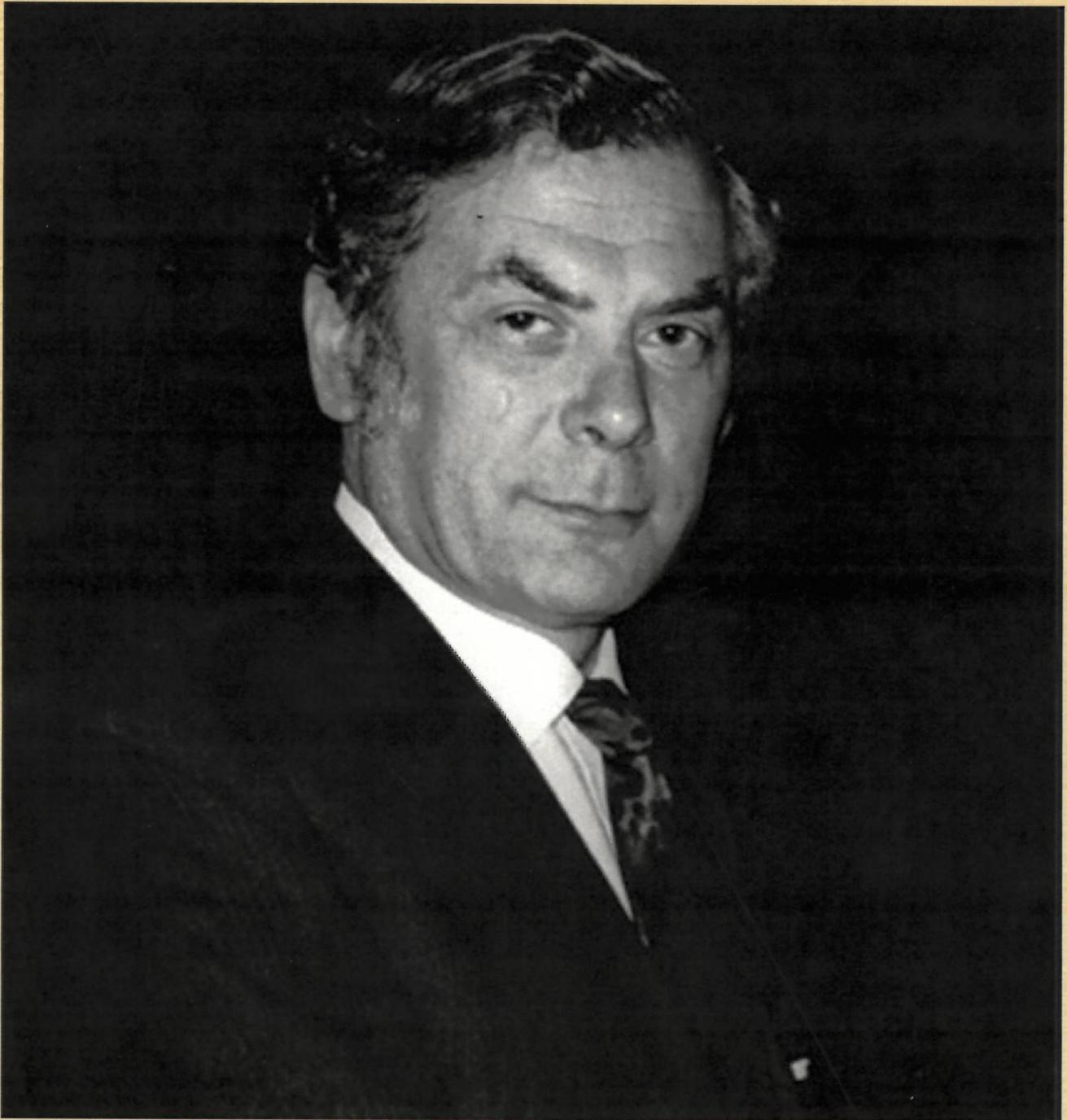


Prof. Wallace Fox
A Pioneer In TB Research



(1920-2010)

I was first introduced to Wallace by some friends of the family in February 1956. I think it was a “set up” - the Western equivalent of an Indian arranged marriage! Wallace was tall, very handsome, serious and clever. He was also charismatic and, like the sun, people were



*Prof. Wallace Fox with
Shri. Rajendra Prasad, 1st
President of India*

drawn to him. He proposed to me in August 1956 on the night before leaving for India on what was to be a two-year assignment but which became five years. I followed him out and in early September 1956 we had a wonderful romantic marriage in Cochin. The honeymoon lasted two days before he headed back to Madras to attend a public health nurses course. I returned to England where he promised to meet me two weeks later. Six weeks later he finally came back! I got the message, the project in Madras was priority for all of us involved.

So how did Wallace become involved in the fight against TB? There was a background to this. Wallace was a brilliant medical student. Tall and athletic he played rugby for Guy’s Hospital. However on qualifying at the early age of 21 (doctors’ degrees were shortened in 1942 because during the war doctors were badly needed at the front) he contracted TB for which there was then no cure. The best medical advice at the time was to get lots of “fresh air” and the next two years of his life were spent on the balcony of the Bristol Royal Infirmary, including through two freezing winters!

It is sixty years since Wallace and I left India. Now at the age of eighty-six, some names and places have faded but I can recall the atmosphere of those years as if they were today. For both of us, arriving in India for the first time there was a steep learning curve. Wallace wanted to understand and respect cultural norms but he also didn’t want traditional niceties to get in the way of getting things done. On his first meeting with Dr. Hamid who was the Director of the Madras Government Chest Institute at the front part of the building, he unwittingly upset his host by sitting casually, as usual, with legs crossed, thereby showing the leather soles of his shoes. Hamid never forgave him this very unintentional insult.

Back to the drawing board, we both read everything we could get hold of on Indian customs and manners. However Wallace didn’t always follow local practices. Early on after arriving at the Tuberculosis Chemotherapy centre or “TCC” (now the ICMR National Institute for Research in Tuberculosis or “NIRT”), Wallace noticed a refrigerator in the middle of the corridor at the unit and politely asked for it to be moved. Nothing happened

and so he asked again. On the third day when it was still *in situ*, to the consternation of all around, he moved it himself. People quickly learned that if Wallace asked for something to be done, he expected it to be done. Wallace didn't believe in hierarchy and was a great believer that on a team everyone had a role to play and the team was only as good as its weakest link. He used to regularly hold team meetings and invite everyone including the



Group picture near plaque of Dr. Fox installed NIRT clinic Building during the year 2014

drivers.

Conditions were difficult. As yet there was no air conditioning. The Madras climate was often described as "hot, hotter, hottest". It was also very humid. All records for the trials were kept on cards and there were thousands of these. Normally one would have used a fan for a little breeze but this would have blown all the cards all over the place, so they had to sweat it out. But the atmosphere was

always inspiring. Both of us greatly enjoyed the company of our Indian friends and colleagues. I remember in particular doctors Velu, Ramakrishnan & Devadatta, Lab Assistant Subbaiah, public health nurse Mary Jayalakshmi, health visitor Mrs. Mary Samuels and of course Dr. Radhakrishna who was like a son to Wallace and with whom I have stayed closely in touch ever since.

Wallace wanted one hundred per cent patient cooperation and results from the studies he carried out. He knew that in real life this is hard to achieve, but he knew what was possible. Many a weekend he and I would go a hundred miles up country to chase up a patient who had signed up for a trial and then absconded up to his village for a wedding or a funeral perhaps and wasn't taking his or her medicine. Once in the village he would enlist the help of a village elder to ensure the patient took his medicine regularly.

So there were medical challenges, cultural challenges and physical challenges. There were also political challenges for Wallace. It was written in the gospel that "No man can serve two masters" but Wallace had to answer to four, reporting regularly to the WHO, the Medical Research Council in the UK, the Indian Council for Medical Research and finally the Madras Government! However, Wallace was always polite and usually managed to get people on his side.



Prof. Fox and Gaye Fox : horse riding on his farewell

After five years at the TRC we were given a wonderful send off with tears and flowers and a horse - which was meant to be ridden by me but because my dress was too tight Wallace was put on it (see the photo)! Those years were the most important and perhaps the



Group picture with Prof. Fox and TCC Staff at Hotel Woodlands 1961

happiest of our lives. Wallace returned to England in the Autumn of 1961. He had been promised his own unit on return but it was some years before that was delivered. Eventually he had both his own unit and his own building at the Brompton Hospital where he continued his research in tuberculosis until his retirement. His initial work back in the UK was to preach the new gospel, namely that TB could be cured in about four months with the powerful drugs now available and that the patients could carry on working during treatment. The GPs were dubious and it took time for them finally to accept the new ways of treating TB. For as long as anyone could remember, regime, at least in the UK, was for



Mr. Jason Fox's visit to NIRT, together with Dr. S.P. Tripathy

2 year's bed rest and I believe that in some countries it was viewed as a life sentence. Naturally these new ideas did not go down well with the sanatoria who had made a nice income out of the disease!

Until his retirement Wallace went back to Madras every January to help write up papers and chew over issues that had cropped up. However I secretly believed he went back to see his old colleagues and

2 year's bed rest and I believe that in some countries it was viewed as a life sentence. Naturally these new ideas did not go down well with the sanatoria who had made a nice income out of the disease!



Mrs. Fox and eldest Adam in Mrs. Fox's garden in Tauntan (UK) in summer 2017

friends! I was lucky enough to return to Madras and see what is now the NIRT, just twice. One of my sons visited a few months ago and met with Dr Srikanth Tripathy the Director-in-charge of the NIRT (whose father was a previous director with whom Wallace worked closely for many years). I know of course that the research done at the TRC in the late 50s and early 60s was world changing and radically impacted the course of tuberculosis treatment for ever, but I am also very moved to know that the NIRT is still at the forefront of TB research and continuing work that was started there by my husband over 50 years ago. Indeed, I was amazed and thrilled to learn from my son's recent meeting with Dr. Tripathy that when new studies are undertaken, some of the same methods for carrying out trials that Wallace laid down remain protocols that are still considered best practice and are followed today.

Bravo TRC and all those wonderful colleagues, friends and staff who threw away the rule books and changed the world. I remember you all with love and I know Wallace did too.

Mrs. G J Fox

SECTION – 2

Dr. S.RADHAKRISHNA

*(Formerly Chief Statistician, Tuberculosis Research Centre,
Chennai and Director, Institute for Research in
Medical Statistics, Chennai)*

WALLACE FOX: the man and his mission in India (1956 – 1961)

It is both a privilege and an honour to be asked to write a short piece for this historic booklet on Wallace Fox. I knew him professionally and personally for over five decades, and shall share some of my personal insights of him, concentrating more on the man and his methods than on his scientific contributions as the latter are too well-known. Missions often start with a dream. So let us start with my imagination of a dream that Fox must have had in the 1940s!

FOX'S DREAM IN BRISTOL ROYAL INFIRMARY IN 1941-1943

(Adapted from a poem on Abou Ben Adhem by J.H.L.Hunt)

Wallace Fox (May his tribe increase!)
Awoke one night from a deep dream of peace,
And saw, within the moonlight in his room,
Making it rich, and like a lily in bloom,
An angel writing in a book of gold.
Fox asked "What writest thou?" The angel answered
"Prospects for global tuberculosis control".

At that moment in time, Fox decided that **HIS** contributions should constitute, the most significant part of that book! **And the rest is history!**

Fox joined the BMRC Tuberculosis Research Unit in London in 1952 just as the first effective new antibacterial drugs were being introduced, and bacterial resistance to



streptomycin was observed in the first clinical trial in TB patients. Fox's clinical trials in the UK demonstrated that this resistance could be prevented by combining streptomycin with PAS or isoniazid, a finding which led to a standard three drug regimen (SPH in the initial phase followed by PH) that was used throughout Western Europe for the next 15 years. Although this was a major breakthrough for the developed

world, half the patients did not complete their treatment course in a European trial and the

cost of drugs and hospital stay made it unaffordable for many countries. Substituting Thioacetazone for PAS was a partial answer, but even with cheaper drugs, the cost of a year in hospital was impossibly high for developing countries.

It was against this background that Fox first visited India with Philip D'Arcy Hart in 1955 to explore the feasibility of establishing a tuberculosis research centre in this country, and chose Madras as the site because it was a low-profile city far away from the public glare and the corridors of power. Also, subconsciously perhaps, because it was the first foothold the East India Company had had in India! The Centre itself was actually established in May 1956 as a collaborative venture of the Madras State Government, Indian Council of Medical Research(ICMR), British Medical Research Council (BMRC), and the World Health Organization (WHO). It was not known at the time that Fox had contracted tuberculosis himself soon after graduation, and received only 'standard treatment with bed-rest and fresh air' for two years in Bristol Royal Infirmary. Perhaps there is poetic justice in that he made his name and fame from a home versus sanatorium trial (with anti-tuberculosis drugs) that is often referred to as the 'Madras classic'. At the time, India's TB disease burden was 2½ million active cases of which 1½ million were infectious. The accepted method of treatment was isolation in sanatorium with bed rest, a balanced diet and supervised medication for a year, but only 23,000 sanatorium beds were available for the entire country, i.e. one bed for every 65 infectious patients. In this hopeless scenario, self-administered chemotherapy at home was an attractive proposition, but could not readily be made national practice for it was not known whether it would provide long-term cure to the patient without causing any extra risk to the family contacts or deluging the community with drug-resistant strains. This study then raised hopes of the possibility of better management of the disease on a national scale.

What did the prophets of doom say?

When this randomized control trial was initiated in 1956, the prophets of doom were many, some saying that randomization was an alien concept in a developing country such as India, while others were emphatic that no patient could be confined to sanatorium for a year or expected to self-administer drugs at home daily for long periods; also, that long-term follow up was simply inconceivable under local conditions. So, what did Fox do?

What was Fox's 'Mantra' for overcoming problems?

