to ensure that:

Only the most important published papers related directly to the study in hand are cited in the text.

Text reference should be numbered in Arabic numerals as a suffix in the order of their mention, avoiding the names(s) of authors(s) and year of publication.

White citing an abstract (when it is the sole source of information) or personal communication or unpublished work in the text, authors must provide the necessary particulars of the source, but this is not a preferred mode of citation. Permission from the source(s) of information of citing their work must be obtained beforehand.

All the numbered references in the text should be typed out in detail, in the same consecutive order, on a separate page and attached at the end. Abbreviation of the titles of the cited journals should be according to the Index Medicus. Example;

Kakar, A., Aranya, R.C. and Nair, S.K.: Isolated gastric tuberculosis; *Ind.J. Tuber.*; 1979,26,205.

Crofton, J. and Douglas, A.: *Respiratory Diseases*, 1st Edition, Edinburgh, Blackwell Scientific Publications Ltd. 1969.

13. The abbreviations or acronyms used in the text must be defined at the first mention. Their number should be kept to a minimum.

14. Contributions to Forum should be in the form of letters to the Editor. Such letters must be brief and to the point: only the most important agreements/disagreements/suggestions on published papers may be chosen for commenting. It is usual to send a copy of such letters to the author concerned for obtaining a response, if any, after editorial reformulation. The response, similarly, has to be selective, brief and relevant.