To persuade sanatorium patients to stay put, he visited them every week and discussed with his clinic staff the next day any domestic problems arising from their hospitalization. To monitor compliance of patients treated at home, he introduced pill counts at periodic intervals and surprise urine tests to check on drug ingestion; also, he arranged for home visits to retrieve defaulters. To facilitate retrieval of defaulters, he had the complete address of the patient taken along with landmarks, and also, for good measure, the contact

addresses of important relatives/friends. If a patient did not attend the clinic on the due date, he arranged for a home visit by a health visitor, then a social worker, then a clinic doctor and if all these efforts failed, **HE** himself went. This was a great novelty, and patients started referring to him in awe as the ‘American Doctor’ and the Centre itself as ‘American Hospital’. When this was brought to his notice by a clinic staff member, he smiled uncomfortably, but as soon as she left, he thundered to me “I am British and hate to be called an American”, but after a moment’s reflection, he added “But, Radha, as long as the patients attend regularly, and consume all of their prescribed medicaments, I don’t give a damn what they call me or this Centre!” That was the extent of his commitment to the trial.

Fox was very particular that the trial should be conducted strictly according to the research protocol and measure up to international scrutiny. He therefore conducted weekly meetings of his staff to emphasize these points, and arranged for his senior statistician (myself) to deliver weekly lectures on the ingredients of good research methodology. Although he had no formal training in statistics himself, he had an intuitive grasp of the issues and the analysis of the data. Before taking any major decision, he would consult his BMRC statistician Dr. Ian Sutherland who had visited Madras with him as a WHO consultant. Fox believed that active collaboration with statisticians was critical for the success of any research study, and he made sure that all his colleagues got this message too. I was so convinced by the success of his approach that I remarked at an annual conference of statisticians that “The doctor-statistician relationship is as vital for productive research as the doctor-patient relationship is in clinical medicine”.

MAIN CONCLUSIONS FROM HOME/SAN TRIAL

- (1) Treatment at home for one year with daily PAS plus isoniazid was as effective as the same treatment in sanatorium
- (2) Diet, Physical Activity and Accommodation were unimportant *in the presence of good chemotherapy*
- (3) Relapse rates over subsequent 4 years were similar
- (4) There was *no extra risk* to family contacts at home over 5 years
- (5) Failures of initial chemotherapy could be successfully treated with second-line drugs, irrespective of whether initial treatment was at home or in sanatorium.
- (6) The disease status at 5 years was similar in Home and San patients

This Madras classic showed that treatment at home for a year was as effective as at sanatorium, both short-term and long-term, and there was no additional risk accruing to close family contacts of infectious patients treated at home. This finding revolutionized the management of TB in India and other developing countries, led to the closure of several hospitals elsewhere *and had great impact on global WHO policy.*

However, Fox was quick to realize that the excellent results of domiciliary treatment in the randomized control trial would not be easy to replicate under routine programme conditions. His understanding of the problem of patient compliance was simply profound. When he noticed that some patients on daily chemotherapy responded well despite minor degrees of irregularity, he wondered if less frequent chemotherapy but fully supervised, might not be equally effective, a concept also suggested by studies of serial serum isoniazid concentrations in patients on daily chemotherapy. This was the rationale of a subsequent randomized control trial of fully supervised twice-weekly treatment and self-administered daily treatment (Streptomycin plus isoniazid twice a week vs PAS plus isoniazid daily), and the successful outcome of this study was to become the genesis for the present global DOTS strategy.

Subsequent trials showed that supervised twice-weekly drug therapy (with isoniazid plus PAS, or isoniazid plus ethambutol) was no less effective than self-administered daily therapy with the same drugs, if augmented by daily streptomycin in the first two weeks of a year of chemotherapy.

SUPERVISED TWICE-WEEKLY vs SELF-ADMINISTERED DAILY TREATMENT*

| Regimen | No. of patients | Fav. Response at one year | Relapse in | |
|-------------|-----------------|---------------------------|----------------------|-----------|
| | | | 2 nd year | 2-5 years |
| PH | 71 | 85% | 12% | 15% |
| SHtw | 79 | 94% | 8% | 12% |
| 0.5SPH/PH | 83 | 87% | 4% | NA |
| 0.5SPH/PHtw | 90 | 88% | 3% | NA |
| 0.5SEH/EH | 107 | 96% | 15% | NA |
| 0.5SEH/EHtw | 101 | 88% | 26% | NA |

*In one-year regimens of chemotherapy

Besides the above ‘shattering-impact’ studies, Fox undertook other randomized trials that yielded valuable information on treatment regimens and underlying principles of chemotherapy. Some of these were:

- (a) Treatment with isoniazid alone is substantially less effective, but isoniazid in a single daily dose is more effective than in two doses
- (b) Thioacetazone can replace PAS as the companion drug for isoniazid.
- (c) Once-weekly chemotherapy is not highly effective in rapid inactivators of isoniazid, even after an initial 4-week daily phase with three drugs.

Less recognized and talked about are Fox’s concern with the practical aspects of replicating research findings under programme conditions, fashionably called ‘Implementation Research’ nowadays – e.g. accuracy of patient’s home address for contacting patients by post and procedures for retrieving defaulters.

OPERATIONAL RESEARCH STUDIES IN PROGRAMME IMPLEMENTATION



Prof. Fox and Gaye Fox in Later years

in retrieving defaulters than reminder letters by post.

- Home address elicited by registry clerk was unsatisfactory for postal purposes. There was no betterment when HVs, Social workers or Doctors did the job instead.

- ‘Address card’ evolved – address is to be obtained by the patient on a card from the local post man or a literate neighbour. This address enabled successful contact with a substantially larger proportion of patients in the TB clinics of Madras city. Subsequently, these good results were reproduced in four large urban cities in Tamil Nadu.

- A randomized trial showed that home visits by health personnel were more effective

These programme-related studies were all undertaken in collaboration with the Madras Government’s Chest Institute, as a wily diversionary tactic by Fox. The real (but not publicly disclosed) reason for undertaking these studies was to ensure that the Government chest clinic, which was the feeder clinic for our trials, did not embark on chemotherapy trials on its own, and starve us of intake for our studies!

There were other notable achievements too.

1. Inculcating research culture in staff who were unexposed to it earlier;
2. Demonstrating that team work is more productive than individual brilliance;
3. Establishing good medical record systems with quality control;
4. Demonstrating the importance of three C's (Commitment, Collaboration and Coordination) in research; an anecdote about his idea of commitment might help. When he first interviewed me in October 1956, he asked me "What do you know about TB?" To my answer that it was an infectious disease caused by a germ, he said "If you are selected for this job, you will have to work through a crowded TB clinic carrying case papers for obtaining clarifications from doctors. Would that bother you?". I replied in the negative, more out of a sense of bravado than conviction (I was just 20). He then stumped me with the next question "Are you married"? , and on receiving a negative reply, added "If you were to get married, and your wife objected, what would you do?". I cheekily replied "In India (in 1956), marriages are 'arranged' marriages, and the girl would know in advance the details of my job, and if she had reservations, she could decline before we got to first base". That assuaged the great man, and I got the job. (Many months later, he confided that training one to become a good research worker was a substantial investment involving a lot of effort over many months, and he couldn't take a chance on me quitting the job because of my wife's unfounded fears!).
5. Instilling a 'Publish or Perish' philosophy in scientific staff. One of Fox's favourite quotes was "*Research unpublished is equivalent to Research not undertaken*".

To appreciate the real merit of Fox's achievements, one must recall the unfavourable conditions in which he had to operate, for these have not been documented in research publications and the number of survivors of yester-years is fast diminishing! He was given a small contingent of staff totally untrained in research methodology, a ramshackle clinic and the nearest telephone was 300 yards away in the first floor of a neighbouring building that housed the Madras Government TB Institute, and he did not know the local language and had to communicate with patients through interpreters.

How then did Fox achieve what he did under these adverse conditions?

The answer is that, apart from his brilliance, he was a charismatic and assertive leader, who practised what he preached, respected co-workers greatly, and made even the junior-most cog feel he was indispensable for the success of the Project. It was hardly surprising then that he was able to get the best out of every body. He was unwavering in his basic beliefs but always willing to reason and debate. He had an uncanny ability to make people do what he wanted, but never by authority or dogma, only by reasoning, sometimes bordering on attrition! (He even persuaded me to postpone my WHO Fellowship to London by a year so that a number of reports on the pipeline could be completed!). In the

opinion of his life-long colleague, Prof. Mitchison, Fox had the rare ability of foreseeing problems long before others did, and evolving appropriate solutions in advance. Apart from his vast knowledge and intelligence, Fox had loads of enthusiasm, which he readily imparted to all who worked with him. His middle name could well have been Speed and he was impatient and demanding. (“I want it by yesterday night!”) He expected everybody to slave for the cause, but inflicted maximum punishment on himself, quoting a mythical aunt who told him that “Hard work never killed anybody!”. His typical day began at 6.50 A.M. and he usually left office at 6 P.M., and there was always plenty of home work too. On one occasion, he had to agree to act as ‘independent x-ray reader’ for Frimodt-Moller, our independent radiographic assessor, purely as a reciprocal favour. The task involved reading about 22000 miniature films in a very short span of time. He agreed and completed the job on schedule. When I asked him how he managed to complete the task without jeopardizing his Institute’s work, he smiled and said “I sneaked in 30 minutes before I left for the office, about one hour during the lunch break between 1 and 2.30 P.M. and an hour at the end of the day!” I asked incredulously “But didn’t your newly-wed wife protest?”. He replied “At first she did, but then I convinced her that it would be a great privilege for her to record my assessments for a historic study!”. Quite frankly, I see this as a modernized version of Shakespeare’s ‘Tempest’ scene of the young lovers Ferdinand and Miranda playing chess in a dark cave!

Prof. Fox’s views on research workers need special mention. A famous Fox quote is: A good research worker should always be asking of his seniors “WHY should we do it this way, and when he is not doing this, he should be asking WHY NOT we do it another way?”. He strongly encouraged independent thinking and uninhibited expression of new



Farewell picture for Prof. Fox at TCC held at Hotel Woodlands 1961

ideas, *a sacrilege in the Indian bureaucratic set-up of the 1950s*. According to Fox, a wise research worker should record in writing every decision taken by him and its rationale. This was advice he had received from his illustrious colleague Marc Daniels who had developed cancer. One is left to wonder if the two of them anticipated *post facto* audits of

research that are sometimes undertaken these days. The hallmarks

bush or undue concern about ruffling feathers), and unswerving loyalty to his principles and to fellow workers. He insisted on advance tabulation plans being made for all analyses, so that the temptation to formulate hypotheses after seeing the results could be avoided. At the time, the importance of intention-to-treat analyses had not become generally accepted but Fox was always very thorough in the presentation of the data to ensure that they were presented in a way that accounted for all of the patients admitted to the trial. All these are well-accepted procedures today with GOPs and SOPs in plenty, but not really known in the 1950s.

Fox was neurotic about perfection in preparing scientific reports. He made it mandatory for draft reports to be circulated to all senior staff (irrespective of their parent discipline), giving a firm dead-line for their suggestions. On one occasion, he was asking for comments on a page by page basis for an 8-page report he had circulated to us all. I gave my comments but when we came to page 6, I had no comments and said so. He thundered “What do you mean, No comments?” I reiterated what I had said earlier. In exasperation, he countered “Not one comment, not even on spelling, punctuation or syntax?” I was petrified but managed to say ‘No’. He then admonished me saying “Radha, you must have fallen asleep when you came to that page”, but added as a kindly after-thought “Or you must have turned over two pages at a time” He would personally read drafts over and over again, and get his typist to re-type and re-check the ‘improved’ versions, and once remarked, not entirely in jest, that he could even annotate his reprints!

Fox’s diplomatic skills need special mention.

GOSPEL DEFIED?

“No man can serve two masters” **St.Mathew, Chapter 6, Verse 24**

But Fox more than satisfied four! and won their approbation.

- (1) Indian Council of Medical Research
- (2) Madras Government
- (3) British Medical Research Council
- (4) World Health Organization

This unique experience was published subsequently in the London School of Economics Society Magazine, as ‘a model of collaboration and cooperation’.

After 5 years at Madras, Fox returned to London in 1961. He could well have proclaimed then, like Julius Caesar did after vanquishing King Pontus, “Veni Vidi Vici”, a saying in Latin that translates to “I came, I saw, I conquered”. Or bragged like Alexander the Great after he had tamed the wild horse Bucephalus (see Photo below).



Taming of the Bucephalus

But Fox was modest and stated that while he may have put Madras on the TB map, it was equally true that the Madras experience had led to his evolution as a mature research worker and prepared him for stiffer challenges. A grateful horde of TCC staff bid him a warm farewell at Hotel Woodlands in Mylapore on 20th January 1961 (Photo 2).

For the rest of his professional career, he maintained close contact with the Centre in all its research studies, notably of short course regimens, through meticulous correspondence and periodic short-term consultant visits.

On the personal side, we here remember Fox as a tall and handsome person with long strides, a partially buttoned handloom shirt, a basket containing three flasks of tea, a shirt pocket bulging with correspondence and a mouth full of chewing gum. He had a gifted sense of humour, great tenacity, and a remarkable ability to make and sustain contacts over several decades. He was often very smart in disguising his real intent – for instance, he would walk in to the clinic every morning at 7 A.M. sharp, ostensibly to say a cheery hello to all his clinic doctors but in fact to do a reality check on whether they were all punctual! He was a voracious reader of books on art and culture, lover of cinema, classical music, Indian cuisine and south Indian ‘Brahmin’ coffee, an excellent host and a great cricket fanatic. Lest you think I have only nice things to say of him, he was simply terrible at remembering names and invariably referred to people as Miss Doodar or Mr. Bugggerlegs (he had to write his personal secretary’s name, Mrs. Noronha, on the black board when she took offence at being called Miss Doodar!); a hard task master (we fondly called him Slave driver); and had a terrible handwriting that made the deciphering of Egyptian hieroglyphics mere child’s play! Two anecdotes will prove the point. Fox himself told me that when he was at medical school one of the examiners reviewing his answer paper wrote in the margin “I know you are aspiring to become a doctor. But you haven’t become one yet. Improve your hand writing!” The other was an incident involving him, his secretary and me. He gave me a hand-written list of analyses he wanted. I could decipher it all except three lines. When I asked him what it was, he remonstrated “You

can't read my hand writing, eh?" looked at it closely himself for a minute and found he couldn't read it either! But while I was wondering how he would couch his apology, he pressed the bell to summon his secretary, and when she appeared, he gave the paper to her and tersely said "Read it aloud". And, lo and behold, she actually read it, whereupon he turned to me and thundered "If she can read it, why can't you?" I nearly fainted.

There are three famous quotes with a typical TB flavor that I would like to share with you that exemplify the personality of Fox.

Endogenous

In reading the lives of great men,
I found that the *first* victory they won was over *themselves*
Self-discipline with all of them came first

Harry S.Truman

Exogenous

Our best work is done not in isolation
But in *collaboration* with others

Anon

'Persisters'

We are what we *repeatedly* do
Excellence then is not an act
But a *habit*

Aristotle

Fox's great ability to undertake excellent randomized control trials in all situations and in many countries is unquestioned. But side by side, he also propagated research culture to the locals, so that they could soon become self-sufficient. The most shining example of this is the NIRT, which has developed from a small temporary clinic project in 1956 to evaluate domiciliary chemotherapy to a national premier institute of tuberculosis in 2014 with all state-of-the art facilities and a much wider mandate. Having known Fox very well, I can guarantee that he would insist that great team work is the cause of success and not just his individual brilliance.

I deem it my great good fortune to have worked with such a towering personality in my formative years (it was sheer baptism by fire!) and maintained close contact with him subsequently for over five decades. The icing on the cake was a warm personal relationship I shared with him throughout, and this can be seen in the casual picture below that was taken in his garden in Richmond, Surrey. All young research workers in tuberculosis would do well to be inspired by the life, missionary zeal and achievements of Wallace Fox, recalling Longfellow's words below:

*"Lives of great men all remind us
We can make our lives sublime
And, in passing, leave behind us
Footprints on the sands of time"*

Wallace Fox – twenty years of memories

I first met Wallace Fox (and Denny Mitchison) in May 1966 at Holly Hill, Hampstead; they were two members of the panel that interviewed me for the post of statistician in the Medical Research Council's Tuberculosis and Chest Diseases Unit (TCDU). I have no recollection of my first impressions of either of them.



Four months later I started work at the TCDU in Tavistock Square; this was a temporary arrangement for the unit until the completion of the new building at the Brompton Hospital in South Kensington. On my first day, Dr Fox took me round the various offices to introduce me to the staff, clutching a piece of paper given to him by Mrs. Agnew, his PA, with the names of who was in which office. Names were never a strong point with him.

My knowledge of TB was very limited and there was no Google or Wikipedia to provide quick answers and so early months at the TCDU were a steep learning curve. Looking back, one of the things which impressed me from the beginning was Prof. Wallace Fox's practice of involving statisticians in the discussions from the very earliest discussions about a new trial. I learnt quickly that he had high standards and high expectations of his staff; whenever he called me to go to his office he expected me to go with a note book to write down what he wanted me to do.



One of the major landmarks in the history of the TCDU was the meeting when it was decided to conduct a trial to assess whether a rifampicin-based regimen could dramatically shorten treatment duration for pulmonary TB. As with other meetings of this kind, Denny Mitchison joined us from his unit in Hammersmith and the study design was thrashed out in the TCDU library. The reason for thinking that rifampicin might be the key to shortening treatment from 18 or more months to 6 months was the encouraging finding from laboratory studies in mice demonstrating its bactericidal and sterilising properties.

The first East African Short Course study, which included four 6-month regimens and the standard 18 months thiacetazone-isoniazid based control regimen, began in 1970. Detailed analyses of the data indicated that the results in the rifampicin-based regimen looked particularly encouraging and this led to early release of data in the Lancet in 1972. I still remember the excitement of seeing those first results. Those results obtained over 40 years ago, were to revolutionise the treatment of TB world-wide; six months of treatment with a rifampicin and isoniazid based regimen remains the gold standard for TB treatment to this day.

While expecting high standards from his staff, particularly in the public presentation of our work to the wider scientific community, Prof. Wallace Fox also rehearsed his lectures in front of the senior staff and asked us to critically appraise the content and delivery of his talk.

Most of my memories of Prof. Wallace Fox are work-related; there was not much by way of social interaction. He liked to go to the hospital canteen and when the nearby church clock struck 12 noon he would call me on the phone to go with him to lunch. He ate quickly and waited for me to finish so he could get back to his office! My first overseas trip was an IUAT conference in Ankara in 1970 and as only the two of us went from the unit that was an opportunity to get to know him better.

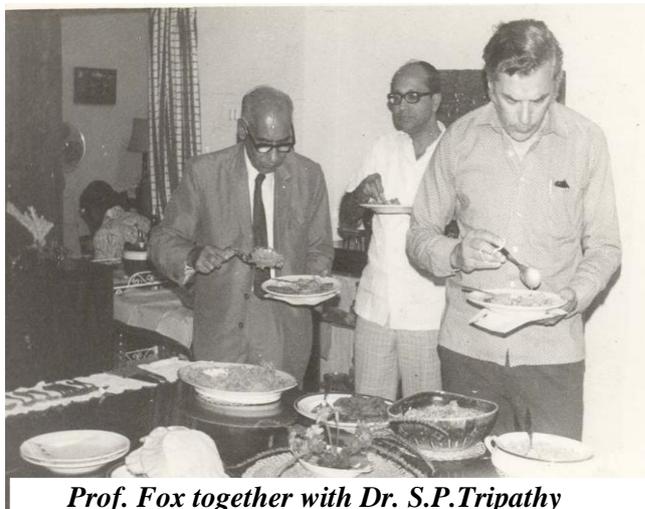
Working for Prof. Wallace Fox for twenty years was a great privilege, I learnt a lot which has I hope stayed with me throughout the last thirty years and been passed on to others.

Prof. Fox, my Mentor :

It is my privilege to write this note on Prof. Wallace Fox, the Founder-Director (then called WHO Senior Medical Officer) of the Tuberculosis Chemotherapy Centre which was established in Chennai in 1956. When I joined the Centre in 1962, it had already achieved distinction as a highly successful tuberculosis institution, having demonstrated the effectiveness of domiciliary treatment of TB patients. This paved the way for large scale expansion of tuberculosis control programmes globally. The research studies conducted at the Centre had the advantage of the guidance of Prof. Wallace Fox and Prof. D.A.Mitchison of the Bacteriology Department of Post Graduate Medical School, London. Both of them continued to function as advisors to the Centre for several years after the conclusion of their assignments at the Centre.

I first met Prof. Fox in January, 1963 as a new recruit to a junior post (Senior Research Officer) in the Bacteriology department. I had resigned from the teaching profession in a medical college to work at the Tuberculosis Research Centre with the intention of gaining research experience in 2-3 years, and then to go back to a teaching profession. In my first meeting with Prof. Fox, I sought his guidance for selection of a suitable area for research. His immediate reply was “If I were you, I would keep away from taking up any research project now, but spend my first few months in learning the various laboratory procedures and get a thorough grip on what is currently being done in the Bacteriology laboratory”. This was the best advice for me, because it enabled me to fully understand the functioning of the laboratory, which I was to head three years later.

When I was awarded an American Thoracic Society Fellowship to work at the Trudeau Institute in Saranac Lake, USA in 1966, the Centre was put to a stress. The laboratory



*Prof. Fox together with Dr. S.P.Tripathy
(Former Director General, ICMR Delhi)*

could not afford to let me go immediately but I did not want to lose the fellowship either. I was sceptical about Prof. Fox who suggested that he would negotiate with the American Thoracic Society (ATS) for postponement by a year. I was rather pessimistic about the possible outcome of such an attempt, but such was his great influence at the ATS, the postponement was readily agreed to, and that too, indefinitely till I was ready for it! In the event, I availed of

it a year later. The postponement turned out to be a blessing in disguise as it gave me an opportunity to work under a second mentor, Prof. G.B. Mackaness who had just joined as Director, Trudeau Institute, Saranac Lake, New York State in 1967. I worked on an Immunology project which helped me immensely in planning future research projects at the Madras Centre.

As Director of the Tuberculosis Research Centre (formerly Tuberculosis Chemotherapy Centre) I had the advantage of having Prof. Fox as Advisor to the Centre, and also his guidance as annual consultancy courtesy WHO for 2-4 weeks. His guidance in the planning of new studies was valuable. He continued to collaborate with us in several projects till the last day of his official posting as Chief of the MRC's Tuberculosis & Chest Diseases Unit (TCDU). I had visited this several times on invitation and had guidance from him regarding current and future research in tuberculosis.

The International Union Against Tuberculosis (IUAT) organised annual Conferences in different countries by rotation. Dr. Fox had a close working relationship with Dr. Annik Rouillon, Chief of the IUAT and played an important role in the planning of the programme and content of these conferences. At his suggestion, the IUAT extended support to representatives from his collaborating research organisations in India, Hong Kong, Singapore and Africa to attend the international conferences and present their research findings.

Prof. Fox's close association with these organisations ensured that the research programmes in tuberculosis in these organisations did not duplicate studies but conducted complementary studies that ensured that TB Control was approached from different angles and achieved greater success due to adequate coordination.



*Prof. Fox with Dr. Gopalan
(Former DG, ICMR) along with
Dr. K.V. Krishnaswami
(State TB Chief, Tamilnadu)*

Prof. Fox was a genius. He treated fellow scientists with understanding, respect and always adopted a persuasive and friendly approach. He developed the concept of team work and also ensured that all who contributed to the research work received appropriate credit through authorship of papers published. Some of the publications had as many as ten authors!

Prof. Fox utilised the potential of the BMRC to the fullest extent for formation of a global network of tuberculosis research. In this effort, he succeeded fully, and left behind several tuberculosis research organisations in different countries who have continued to function effectively after his relinquishing the stewardship of the TCDU.

After retirement from the TCDU, he totally cut himself off from TB research. For some time, he was interested in art, and even took some courses in Paris. He continued to maintain social relationship with his former collaborators. While in service, his mind was supersaturated. After retirement, he unfortunately developed Alzheimer's disease with slowly progressing dementia. In those days, there was no clinical trial with a drug like aducanumab for trial on dementia. He would surely had opted for participating in clinical trials had it been available then. His last few months were spent in a rehabilitation centre where he breathed his last.

The world in general, and the Tuberculosis Research Centre in particular, have benefited substantially from association with Prof. Fox. Personally, I have gained a lot, changing from a goal of a teaching job to a research career in TB through my close association with Prof. Fox. He will continue to be remembered by me and all others who had the good fortune to be associated with him.

Prof. K.V. Thiruvengadam, B.Sc., M.D., D.Sc., (Hon), FRCP (EDIN),

FELLOW

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Dr.Wallace Fox

Dr. Wallace Fox who led the MRC team in TB Research , transformed anti TB treatment by introducing the short course chemotherapy.

A skilled organizer , he brought into being a well organized Research Centre . A person with leadership qualities he could answer critics on short course chemotherapy in its early stages .

Clear thinking , a critical mind and scientific outlook were his forte .

His interest in new developments in Medicine was evident when he came over to Government Stanly Hospital to see Pleural Biopsy , that I and my colleagues were doing in the early 1960s.

Memory of Dr. Fox always brings to mind a dignified , competent gentleman Physician .

K.V. Thiruvengadam

Prof. Wallace Fox -A Dynamic Leader and Role Model

Dr. Wallace Fox established the Tuberculosis Chemotherapy Centre in Madras (now Chennai) and led a team of WHO specialists and Indian staff for 5 years, formulating various procedures for meticulously conducting randomized controlled clinical trials. The first study established the short and long-term efficacy of out-patient treatment of pulmonary tuberculosis and the safety to family contacts. This led to domiciliary treatment as a national policy in India and other developing countries.

He gave great importance to statisticians for monitoring the conduct of the trials, to ensure that all the procedures were done as specified in the protocols and that all the data required were recorded.

Having joined the Centre as Junior Assistant Statistician one year after the Centre was started, I had ample opportunity to observe for the next 4 years how he and Dr. Radhakrishna, the Senior Statistician, took meticulous care to ensure that scientifically valid answers could be obtained to the research subjects that were investigated. Dr. Fox ensured that the various findings were communicated widely to the medical and scientific workers by publishing the findings in prestigious research journals such as the Bulletin of the World Health Organization, the Tubercle and the American Review of Respiratory Diseases. As and when analyses were done, he would dictate the findings and, by the end of the day, give a draft to go through at home that night and give comments the next day. His insistence on going through draft reports to pick up mistakes and ensure that the textual description accurately reflected the tables, led me to give extensive comments to improve the reports of scientific publications at the Centre and even pick up mistakes in printed publications. For example the definition of isolated positive cultures in an early report (namely, one positive culture in a six-month period) was incorrect. It was changed in later reports to “A single positive culture preceded and succeeded by six months of negative cultures”. When I was being trained in the methodology of multi-centric collaborative clinical trials in his unit in London, I gave a comment on a report which had been accepted for publication. But he felt that it was important enough to persuade the Editor to make suitable changes at the proof stage.

His method of getting work done by the assistants was gentle repetition. He would ask for some analysis or data and say, “No hurry, take your time“, but return a couple of hours later and ask “How is it going?”, and again say “No hurry”. Then we would take a break in what we were doing and get the information before he came again and said “No hurry”.

The other path-breaking findings were that intermittent (twice-weekly) supervised chemotherapy was as effective in the short and long term as the then standard daily

chemotherapy. The clinical trial findings were supported by serial drug concentration studies in the laboratory. The other finding was in Spinal Tuberculosis. In Hong-Kong, all such patients underwent radical surgery. In Korea, and other places, where facilities and expertise for the surgery were not available, patients were treated with chemotherapy alone. In Madras, a randomized control trial of radical resection of the diseased vertebrae and chemotherapy for six months with Rifampicin and Isoniazid (RH) was compared with six or nine months of RH without surgery . This study showed that surgery for Spinal Tuberculosis could be avoided, especially if the angle of kyphosis was less than 30 degrees.

“Homer nods”. The Tamil equivalent states “Even an elephant’s foot can skid”. Prof. Fox had his blind spots. He refused to accept late relapses after short course chemotherapy, saying that once a patient attained culture negativity by 6 months of chemotherapy, there was no need for further follow-up. But we could have convinced him if we had set out the detailed bacteriological findings at the time of late relapses. He also pooh poohed high incidence of arthralgia with pyrazinamide, saying that the doctors were probably biased due to the observations of severe giddiness with high dosage slow-release (Matrix) isoniazid. We could probably have convinced him if, during his consultancy visit, we had produced a dozen cases for his detailed examination and questioning.

Prof. Fox was hardworking and a hard task master. But he enthused his assistants and led them to enjoy the hard work. He did not stand on ceremony. When we were walking across from one side of the Clinic building to the other, I told him that an analysis that he wanted had been done. He asked me whether I had it with me and when I said “Yes” he took it, and standing there itself, went through it and discussed the findings. On another occasion, during the lunch break of a conference, he scrutinized the findings of an analysis and discussed the implications.

Prof. Fox had successfully tackled the lack of Sanatorium beds, the problems with self-administration of drugs by patients daily for long periods, and the lack of surgical facilities and expertise. There is felt-need for persons of his calibre in these days of incidence of extreme drug resistance and shortage of new-generation drugs such as BEDAQUILINE and DELAMINID.

My first meeting with Prof. Wallace Fox was in 1970. This was the time when the then Tuberculosis Chemotherapy Centre (TCC) was planning a clinical trial, introducing ethambutol in the treatment of tuberculosis. Though I was a junior clinician at TCC, he gave me freedom to express my opinion and that impressed me a lot and gave the courage for critically analysing and commenting on the protocols and all the drafts circulated to all the scientific staff, which was the practice at TCC then.

Even afterwards, he used to visit the centre at least once a year to guide our research activities. At one of the senior staff meeting, when we were discussing about defaulter retrieval, and home visit for the patient, he said “Why not the medical officer make the first visit?” and that became a routine subsequently. For difficult patients, even he used to



*Prof. Fox together with Dr. S.P.Tirpathy,
Dr.R.Prabhakar and with Madurai TRC Staff*

visit and the “American Doctor” visiting made the patient to attend more regularly.

The first study on extra-pulmonary tuberculosis, undertaken by the Tuberculosis Research Centre (TRC) was on spinal tuberculosis, in collaboration with the British Medical Research Council (BMRC) and the Medical College Hospitals of Chennai. I came to know Prof. Fox more during this trial and used to have

close interactions with him regarding the conduct of the trial. This study was a classic where we compared the role of surgery in spinal tuberculosis and were able to follow up the patients for 15 years.

The clinical trials he had been involved in at BMRC, Chennai, East Africa, Korea and Hong Kong paved the way to establish the main principles for chemotherapy for tuberculosis. Some of the land-mark findings were that Tuberculosis should never be treated with a single drug; Treatment at home was as effective as treatment in sanatorium;. Treatment can be given intermittently (twice or thrice a week). With the advent of rifampicin and reintroduction of Pyrazinamide for treatment of tuberculosis, the role of each drug was demonstrated by well-designed clinical trials. Treatment duration can be shortened to 6-months; intermittent and short course chemotherapy can be combined.

Prof. Fox has helped a lot to mould my research career and I owe a lot to him for what I am today. He taught the way to write a clinical trial protocol, to conduct research by adhering to the protocol and to write the report, all by making us do the work and learn while working. I feel proud to have been associated with such an intellectual person in the early part of my career.

His punctuality was astonishing. One of my senior colleague always said that Prof. Fox had scheduled a meeting at 2:00 pm and he came at 2:01 pm. And Fox had said that when I say we will meet at 2:00 pm, I mean we meet at 2:00 pm.

His towering personality and capacity to communicate and convince with his ideas were very impressive. A colleague of mine who had worked with him commented “When fox walks across the corridor to go to his office, I am reminded of a Mills and Boon hero”.

Dr. Wallace Fox

I had the privilege of having the opportunity to meet and interact with Dr. Wallace Fox on many occasions during my early days at the Tuberculosis Research Centre (TRC), now called the National Institute for Research in Tuberculosis (NIRT). Dr. Fox and his illustrious colleague Dr. Denis Mitchison visited TRC once or twice a year as Consultants from the British Medical Research Council (BMRC). These visits, which were eagerly looked forward to, provided opportunities for the staff at TRC, both from the clinic and the laboratories, to discuss the ongoing clinical trials with these eminent gentlemen. In 1980, soon after I joined TRC, I became the Principal Investigator for a clinical trial on TB lymphadenitis in children, done in collaboration with the Institute of Child Health, Egmore. Whenever Dr. Fox visited TRC, I had personal discussions with him in which we analysed the progress of the study. I benefited tremendously in being able to pick his brain about the nuances of clinical research and particularly randomised clinical trials. He had a very sharp mind and very little escaped him. One particularly memorable occasion for me was when Dr Fox decided to join me on the afternoon visit to the homes of patients who had failed to turn up for treatment on that day. These were called FTA (Failed to Attend) visits and on this particular day we had a heavy patient load. I was amazed at how completely at ease Dr. Fox was in visiting the slums where most of our patients lived and informally chatting with the patients and their relatives. His imposing height and persona was striking and his genuine concern for the patient was so patent He was a great hit with the patients who used to call him 'Dorai'. After Dorai's visit the patient invariably turned up for treatment the next day.

It was a great tragedy that Alzheimer's claimed this brilliant physician and scientist at an age when he could have contributed so much more to the control of TB globally. His contribution to TB research both in TRC in its formative years and other BMRC sites later laid the framework for the modern management of TB, particularly its treatment. Dr. Fox left a lasting legacy that will forever be a milestone in the history of this Institute. The award of the '2017 Kochan Prize for TB Research' to the Indian Council of Medical Research (ICMR) is in a way the flowering of the seed that was sown by Dr. Wallace Fox many years ago here in Chennai.

Tubercle, 1958, 39, 269-274

The problem of self administration of drugs; with particular reference to pulmonary tuberculosis.

Fox W.

There has been much discussion recently on the most suitable form of tuberculosis chemotherapy for mass application. The discussion has centered largely on oral medicaments, and particularly on the relative merits of isoniazid alone and two-drug therapy with isoniazid and PAS. Although this is a very important issue it is less fundamental than the regularity with which patients will administer such medicaments to themselves for long periods of time. This is a major problem of long-term chemotherapy in the treatment of any disease. In the field of tuberculosis it has tended to become overlooked in general discussion concerning the use of particular drugs. The issue to be settled is whether patients will take any form of medicine by self-administration regularly for a period of many months or possibly even years, and, if not, how regularity may be achieved. Before specifically considering chemotherapy for pulmonary tuberculosis it is of interest to review the experience of workers in some other fields.

Bull. World Health Org. 1959, 21, 51-144

A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India

Tuberculosis Chemotherapy Centre, Madras

In India, as in most under-developed countries, the tuberculosis problem is aggravated by an acute shortage of sanatorium beds. The number of active cases of tuberculosis in the country has been estimated at 2½ million, but only 23,000 tuberculosis beds are available. In these circumstances great importance attaches to the possibility of applying mass domiciliary chemotherapy as a substitute for sanatorium treatment in cases of pulmonary tuberculosis. The findings of the present study, based on a comparison of the two types of treatment over a period of 12 months, show that despite the manifest advantages of sanatorium care-rest, adequate diet, nursing and supervised medicine-taking-the merits of domiciliary chemotherapy are comparable to those sanatorium treatment, and that it would therefore be appropriate to treat the majority of patients at home, provided an adequate service were established.

Bull. World Health Org. 1960, 23, 463-510

Prevalence of Tuberculosis among close family contacts of tuberculosis patients in South India, and influence of segregation of the patient on the early attack rate

**R. H. Andrews, S. Devadatta, Wallace Fox, S. Radhakrishna,
C. V. Ramakrishnan & S. Velu**

The results of a study by the Tuberculosis Chemotherapy Centre, Madras, of the merits of home as compared with sanatorium treatment for pulmonary tuberculosis have indicated that treatment at home is satisfactory in the majority of cases. Before domiciliary chemotherapy can be introduced on a large scale, however, it must be established that it does not expose the patient's contacts to a special risk of infection, avoided by his isolation in a sanatorium. Accordingly, a further study was undertaken by the Centre to determine (a) the prevalence of tuberculosis among the family contacts of patients, and (b) the incidence of clinical tuberculosis and of tuberculosis infections in the family contacts of the home and sanatorium groups of patients during the first year of treatment. The findings of this study indicate that the major risk for contacts lies in exposure to the infectious case before diagnosis, whether the patient subsequently remains at home or is isolated in a sanatorium appearing to have little importance, if the patients at home are treated with effective chemotherapy. Children under seven years of age proved to be particularly vulnerable to infection. The management of young contacts by chemoprophylaxis or by BCG vaccination, or by both measures, has been discussed.

Bull. World Health Org. 1960, 23, 511- 533

Progress in the Second Year of Patients with Quiescent Pulmonary Tuberculosis after a Year of Chemotherapy at Home or in Sanatorium, and Influence of Further Chemotherapy on the Relapse Rate*

**S. Velu, R H. Andrews, S. Devadatta, Wallace Fox, S. Radhakrishana,
C. V. Ramakrishnan, J. B. Selkon, P. R. Somasundaram & T. V. Subbaiah**

A recent report by the Tuberculosis Chemotherapy Centre, Madras, showed that the response of patients to a year's domiciliary treatment for pulmonary tuberculosis with isoniazid plus p-aminosalicylic acid closely approached that of patients to a year's sanatorium treatment with the same combination of drugs. The present report summarizes the findings of a second year's study, carried out on those patients in the first-year study whose disease had attained bacteriological quiescence by the end of the year of combined chemotherapy. The main objects of this follow-up study were to determine (a) whether relapse in the second year was more frequent among the patients originally treated at home than among those originally treated in sanatorium, (b) whether a second year of antituberculosis chemotherapy, with isoniazid alone, would reduce the relapse rate and (c) the influence of residual cavitation at one year, the so-called "open negative" syndrome,

on the results in the second year. During the second year all the patients were treated at home, either with isoniazid or with a placebo, calcium gluconate; in each case the medicine was administered by the patients themselves. It was found that there was very little difference in the relapse rates of “home “ and “ sanatorium’ groups, that a second year of treatment with isoniazid alone did not influence the likelihood of relapse, and that patients with the open negative syndrome fared slightly less well in the second year than patients without residual cavitation.

Bull. World Health Org. 1960, 23, 587- 598

Peripheral Neuritis Due to Isoniazid

**S. Devadatta, P. R. J. Gangadharam, R. H. Andrews, Wallace Fox,
C. V. Ramakrishnan, J. B. Selkon & S. Velu**

It is well known that in the treatment of tuberculosis with isoniazid the complication of peripheral neuritis may arise. This complication is normally rare when small dosages of the drug are used, but a high incidence of the neuropathy has recently been observed in East Africa in a group of malnourished tuberculous patients receiving isoniazid in comparatively low dosage (4-6 mg/kg body-weight daily). The present paper reports on 20 cases of peripheral neuritis encountered in Madras, India, among 338 poorly nourished tuberculous patients during a trial of four isoniazid regimens, two of low and two of high dosage (3.9-5.5 and 7.8-9.6 mg/kg body-weight daily respectively). Nineteen of the 20 cases occurred in the two groups of patients receiving the high dosage and these 19 patients were found to have a higher mean serum level of free isoniazid than the patients in the same groups who did not develop the complication. The authors consider that dosages of 7.8-9.6 mg/kg body-weight daily should not be used for the mass therapy of poorly nourished patients unless steps are taken to prevent the development of peripheral neuritis. Pyridoxine has been reported to be an effective preventive, but is too expensive for use on a large scale. This study indicates, however, that administration of the cheaper vitamin B complex might give satisfactory results and warrants further investigation.

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The Results of Treatment with Streptomycin Plus Pyrazinamide in Patients with Active Pulmonary Tuberculosis Despite Prolonged Treatment with Isoniazid Plus PAS

S. Velu, R. H. Andrews, S. Devadatta, Wallace Fox, C. V. Ramakrishnan and T. V. Subbaiah

(from the Tuberculosis Chemotherapy Centre, Madras*)

There have been a number of reports on the use of pyrazinamide in combination with other drugs in the treatment of pulmonary tuberculosis. It has been used in combination with isoniazid (Donnerberg et al., 1957; United States Public Health Service, 1959a), with cycloserine (Schwartz & Moyer, 1957; Toguri & Atwell, 1958) and with viomycin (Pfeutze & Pyle, 1957) in the treatment of patients who had failed to attain quiescence with previous anti tuberculosis chemotherapy. It has also been used successfully in the treatment of newly-diagnosed disease in combination with isoniazid, with daily and bi-weekly streptomycin and with PAS (Muschenheim et al., 1954; Allison, 1959; Tucker & Matthews, 1959; United States Public Health Service, 1959b). A major disadvantage of pyrazinamide, however, is the occurrence of hepatic toxicity, which sometimes results in jaundice or death, especially since liver function tests do not always give adequate warning of impending hepatic damage (American Trudeau Society, 1957 ; Potter & Chang, 1955 ; Spengos & Cuizon, 1958 ; United States Public Health Service, 1959a). In a controlled study, the United States Public Health Service (1959a) reported hepatic toxicity of between 2% and 3% in a 12 week period with daily dosages of 25 or 40 mg of pyrazinamide per kg body weight. In a 24 week period the toxicity increased to 6.6% with the larger dose but remained unaltered with the 25 mg dose. Joint pains, elevation of the serum uric acid and frank clinical gout have also been reported (Yaeger et al., 1952 ; Cullen et al., 1956).

Bull .World Health Org. 1960, 23,535-585

A Concurrent Comparison of Isoniazid plus PAS with Three Regimens of Isoniazid Alone in the Domiciliary Treatment of Pulmonary Tuberculosis in South India

Tuberculosis Chemotherapy Centre, Madras

Recent studies have shown that treatment of pulmonary tuberculosis with isoniazid plus p-aminosalicylic acid (PAS) at home is, in the majority of cases, as satisfactory as treatment with the same combination of drugs in sanatorium and does not appear to expose the patient's contacts to any special risk. Before mass domiciliary chemotherapy can be

introduced, however, a question that has to be decided is what drug or drugs and what dosage and rhythm of administration will be most effective.

This paper presents the results of a controlled comparison of four chemotherapeutic regimens : (a) 3.9-5.5 mg/kg body-weight of isoniazid plus 0.2-0.3 g/kg body-weight of PAS (sodium salt) daily in two doses (the standard combined chemotherapy); (b) 7.8-9.6 mg/kg body-weight of isoniazid alone daily in one dose ; (c) 7.8-9.6 mg/kg body-weight of isoniazid alone daily in two doses ; (d) 3.9-5.5 mg/kg body-weight of isoniazid alone daily in two doses. Isoniazid plus PAS proved to be the most satisfactory regimen; it was clinically effective and there were very few toxic manifestations.

Bull .World Health Org. 1961, 24, 129-148

Influence of Segregation of Tuberculous Patients for One Year on the Attack Rate of Tuberculosis in a 2-Year Period in Close Family Contacts in South India*

C. V. Ramakrishnan, R. H. Andrews S. Devadatta, Wallace Fox, S. Radhakrishna, P. R. Somasundaram & S. Velu

The authors present a second report from the Tuberculosis Chemotherapy Centre, Madras, on the incidence of tuberculosis in close family contacts of tuberculous patients. The patients initially received a year's chemotherapy either at home or in sanatorium in a controlled comparison of the merits of domiciliary as opposed to institutional treatment. The first report presented data relating to the prevalence and the attack rate of tuberculosis among the contacts during the first year of treatment of the index cases ; this second report presents the attack rate for the 2-year period since the start of treatment for the index cases. During the second year all the index cases were managed at home, those with active disease, and half of those with quiescent disease, at the end of the first year receiving further chemotherapy. The findings of the 2-year study confirm those of the earlier study—namely, that the incidence of tuberculosis in the contacts of patients originally treated at home was no greater than that in the contacts of patients originally treated in sanatorium and that the major risk to the contacts resulted from exposure to the patient before diagnosis. As in the earlier report, the question of instituting chemoprophylaxis for the young contacts of tuberculous patients is discussed. The authors consider that close family contacts living in over-crowded, urban conditions in the developing countries are valuable groups for chemo-prophylactic investigations.

Bull. World Health Org. 1961, 25, 409-429

Progress in the Second Year of Patients with Quiescent Pulmonary Tuberculosis after a Year of Domiciliary Chemotherapy, and Influence of Further Chemotherapy on the Relapse Rate

**S. Velu, R.H. Andrews, J.H. Angel, S. Devadatta, Wallace Fox,
P.R.J., Gangadharam, A.S.L. Narayana, C.V. Ramakrishnan,
J.B. Selkon & P.R. Somasundaram**

This study from the Tuberculosis Chemotherapy Centre, Madras, summarizes the progress during the second year of those patients in a 1-year comparison of four domiciliary chemotherapeutic regimens (isoniazid plus PAS and three regimens of isoniazid alone) whose pulmonary tuberculosis had attained bacteriological quiescence at the end of the year of chemotherapy. During the second year, about half of the patients received further chemotherapy, with isoniazid alone, and the remainder received a placebo, calcium gluconate. The main objects of the study were to determine the influence on the progress during the second year of (a) a second year of chemotherapy with isoniazid alone, (b) residual cavitation at the end of the first year, and (c) the chemotherapeutic regimen received during the first year, and to compare the results with those obtained in an earlier study by the Centre of the progress during the second year of patients with quiescent pulmonary tuberculosis after a year's chemotherapy with isoniazid plus PAS at home or in sanatorium.

The results of the present study, which was planned on the same lines as the earlier one, showed that relapse in the second year was unrelated to the chemotherapeutic regimen received in the first year, and it was therefore permissible to amalgamate the findings in the two studies. The amalgamated results showed that the relapse rate in the second year was low (5.9%) and that a second year of treatment with isoniazid alone was of definite value for the patients with no residual cavitation at the end of the first year, but had no effect on the relapse rate of those with residual cavitation. The combined data from the two studies have thus clarified the position with regard to the effectiveness of isoniazid in preventing bacteriological relapse in patients without residual cavitation, slight evidence of which was present in the earlier study.

Bull. World Health Org. 1961, 25,779 - 792

Rate of inactivation of isoniazid in South Indian patients with pulmonary tuberculosis.

2. Clinical Implications in the Treatment of Pulmonary Tuberculosis with Isoniazid either Alone or in Combination with PAS

**J. B. Selkon, Wallace Fox, P. R. J. Gangadharam, K. Ramachandran,
C. V. Ramakrishnan & S. Velu**

A series of studies on the rate of inactivation of isoniazid in Indian patients with pulmonary tuberculosis undergoing domiciliary chemotherapy with isoniazid, alone or in combination with p-aminosalicylic acid, has recently been undertaken by the Tuberculosis Chemotherapy Centre, Madras. In the first study, the serum isoniazid levels of the patients were determined four-and-a-half hours after intramuscular administration of a standard dose of 3 mg/kg body-weight of isoniazid and, according to whether the serum level was 0.58 µg/ml or above, or less than 0.58 µg/ml, the patient was classified as a slow or as a rapid inactivator. The present paper describes the second of these studies, in which the response to treatment of the slow and the rapid inactivators was compared. The results of this investigation suggested that there might be an association between response to treatment and rate of inactivation of isoniazid, since the slow inactivators were more often culture-negative during treatment and showed a higher proportion of individuals with bacteriologically quiescent disease at 12 months and a lower proportion with radiographic deterioration at six months than the rapid inactivators, while the slow inactivators who deteriorated radiographically or clinically to an extent warranting a change of treatment during the two years did so later than the corresponding rapid inactivators. There was slight evidence that the slow and the rapid inactivators differed in the speed of conversion to bacteriological negativity of those patients whose disease was bacteriologically quiescent at 12 months, but no evidence that they differed in the degree of positivity of sputum specimens that were positive on culture at six, nine or 12 months, or in the frequency with which the patients showed moderate or greater radiographic improvement at six months.

Rate of Inactivation of Isoniazid in South Indian Patients with Pulmonary Tuberculosis

3. Serum Concentrations of Isoniazid Produced by Three Regimens of Isoniazid Alone and One of Isoniazid plus PAS

**P. R. J. Gangadharam, S. Devadatta, Wallace Fox,
C. Narayanan Nair & J. B. Selkon**

A series of studies on the rate of inactivation of isoniazid in Indian patients with pulmonary tuberculosis in a 1-year comparison of four domiciliary chemotherapeutic regimens— three of isoniazid alone, either in moderate (HI-1 and HI-2 regimens) or in low (H regimen) dosage, and one of isoniazid in low dosage plus p-aminosalicylic acid (PAS) (PH regimen) –has recently been undertaken by the Tuberculosis Chemotherapy Centre, Madras. This paper—the third of the series—presents information on the length of time during which inhibitory concentrations of isoniazid (0.2 µg/ml or more) were maintained in the serum and on the estimated peak serum concentrations of isoniazid produced by the four regimens and relates these factors to the therapeutic effectiveness of the different regimens.

The results suggested that : (a) the therapeutic superiority of the PH regimen over the isoniazid-alone regimens was only in part due to the effect of PAS in enhancing the serum levels of isoniazid; (b) the therapeutic superiority of the HI-1 regimen (moderate dosage, given in one dose a day) over the HI-2 and H regimens (moderate and low dosage, respectively, given in two doses a day) was due to the higher peak serum concentration of isoniazid produced rather than to the period minimal inhibitory concentrations of isoniazid were maintained in the serum ; and (c) there was a possibility that raising the peak serum concentration of isoniazid above a critical concentration of about 3 µg/ml had a greater therapeutic effect than similar proportional increases below this concentration. It also appeared that the slightly better therapeutic response observed in the slow inactivators of isoniazid than in the rapid inactivators was due to the higher peak serum concentrations of isoniazid produced ; the enhanced therapeutic effect was approximately the same as would be expected from a 50 % increase in isoniazid dosage.

The Virulence in the Guinea-pig of Tubercle Bacilli Isolated before Treatment from South Indian Patients with Pulmonary Tuberculosis

3. Virulence related to Pretreatment Status of Disease and to Response to Chemotherapy

C. V. Ramakrishnan, A. L. Bhatia, Wallace Fox, D. A. Mitchison, S. Radhakrishna, J. B. Selkon, T. V. Subbaiah, S. Velu¹ & J. G. Wallace

This is the last of a series of three reports from the Tuberculosis Chemotherapy Centre Madras, on a study undertaken with the object of finding out whether differences in the virulence in the guinea-pig of tubercle bacilli isolated from South Indian tuberculous patients before the start of chemotherapy are related to the severity of the patients' disease on admission to treatment and to the subsequent response to chemotherapy. The 281 patients in this study were drawn from the patients admitted to a 1-year comparison of four domiciliary chemotherapeutic regimens : (a) 3.9-5.5 mg/kg isoniazid plus 0.2-0.3 g/kg sodium PAS daily, divided into two doses (PH series) ; (b) 7.8-9.6 mg/kg isoniazid alone daily in one dose (HI-I series) ; (c) 7.8-9.6 mg/kg isoniazid alone daily, divided into two doses (HI-2 series) ;(d) 3.9-5.5 mg/kg isoniazid alone daily, divided into two doses (H series).

No evidence was found of an association between the virulence of the organisms and any pretreatment condition of known prognostic importance. There was no association between pretreatment virulence and progress during treatment in the PH series (the most effective regimen). In the other series, however, the progress was more satisfactory in patients infected with organisms of low virulence than in those infected with organisms of high virulence, the association between virulence and progress attaining statistical significance in the combined HI-2 and H series (the least effective regimens) and only just failing to do so in the smaller HI-1 series.

Possible explanations are put forward both for the absence of an association between virulence and severity of disease on admission and for the presence of an association between virulence and response in the patients treated with isoniazid alone.

Bull. World Health Org. 1961, 25, 339-359

**The Role of Diet
in the Treatment of Pulmonary Tuberculosis:
An Evaluation in a Controlled Chemotherapy Study in Home and Sanatorium
Patients in South India**

**C.V.Ramakrishnan, Kanthi Rajendran, P. George Jacob,
Wallace Fox & S. Radhakrishna**

Before the advent of anti tuberculosis chemotherapy, a diet rich in calories, proteins, fats, minerals and vitamins was generally considered to be an important, if not essential, factor in the treatment of tuberculosis. The introduction of specific anti tuberculosis drugs, however, has so radically altered the management of the disease that the role of diet has to be reconsidered in the light of the recent advances in treatment. An evaluation of the influence of diet in the treatment of pulmonary tuberculosis with isoniazid plus p-aminosalicylic acid was recently undertaken by the Tuberculosis Chemotherapy Centre, Madras, in the course of a controlled comparison of home and sanatorium chemotherapy for tuberculous patients from a poverty-stricken community in Madras City. Despite the fact that during the year of treatment the home patients subsisted on a markedly poorer diet, were physically more active and, on the average, gained less weight than the sanatorium patients, the overall response to treatment in the home series closely approached that in the sanatorium series, although there was a tendency for tubercle bacilli to disappear earlier in the latter. Direct evidence has been presented that none of the dietary factors studied (calories, carbohydrates, total and animal proteins, fats, minerals and vitamins) appears to influence the attainment of quiescent disease among tuberculous patients treated for one year with an effective combination of antimicrobial drugs, and that initial chemotherapy of patients at home can be successful even if the dietary intake is low throughout the period of treatment.

Bull World Health Org. 1961, 25, 361-407

**Prevalence and Early Attack Rate of Tuberculosis among Close Family Contacts of
Tuberculous Patients in South India under Domiciliary Treatment with Isoniazid
plus PAS or Isoniazid Alone**

**C. V. Ramakrishnan, R. H. Andrews, S. Devadatta, Wallace Fox,
S. Radhakrishna, P. R. Somasundaram & S. Velu**

The authors present a report from the Tuberculosis Chemotherapy Centre, Madras, on the prevalence and attack rate of tuberculosis among close family contacts of tuberculous patients in South India undergoing domiciliary chemotherapy either with isoniazid plus

PAS or with one of three regimens of isoniazid alone. The report gives (a) the prevalence of tuberculosis among the contacts at the time of diagnosis of the disease in the patients and (b) the incidence of tuberculosis in the contacts during the first year of treatment of the patients. The contacts were divided into four series, corresponding to the four chemotherapeutic regimens of the patients.

The prevalence of active tuberculosis was found to be particularly high among children under five years of age, being 12.0 % as compared with 7.6% for all age-groups combined. The incidence of active tuberculosis during the year of treatment of the patients was also found to be highest in the under five years' age-group-a further indication that child contacts are especially vulnerable to infection. The incidence was considerably higher in the first quarter of the year than in the other quarters, and it was lowest in the last quarter. This finding, together with the fact that the attack rates in the four contact series were not related either to the duration of bacteriological positivity in the patients or to the period of excretion of isoniazid-resistant organisms by the patients, suggests that the major risk to contacts in the first year results from exposure to the patient before treatment rather than from exposure during treatment. These results thus confirm the findings in an earlier study by the Centre of the contacts of patients in a controlled comparison of chemotherapy with isoniazid plus PAS at home and in sanatorium.

Bull. World Health Org. 1961, 25, 409-429

Progress in the Second Year of Patients with Quiescent Pulmonary Tuberculosis after a Year of Domiciliary Chemotherapy, and Influence of Further Chemotherapy on the Relapse Rate

**S. Velu, R.H. Andrews, J.H. Angel, S. Devadatta, Wallace Fox,
P.R.J. Gangadharam, A.S.L. Narayana, C.V. Ramakrishnan,
J.B. Selkon & P.R. Somasundaram**

This study from the Tuberculosis Chemotherapy Centre, Madras, summarizes the progress during the second year of those patients in a 1-year comparison of four domiciliary chemotherapeutic regimens (isoniazid plus PAS and three regimens of isoniazid alone) whose pulmonary tuberculosis had attained bacteriological quiescence at the end of the year of chemotherapy. During the second year, about half of the patients received further chemotherapy, with isoniazid alone, and the remainder received a placebo, calcium gluconate. The main objects of the study were to determine the influence on the progress during the second year of (a) a second year of chemotherapy with isoniazid alone, (b) residual cavitation at the end of the first year, and (c) the chemotherapeutic regimen received during the first year, and to compare the results with those obtained in an earlier study by the Centre of the progress during the second year of patients with quiescent

pulmonary tuberculosis after a year's chemotherapy with isoniazid plus PAS at home or in sanatorium.

The results of the present study, which was planned on the same lines as the earlier one, showed that relapse in the second year was unrelated to the chemotherapeutic regimen received in the first year, and it was therefore permissible to amalgamate the findings in the two studies. The amalgamated results showed that the relapse rate in the second year was low (5.9%) and that a second year of treatment with isoniazid alone was of definite value for the patients with no residual cavitation at the end of the first year, but had not effect on the relapse rate of those with residual cavitation. The combined data from the two studies have thus clarified the position with regard to the effectiveness of isoniazid in preventing bacteriological relapse in patients without residual cavitation, slight evidence of which was present in the earlier study.

Bull. World Health Org. 1961, 25, 807-829

Response of Patients Infected with Isoniazid-Resistant Tubercle Bacilli to Treatment with Isoniazid plus PAS or Isoniazid Alone

**S.Devadatta, A.L. Bhatia, R.H. Andrews, Wallace Fox,
D. A. Mitchison, S. Radhakrishna, C.V. Ramakrishnan,
J.B. Selkon & S. Velu**

This study from the Tuberculosis Chemotherapy Centre, Madras, compares patients infected with isoniazid-resistant tubercle bacilli ("R" patients) with those infected with isoniazid-sensitive tubercle bacilli ("S" patients) as regards, first, their pretreatment status and, secondly, their response to a year's chemotherapy, either with isoniazid plus p-aminosalicylic acid (PAS) or with isoniazid alone. With regard to the first comparison, there was, on admission to treatment, little difference between the R and S patients in terms of the extent of the radiographic lesion, the extent of cavitation or the bacterial content of the sputum, but there were major differences in the age and sex distributions, the R patients showing a greater preponderance of young males than the S patients. As to the second comparison, statistically significant differences in the bacteriological response to treatment of the S and the R patients were observed in both the isoniazid-plus-PAS and the isoniazid-alone series, the response of the S patients being much better than that of the R patients. When the response to treatment was assessed in terms of radiographic progress and weight changes, however, hardly any difference was observed between the progress of the S and the R patients. The reasons for the response in the R patients are discussed.

Tubercle, Lond., 1961, 42, 136

Streptomycin plus pyrazinamide in the treatment of patients excreting isoniazid-resistant tubercle bacilli, following previous chemotherapy

**S. Velu, R. H. Andrews, J. H. Angel, S. Devadatta, Wallace Fox,
P. George Jacob, C. Narayanan Nair and C. V. Ramakrishnan**

Tuberculosis Chemotherapy Centre*, Madras, India

Fifty-seven patients with chronic pulmonary tuberculosis and organisms sensitive to streptomycin were treated with daily streptomycin plus pyrazinamide, the majority attending a clinic daily for the therapy; all had previously been treated either with isoniazid plus PAS or with isoniazid alone. The streptomycin plus pyrazinamide regimen was stopped in 20 patients before the end of a year because the disease was active, and 1 more patient died. Of the 36 patients who completed 1 year's treatment, 32 had attained bacteriological quiescence and 1 more is considered to have done so. Sputum conversion was very rapid in those patients who attained bacteriological quiescence. Patients whose response was unsatisfactory usually had a clear 'fall and rise' in the bacterial content of the sputum associated with the emergence of strains highly resistant to streptomycin. Extensive or moderate cavitation, a large total extent of the radiographic lesion and heavily positive sputum on smear examination were relatively unfavourable prognostic signs. Age and sex were not of prognostic importance.

Toxicity to streptomycin was not a problem. Liver toxicity to pyrazinamide was not encountered, but joint pains occurred in 15 patients 6 of whom had a gouty syndrome. Seven patients received the combination throughout pregnancy, without developing toxic manifestations. The study has shown the value of long-term daily streptomycin plus pyrazinamide, as an out-patient treatment in India, for tuberculous patients in whom a first course of chemotherapy has failed.

Bull. World Health Org. 1962, 26, 1-18

**The Course of Pulmonary Tuberculosis in Patients Excreting Organisms
which have Acquired Resistance to Isoniazid. Response to Continued
treatment for a second year with Isoniazid alone or with Isoniazid plus PAS**

**C. V. Ramakrishnan, A. L. Bhatia, S. Devadatta, Wallace Fox,
A. S. L. Narayana, J. B. Selkon & S. Velu**

This study from the Tuberculosis Chemotherapy Centre, Madras, summarizes the progress during the second year of the patients in a concurrent comparison of four domiciliary chemotherapeutic regimens (isoniazid plus PAS and three regimens of isoniazid alone) who had bacteriologically active or bacteriologically relapsed pulmonary tuberculosis, with isoniazid-resistant organisms, at the end of the first year of treatment. Of the 57 patients who continued on the same chemotherapy during the second year, nine had attained bacteriological quiescence by the end of that year, 15 still had bacteriologically active disease and 33 had during the year had a serious radiographic deterioration necessitating a change of treatment. An association was observed between the response to treatment in the second year and both the extent of cavitation and the degree of culture-positivity at the end of the first year, but no association was found between the response to treatment in the second year and the level of isoniazid-resistance, the catalase activity, the susceptibility to hydrogen peroxide or the virulence in the guinea-pig of cultures isolated in the last months of the first year.

It is concluded that persisting bacteriological positivity at the end of one year's treatment with isoniazid, either alone or in combination with PAS, is likely to lead to serious radiographic deterioration, irrespective of the level of isoniazid-resistance or of the catalase activity of the cultures of tubercle bacilli, and that, consequently, treatment of patients with bacteriologically active pulmonary tuberculosis must aim at rendering the sputum culture-negative in all instances.

Lancet 1962, 413-417 & 473-478

**The Chemotherapy and Epidemiology of Tuberculosis. Some Findings of General
Applicability from the Tuberculosis Chemotherapy Centre, Madras**

Fox W.

In this Marc Daniels Lecture the author sums up the work done jointly by the Medical Research Council, the Indian Council of Medical Research, the Madras State Government, and the World Health Organization, who jointly set up the Tuberculosis Chemotherapy Centre in Madras in 1956. It is perhaps the most important investigation to have been carried out on tuberculosis since the introduction of isoniazid. The details of the work as

reported from time to time have already been reviewed in this *Bulletin*. The author's general conclusions may with advantage be mentioned. He discussed home treatment, relapse rates, and the question of isolation of patients under treatment. "Thus, study of the immediate response of the patients to treatment, the subsequent relapse-rates, and the risk to contacts have not shown that any additional benefit results from a year of combined chemotherapy in a good sanatorium compared with the same chemotherapy given at home in very unfavourable environmental conditions." In Madras the patients treated throughout at home did practically as well as those treated in sanatorium for up to 1 year, the patients co-operated better at home, and the disruption of family life was avoided, without much risk to contacts. He says: -"In my view, with modern chemotherapy, it would often be more appropriate for the chest-clinic physician (who has an enthusiastic staff and adequate resources to supervise treatment) to ask himself, on the contrary, if there is any special reason why the patient should not be treated at home. The fact that the time-honoured virtues of sanatorium treatment—rest, a nutritious diet, and good accommodation, combined with isolation—proved remarkably unimportant, is a tribute to the power of effective combined chemotherapy."

For the drug regimen, the value of PAS together with isoniazid was very evident, and it was shown that the efficacy of isoniazid was related more to its peak serum level than to the maintenance of continuous inhibitory levels in the serum. It may eventually prove advantageous to give a day's supply of the combination of PAS with isoniazid in a single dose each day, and these investigations raise the possibility that "even greater intermittence—for example, one dose of drugs every second, third, or even every fourth day—might still prove effective, especially if the size of the doses was increased to produce still higher peak concentrations". The author notes that the action of PAS is antibacterial. Patients vary in the rate at which they inactivate isoniazid, and the incidence of peripheral neuritis is much higher in the slow inactivators than in the rapid inactivators; it is also related to dosage rates. Pyridoxine (50-300 mgm. daily) is useful in preventing or treating this neuritis, but is expensive. A vitamin-B-complex preparation was found to be effective in treatment and probably would be effective in prevention.

In patients with the "open-negative" syndrome, isoniazid at 200 mgm. Daily cannot be relied upon to prevent bacteriological relapse after a year of combined treatment, and combined therapy should therefore be prescribed as a continuation after the first year. But for patients without residual cavitation isoniazid alone was found to be enough after a year of combined treatment. A total of 2 years of chemotherapy is ample for patients without residual cavitation at the end of the first year.

Results in relation to isoniazid resistance are summed up as follows: "This study produced direct evidence that persisting bacteriological positivity with isoniazid-resistant organisms even if they are catalase-negative, is dangerous for the patient, and that the disease is likely to progress under continued treatment which includes isoniazid. The object of treatment must therefore be to render the sputum negative and to keep it so, and the importance of this object cannot be over-stressed. Though an isoniazid-resistant strain is

attenuated and self-limiting in the Guinea pig, this certainly does not apply in man once disease with isoniazid-resistant organisms is established."

"Thus, if primary isoniazid resistance becomes widespread in the community, then it can be predicted that the response of patients to isoniazid given with a companion drug will be seriously impaired."

"In Madras isoniazid-resistant infections see more details, whether primary or acquired, proved harmful to the patient because they militated against successful treatment with isoniazid-containing combinations. Although in the medically advanced countries, there is still relatively little primary isoniazid resistance, acquired resistance results only too commonly from treatment with unsatisfactory drug combinations, and these should never be prescribed. It is still too early to know the long-term risk to close family contacts from exposure to index cases excreting isoniazid-resistant strains."

The author recognizes the difficulties of self-administration of drugs, and analyses them, concluding that: -"The two main reasons for difficulty over the self-administration of drugs in Madras-and there are reasons to believe that they apply generally also ... -are forgetfulness and indifference in patients who usually feel completely fit but who yet are expected to continue regularly with their drugs for many more months. There is also the readiness of some patients to blame all untoward symptoms, whatever the cause, on their anti-tuberculosis drugs.

"Not only may the control of tuberculosis in developing countries see more details be hindered but its eradication in countries with advanced medical services see more details may well be delayed unless a way can be found to overcome this general problem of self-administration of drugs." He ends by emphasizing the fact that research in developing countries is not simply a question of applying information acquired in medically advanced countries, but that local problems demand investigation in their own right.

Tubercle, Res.1963, 12, 28-149

**Ambulatory chemotherapy in a developing country:
Clinical and epidemiological studies. Adv.**

Fox W.

Under this title the author describes the origin and formation of the Tuberculosis Chemotherapy Centre, Madras, a unit under the auspices of the Indian Council for Medical Research, the Madras State Government, WHO, and the British Medical Research Council. It is an independent unit adjacent to the main tuberculosis clinic of Madras, and, while primarily concentrating on domiciliary treatment, has 100 beds available in the local sanatorium. It has out-patient, radiographic and statistical departments, a well-equipped laboratory and an organized domiciliary service. He then goes on to recapitulate the studies carried out at the centre from its beginning in 1956 to the present. Readers of this

Bulletin will be familiar with these studies; but it is convenient to have them together in one monograph.

- A comparison was made of sanatorium and domiciliary treatment with PAS and isoniazid (4.6 mgm./kgm. and 0.23 gm./kgm.), random allocation to the 2 series being used. The results were essentially the same. Patients in sanatorium gained more weight and had lower erythrocyte sedimentation rates, radiographic changes were similar, and bacteriologically, 86% of the 82 patients treated at home and 92% of 81 treated in sanatorium achieved quiescence.
- A comparison of the relapse rate of these two groups was made over the next 2 years. Bacteriological relapse occurred in 5% of those originally treated at home, and 9% of those originally treated in sanatorium, thus offsetting the slight initial advantage to the patients treated in sanatorium.
- A comparison was made of the relapse rate of patients rendered bacteriologically quiescent by a year's treatment (including various schedules, sanatorium and domiciliary) and then treated for a further year by isoniazid alone or by a placebo (calcium gluconate). Of patients with residual cavitation, 10% of 42 receiving the placebo and 7% of 55 receiving isoniazid relapsed; of patients without residual cavitation, 9% of 107 receiving the placebo and none of 103 receiving isoniazid relapsed. There is thus a clear advantage in the use of isoniazid alone for a second year when there is no cavitation.
- No advantage could be demonstrated in isoniazid therapy for a third year.
- Comparison was made of attack rates in contacts of patients treated at home and in a sanatorium. It is most important to know whether the treatment of patients at home results in increase in infection of contacts, especially children. Of tuberculin-negative contacts, 7% of 86 home contacts and 6.9% of 87 sanatorium contacts developed tuberculous lesions in the first year, almost all in the first 3 months, and none developed lesions in the second year. This suggests that all the infections occurred before treatment started, and that home treatment was effective in preventing spread to contacts.
- A further domiciliary treatment study was carried out in which the regime of PAS and isoniazid as before was compared with 3 different regimes in which isoniazid was used alone. These were isoniazid, 1 daily dose of 7.8-9.6 mgm. /kgm, i.e., 400 mgm. for a patient weighing 100 lb; isoniazid, the same amount divided into 2 daily doses and isoniazid, 3.9-5.5 mgm: / kgm. daily, i.e., 200 mgm. for a patient weighing 100 lb., divided into 2 doses. Only the combined PAS and isoniazid series fared well, with 86% of patients bacteriologically quiescent at 12 months the high single dose series did the best of those receiving isoniazid alone, with 67% bacteriologically quiescent; of the other 2 series only 56 and 44 reached this goal. It is suggested that peak serum isoniazid levels are the most important

factor therapeutically. All the, positive cultures became isoniazid-resistant.

- Neuritis occurred in only 1 patient on the lower isoniazid dosage, but in no less than 18% of those on the large, once daily, dose. The incidence was cumulative, more neuritis occurring each month. Neuritis occurred mainly in those who were slow inactivators of isoniazid: 28% of 39 slow inactivators, 6% of 32 rapid inactivators. It was however found that a vitamin B complex preparation giving the low daily dose of 6 mgm, of pyridoxine could cure the neuritis, and would therefore probably prevent it. [Later work, not included in this paper, confirms that 6 mgm. pyridoxine daily without other B vitamins will prevent neuritis due to isoniazid.]
- A follow-up of patients who were sputum positive and excreting isoniazid-resistant organisms at the end of a year, showed that, whether isoniazid was continued or not, serious radiographic deterioration was likely to occur. This was true even if the organisms were catalase-negative.
- Further surveys of home contacts of those on the isoniazid only regimes confirmed that the major risk was exposure to the index patient before treatment began.
- It was found that although patients with initially isoniazid-resistant organisms improved at first on isoniazid and PAS or isoniazid alone, the improvement was not maintained, and results were unsatisfactory.
- The treatment of failure (isoniazid-resistant) patients with second order drugs was studied, with the use of drugs for domiciliary, not hospital, treatment but the patient was asked to attend the clinic 6 days a week. Streptomycin (1 gm. intramuscularly daily for 6 days) plus pyrazinamide (1-1.5 gm. daily) resulted in 56% attaining bacteriological quiescence at a year. Successful sputum conversion took place very quickly and it became obvious at 3 months who were failures, so that fruitless treatment could be discontinued. Liver damage was not a problem.
- Cycloserine 500 mgm. plus ethionamide 500 mgm. daily resulted in 9 of 14 patients attaining bacteriological quiescence. Cycloserine 500 mgm. plus thiacetazone 100 mgm. Daily was not successful.

The author reviews the problems of self-administration and supervised administration of drugs on a domiciliary basis, and emphasizes the need for close supervision and checks on the urine. Irregularity occurred equally with isoniazid alone in small tablets, placebo tablets, or large cachets of PAS and isoniazid, and although various reasons exist for omission, mostly it is a result of forgetfulness or indolence. The irregular drug taker did not do quite so well as the regular. Daily attendance for supervised consumption or for injections seemed to work well in Madras.

Finally, the author gives his views, also previously published [this Bulletin, 1964, v. 39, 512], on the organization of tuberculosis in poor countries, with particular emphasis on how many of what are normally regarded as necessities may under financial stress be omitted. *A. C. E. Cole.*

Tubercle, 1963, 44 , 218 - 224.

A controlled comparison of cycloserine plus ethionamide with cycloserine plus thiacetazone in patients with active pulmonary tuberculosis despite prolonged previous chemotherapy

J. H. Angel, A. L. Bhatia, S. Devadatta , Wallace Fox, B. Janardhanam, S. Radhakrishna , C. V. Ramakrishnan, J. B. Selkon, H. Stott and S. Velu

Tuberculosis Chemotherapy Centre, Madras, India

Twenty-seven patients with chronic pulmonary tuberculosis who had failed to respond to two previous chemotherapeutic regimens were allocated to treatment with cycloserine plus ethionamide (14 patients), or with cycloserine plus thiacetazone (13 patients). All had isoniazid-resistant strains and all but one had streptomycin-resistant strains at the start of the study. At the end of a year nine of 14 patients in the ethionamide series compared with three of 13 in the thiacetazone series had bacteriologically quiescent disease, one and three, respectively, had bacteriologically active disease; during the year, two patients (one in each series) deteriorated and had their chemotherapy changed and two patients (both on thiacetazone) died of tuberculosis. The difference in the proportions of unfavourable response attained statistical significance. There was one case of peripheral neuropathy due to ethionamide. Definite toxicity to thiacetazone was not observed. One of nine patients excluded from the main analysis had had intractable vomiting due to cycloserine.

Wallace Fox. Ambulatory chemotherapy in a developing country: Clinical and epidemiological studies. *Adv. Tuberc. Res.*1963:12:28-149.

Lancet, 1963, 1078-1080

**Intermittent treatment of pulmonary tuberculosis:
A Concurrent Comparison of Twice-weekly Isoniazid plus Streptomycin and Daily
Isoniazid plus p-Aminosalicylic Acid in Domiciliary Treatment**

Tuberculosis Chemotherapy Centre, Madras

DOMICILIARY chemotherapy of tuberculosis has become accepted practice in developing countries, but the best method of administering the drugs is still in question. Self-medication for long periods may result in irregularities, and, although fully supervised daily chemotherapy has been used to avoid these, it imposes a considerable strain on clinic and patients, and is hardly practicable in developing countries (see review by Fox). If, instead, supervised therapy could be given intermittently—e.g., twice a week—the method could become more generally applicable.

Bull. Org. mond. Santé } 1963, 28, 455-475
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The Prevention and Treatment of Isoniazid Toxicity in the Therapy of Pulmonary Tuberculosis

1. An Assessment of Two Vitamin B Preparations and Glutamic Acid*

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS¹

This paper from the Tuberculosis Chemotherapy Centre, Madras, presents the results of a study designed primarily (a) to assess the efficacy of two preparations—Tab. Aneurin. Co. (a vitamin B compound not containing pyridoxine) and glutamic acid—in preventing the development of peripheral neuropathy during high-dosage (12.5-15.2 mg/kg) isoniazid therapy for pulmonary tuberculosis, and (b) to compare the therapeutic efficacy, once isoniazid neuropathy has developed, of Tab. Aneurin. Co., administered at twice the prophylactic dosage, and a vitamin-B-complex preparation containing a small amount of pyridoxine (amounting to 6 mg daily).

Tab. Aneurin. Co. was found to be ineffective in preventing peripheral neuropathy, which occurred in five of the 18 patients receiving this preparation, as compared with six of the 18 who received a placebo, calcium gluconate. Glutamic acid appeared to have some prophylactic effect, since only two of the 19 patients receiving it developed the neuropathy, but the difference between the frequency in the glutamic series and that in the placebo series did not attain statistical significance.

As to the therapeutic efficacy of the two vitamin B preparations, Tab. Aneurin. Co., at twice the prophylactic dosage, did not prevent the progression of the neuropathy in five out of seven patients, whereas improvement occurred in eight of the nine patients who received the vitamin-B-complex preparation containing the small amount of pyridoxine.

This study has confirmed that the frequency of peripheral neuropathy is significantly higher among slow than among rapid inactivators of isoniazid and has indicated that the therapeutic response of the tuberculosis is not materially affected by increasing the dosage of isoniazid from 7.8-9.6 mg/kg (the dosage used in a previous study) to 12.5-15.2 mg/kg.

The Prevention and Treatment of Isoniazid Toxicity in the Therapy of Pulmonary Tuberculosis

2. An Assessment of the Prophylactic Effect of Pyridoxine in Low Dosage *

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS ¹

A recent report from the Tuberculosis Chemotherapy Centre, Madras, showed that a vitamin-B-complex preparation containing a small amount of pyridoxine (as well as aneurine hydrochloride, riboflavine, nicotinamide, panthenol and cyanocobalamin) was effective in the treatment of peripheral neuropathy caused by daily high-dosage (12.5-15.2 mg/kg body-weight) isoniazid therapy of pulmonary tuberculosis. The present report gives results which show that the B-complex preparation is fully effective in preventing peripheral neuropathy in patients receiving the same high dosage of isoniazid, and that this is due to the small pyridoxine content of only 6 mg daily, and not to any of its other constituents. The low cost of this small dose of pyridoxine makes high-dosage isoniazid therapy, given in combination with other drugs or alone, a possible proposition in developing countries.

Studies in the Centre have produced clear evidence that there is an increase in the frequency of peripheral neuropathy when the dosage of isoniazid is increased from 7.8-9.6 mg/kg body-weight to 12.5-15.6 mg/kg daily, and that its incidence is higher among slow than among rapid inactivators of isoniazid.

The studies also show that increasing the dosage of isoniazid when given alone from a moderate daily dosage of 7.8-9.6 mg/kg to the high daily dosage of 12.5-15.6 mg/kg has not materially altered the radiographic or the bacteriological response to treatment.

Bull. World Health Org. 1964, 31, 247-271

A Concurrent Comparison of Intermittent (Twice-Weekly) Isoniazid plus Streptomycin and Daily Isoniazid plus PAS in the Domiciliary Treatment of Pulmonary Tuberculosis

Tuberculosis Chemotherapy Centre, Madras

Previous reports from the Tuberculosis Chemotherapy Centre, Madras, have established that ambulatory treatment of pulmonary tuberculosis with the combination of isoniazid and PAS, administered daily, yields satisfactory results. However, in the usage of any unsupervised regimen, reliance must be placed on the co-operation of patients in self-administering their drugs. Irregularities in drug-taking, which are not uncommon, may lead to unfavourable therapeutic results; this might be avoided by supervised administration of the drugs. Daily supervision is clearly impracticable in developing countries but regimens in which the drug is administered intermittently-say, twice a week or less frequently-are, if effective, more likely to gain general application.

This paper presents the results of a controlled study of a fully supervised intermittent regimen of isoniazid (12.5-16.1 mg/kg body-weight, orally) plus streptomycin (injected in a uniform dose of 1 g), given together twice weekly, compared with a standard, unsupervised, daily, oral regimen of isoniazid (3.7-63 mg/kg body-weight) plus sodium PAS (0.2-0.3 g/kg body-weight), given in two doses. The intermittent regimen was at least as effective as the standard oral regimen, and although the incidence of temporary giddiness in patients receiving this regimen was rather high, this did not appear to have any long-term importance nor did it appear unduly to affect the co-operation of the patients. These encouraging findings suggest a possible change in the orientation of drug-administration for tuberculosis in developing countries.

Tubercle, Lond., 1964, 45, 144

A controlled comparison of streptomycin plus pyrazinamide and streptomycin plus PAS in the retreatment of patients excreting isoniazid-resistant organisms

**S. Velu, J. J. Y. Dawson, S. Devadatta, Wallace Fox, K.G. Kulkarni, K. Mohan,
C.V. Ramakrishnan and H. Stott**

Tuberculosis Chemotherapy Centre, Madras, India

A controlled comparison has been made of streptomycin plus pyrazinamide (46 patients) and streptomycin plus PAS (36 patients) in the retreatment of patients with pulmonary tuberculosis. The patients had either failed to attain bacteriological quiescence on isoniazid alone or had relapsed bacteriologically after attaining quiescence; all were excreting strains of tubercle bacilli resistant to isoniazid but sensitive to streptomycin and PAS at the start of the trial.

The disease status at 1 year was assessed in 41 patients on pyrazinamide and 24 on PAS, and of these, 29 (71 %) and 12 (50%) respectively, had bacteriologically quiescent disease.

Seven patients (2 on pyrazinamide, 5 on PAS) had their treatment terminated for toxicity, 1 due to a pyrazinamide polyarthrititis, 2 on account of hypersensitivity to PAS, and 4 (1 on pyrazinamide, 3 on PAS) because of streptomycin toxicity. Nine patients (2 on pyrazinamide, 7 on PAS) became unto-operative and stopped treatment, and 2 patients (on pyrazinamide) died, 1 of a non-tuberculous condition.

Thus, streptomycin plus pyrazinamide was slightly more effective therapeutically than streptomycin plus PAS and was not more toxic or less acceptable to the patients.

Bull. World Health Org. 1966, 34, 517-532

A Controlled Study of the Influence of Segregation of Tuberculous Patients for One Year on the Attack Rate of Tuberculosis in a 5-Year Period in Close Family Contacts in South India

S. R. Kamat, J. J. Y. Dawson, S. Devadatta, Wallace Fox, B. Janardhanam, S. Radhakrishna, C. V. Ramakrishnan, P. R. Somasundaram, H. Stott & S. Velu

This report is the last of a series of nine publications from the Tuberculosis Chemotherapy Centre, Madras, concerning various aspects of an investigation of the role of ambulatory chemotherapy for pulmonary tuberculosis. It presents the attack rates of tuberculosis over a 5-year period of follow-up of close family contacts of patients, all of whom were treated for one year with isoniazid plus PAS, half (selected at random) in sanatorium and half at home. The incidence of active tuberculosis and of tuberculous infections was no greater in the contacts of patients treated at home than in the contacts of patients treated in sanatorium, either in the first year or over the subsequent four years. The major risk to the contacts resulted from exposure to the patient before diagnosis. These findings reaffirm that close family contacts of patients treated at home were at no additional risk of developing tuberculosis, provided the patients received effective chemotherapy. Finally, this study has shown that it is possible in South India to obtain extremely good co-operation from a group of families over a period of several years.

Bull. World Health Org. 1966, 34, 483-515

Isoniazid plus Thioacetazone compared with Two Regimens of Isoniazid plus PAS in the Domiciliary Treatment of Pulmonary Tuberculosis in South Indian Patients

Tuberculosis Chemotherapy Centre, Madras

Previous reports from the Tuberculosis Chemotherapy Centre, Madras, have established that ambulatory treatment of pulmonary tuberculosis with a standard daily regimen of isoniazid plus PAS for one year yields satisfactory results. However, this regimen may be unsuitable for large-scale use in many developing countries, because PAS is expensive, bulky and unpleasant to take, and has poor keeping qualities, especially in tropical countries. It might be possible to overcome these disadvantages, by substituting for the PAS a drug which is equally effective but less expensive and more acceptable, or by reducing the daily dosage of PAS and the period for which it is prescribed.

This paper presents the results over a 11-month period of a controlled comparison of (a) the standard regimen of isoniazid (average 4.5 mg/kg body-weight) plus sodium PAS (average

0.22 g/kg), daily in two divided doses ; (b) a regimen of isoniazid (average 6.9 mg/kg) plus thioacetazone (average 3.4 mg/kg), daily in one dose ; and (c) a 2-phase regimen of isoniazid (average 5.5 mg/kg) plus sodium PAS (average 0.17 g/kg), daily in one dose for 6 months, followed by isoniazid alone (average 6.8 mg/kg), daily in one dose for the second 6 months. The regimen of isoniazid plus thioacetazone was found to be therapeutically as effective as the standard regimen of isoniazid plus PAS ; however, it was associated with a higher incidence of minor side-effects, and three cases of exfoliative dermatitis. The 2-phase regimen of isoniazid plus PAS followed by isoniazid alone was less effective. These findings are encouraging for the large-scale use in developing countries of the relatively inexpensive regimen of isoniazid plus thioacetazone ; however, any such step should be preceded by carefully planned studies to investigate, under local conditions, the toxicity and the efficacy of the regimen.

Bull. World Health Org. 1966, 34, 533 - 551

**A 5-Year Study of Patients with Pulmonary Tuberculosis in a Concurrent
Comparison of Home and Sanatorium Treatment for One Year
with Isoniazid plus PAS**

**J. J. Y. Dawson, S. Devadatta, Wallace Fox, S. Radhakrishna,
C. V. Ramakrishnan, P. R. Somasundaram, H. Stott,
S. P. Tripathy & S. Velu**

This report from the Tuberculosis Chemotherapy Centre, Madras, summarizes the progress over a 5-year period of 193 patients with newly diagnosed, sputum-positive pulmonary tuberculosis who were admitted to a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. Previous reports have shown that, despite the traditional advantages of sanatorium treatment-rest, adequate diet, nursing and supervised drug-administration-the home patients responded nearly as well as the sanatorium patients in the first year; further, the relapse rates over a 2-year period of follow-up were similar. The findings in the present report are based on a 4-year period of follow-up and extend these conclusions, the relapse rates over the period being 7 % for the home patients and 10 % for the sanatorium patients.

Patients who failed to respond to treatment in the first year and those who had a bacteriological relapse in the second or subsequent years were usually re-treated with reserve regimens, first with streptomycin plus pyrazinamide and, if this was ineffective, with cycloserine plus ethionamide. Considering the findings over the entire 5-year period, five home patients and three sanatorium patients died from non-tuberculous causes. Of the remainder, 5 % of the home patients and 6 % of the sanatorium patients died of tuberculosis, 4 % in each series had bacteriologically active disease at five years and 90 % and 89 %, respectively, had bacteriologically quiescent disease at that time. These findings

are very encouraging, particularly for developing countries such as India, where tuberculosis is a major problem and sanatorium beds are very few.

Bull. World Health Org. 1966, 34, 553-571

**The Diet, Physical Activity and Accommodation of Patients with Quiescent
Pulmonary Tuberculosis in a Poor South Indian Community.
A Four-Year Follow-up Study**

**C. V. Ramakrishnan, Kanthi Rajendran, K. Mohan,
Wallace Fox & S. Radhakrishna**

A previous report from the Tuberculosis Chemotherapy Centre, Madras, has shown that, if standard chemotherapy is given for one year, the response of patients treated at home in very poor environmental circumstances is nearly as good as that of those treated in sanatorium under much more favourable conditions. This paper reports on a four-year follow-up of all the patients whose disease was bacteriologically quiescent at the end of the year's treatment. During this period, all the patients were managed on a domiciliary basis : about a quarter of them received chemotherapy with isoniazid alone for two years, another quarter received the drug for one year and the rest received no specific chemotherapy. Despite adverse environmental factors (poor diet ; long hours of work often involving strenuous physical activity ; overcrowded living conditions ; and, for the sanatorium patients, the stresses of returning suddenly to the unfavourable home environment), the great majority of patients in both series maintained quiescent disease throughout the follow-up period. Furthermore, the few patients whose disease relapsed bacteriologically were at no special dietary disadvantage in comparison with those who maintained quiescent disease throughout, nor did they show any appreciable differences in occupation, physical activity or living accommodation. These findings, together with the earlier ones, indicate that, despite adverse environmental circumstances, standard chemotherapy for an adequate period of time is sufficient in the great majority of patients for the attainment of bacteriological quiescence and its maintenance thereafter.

Bull. World Health Org. 1966, 34, 573-587

**Comparative Value of Sputum Smear Examination and Culture Examination in
Assessing the Progress of Tuberculous Patients Receiving Chemotherapy**

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Bacteriological response is generally considered the best criterion for assessing the efficacy of chemotherapy in patients with pulmonary tuberculosis. The bacteriological methods most commonly used are examination of sputum smears for tubercle bacilli, culture of bacilli from sputum specimens, and drug-sensitivity tests on positive cultures. Culture examination, though more sensitive than smear examination in detecting tubercle bacilli, is time-consuming and economically impracticable as a routine method in most developing countries. A study was therefore undertaken at the Tuberculosis Chemotherapy Centre, Madras, to determine the relative value of smear examination and culture examination in predicting the outcome of treatment and assessing the efficacy of chemotherapeutic regimens in 515 patients (all with bacteriologically confirmed disease and isoniazid-sensitive organisms on admission) receiving isoniazid, alone or with sodium PAS. The results showed that the value of smear examination of overnight sputum specimens at monthly intervals closely approached that of culture examination in assessing the progress of the patients, the percentages of correct predictions by smear and by culture being of the same order. Smear examination was slightly less effective than culture examination in detecting differences in the efficacies of regimens, but it has been estimated that this disadvantage can usually be compensated for by increasing the study population by about 20 %.

Tubercle, Lond., 1966, 47, 178-189

**A two-year follow-up of patients with quiescent pulmonary tuberculosis following a
year of chemotherapy with an intermittent (twice-weekly) regimen of isoniazid plus
streptomycin or a daily regimen of isoniazid plus PAS**

**O. Nazareth, S. Devadatta, C. Evans, Wallace Fox, B. Janardhanam,
N.K. Menon, S. Radhakrishna, C. V. Ramakrishnan, H. Stott,
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Tuberculosis Chemotherapy Centre, Madras-31, India

In the main analysis of a year's study of twice-weekly high dosage isoniazid plus streptomycin (SHTW) in comparison with a standard daily regimen of isoniazid plus PAS (PH) under domiciliary conditions, 66 SHTW and 53 PH patients had attained

bacteriologically quiescent disease at one year. All the patients have now been followed-up over a two-year period. Of these, 66 SHTW and 52 PH patients had been allocated at random to treatment the second year with isoniazid alone or with placebo. No patient was prescribed anti-tuberculosis drugs for the third year.

The condition of the patients in the two series was broadly similar, both at the time of their original admission to treatment and also at the start of the period of follow-up.

There were five deaths (four SHTW, one PH) in the follow-up period, all in the second year and all from non-tuberculous causes; all five patients produced only negative cultures in the second year and for at least six months immediately before death.

The radiographic progress was similar for the two series in the second and third years, the majority of patients in both series showing little change.

The patients were under intensive bacteriological investigation, an average of 14 cultures being examined per patient in the second year and nine in the third year. A bacteriological relapse occurred in five (8 %) SHTW and six (12 %) PH patients. In one and two patients respectively, this was associated with a serious radiographic deterioration. An isolated positive culture was produced by 17 % of the SHTW and 27 % of the PH patients. Four of the SHTW patients had a relapse with streptomycin- and isoniazid-sensitive cultures and four of the PH patients with isoniazid-sensitive cultures. It is concluded that bacteriological quiescence following a year of twice-weekly isoniazid plus streptomycin is at least as stable, over a two-year period of follow-up, as that attained following a year of a standard daily oral regimen of isoniazid plus PAS.

Ind. Jour. Med. Res., 1968, 56, 11,1617-1630.

Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India.

Part I. Findings in urban clinics among patients giving no history of previous chemotherapy.

(Indian Council of Medical Research)

It is generally accepted that information on the prevalence of drug resistance is essential for countries which contemplate mass chemotherapy programme for tuberculosis (International Union against Tuberculosis, 1961). In India in 1964, information on this subject was confined to certain limited areas only (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 1964; Frimodt-Moller, 1962 ; Menon, 1963; Balbir Singh, 1964). Therefore, the Indian Council of Medical Research (I.C.M.R.) launched a series of investigations to determine the prevalence of drug resistance in tuberculous patients

reporting for the first time with symptoms at chest clinics; chest clinics were chosen since they are an obvious starting point for any mass chemotherapy programme. A special sub-committee of the Indian Council of Medical Research (see footnote) was constituted to organise the execution of these investigations, and a Central Laboratory set up on the premises of the Tuberculosis Chemotherapy Centre, Madras, to undertake all the necessary bacteriological investigations.

Ind. Jour. Med. Res., 1969, 57, 5, 823-835.

Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India.

**Part II. Findings in urban clinics among all patients, with or without history of previous chemotherapy.
(Indian Council of Medical Research.)**

A previous report (Indian Council of Medical Research First Drug Resistance Investigation, 1968) presented the results of a co-operative investigation on the prevalence of drug resistance in patients with pulmonary tuberculosis, presenting for the first time with symptoms at chest clinics in India and giving no history of previous anti-tuberculosis chemotherapy. However, the information obtained from that investigation is of rather limited value because, in most clinics, fairly large proportions of patients reporting for the first time do so with a history of previous treatment. This is because anti-tuberculosis chemotherapy is offered not only by chest clinics, but also by general hospitals and private practitioners. In these circumstances, information on the prevalence of drug resistance among all patients, irrespective of the history of previous anti-tuberculosis chemotherapy, will be of great value, not only to the clinicians-in-charge of the chest clinics but also to those responsible for formulating general policies of treatment in the country. The second drug resistance investigation was undertaken

Bull. World Health Org. 1969 41, 1-16

A 5-year study of patients with pulmonary tuberculosis treated at home in a controlled comparison of isoniazid plus PAS with 3 regimens of isoniazid alone

**C. Evans, S. Devadatta, Wallace Fox, P. R. J. Gangadharam,
N. K. Menon, C. V. Ramakrishnan, S. Sivasubramanian,
P. R. Somasundaram, H. Stott & S. Velu**

This report from the Tuberculosis Chemotherapy Centre, Madras, describes the progress, over a 5-year period, of 341 patients with newly diagnosed, sputum-positive tuberculosis. All the patients were treated on a domiciliary basis. In the first year, the patients received,

on the basis of random allocation, a standard regimen of isoniazid plus PAS or 1 of 3 regimens of isoniazid alone. Previous reports have shown that the response in the first year was substantially superior with the standard regimen, and that the bacteriological relapse rates in the second year were fairly similar for the 4 regimens. The findings in the present report extend the latter conclusion to the end of 5 years. Further, when considered together with the findings in an earlier study, they have shown that isoniazid, given as maintenance chemotherapy in the second year, was highly effective in preventing bacteriological relapse in patients who, at 1 year, had bacteriologically quiescent disease and no residual cavitation; the effect was, however, less marked in patients with residual cavitation at 1 year.

Patients who were clear-cut failures of the allocated chemotherapy and those who had a bacteriological relapse in the second or subsequent years were usually re-treated with streptomycin plus PAS or streptomycin plus pyrazinamide, and if this was ineffective, with cycloserine plus thioacetazone or cycloserine plus ethionamide.

Considering the findings over the 5-year period for all patients, 16 died from non-tuberculous causes and 1 took his discharge prematurely. Of the remainder, 86% had bacteriologically quiescent disease at 5 years, 6 % had bacteriologically active disease and 8 % had died of tuberculosis. These findings confirm the value of well-organized domiciliary chemotherapy, which was established by an earlier report from the Centre, and are particularly encouraging for developing countries such as India, where tuberculosis is a major problem and resources are limited.

Tubercle, Lond., 1969, 50, 115-124

**A four-year follow-up of patients with quiescent pulmonary tuberculosis
at the end of a year of chemotherapy with twice-weekly isoniazid
plus streptomycin or daily isoniazid plus PAS**

**C. V. Ramakrishnan, S. Devadatta, C. Evans, Wallace Fox, N. K. Menon,
O. Nazareth, S. Radhakrishna, S. Sambamoorthy, H. Stott,
S. P. Tripathy and S. Velu**

Tuberculosis Chemotherapy Centre, Madras 31, India

This report describes the progress over a four-year period of follow-up of 119 patients who had bacteriologically quiescent pulmonary tuberculosis at the end of a year of chemotherapy with either a fully supervised twice-weekly regimen of isoniazid plus streptomycin (SHTW, 66 patients) or a standard self-administered daily regimen of isoniazid plus PAS (PH, 53 patients). (In the second year, that is, in the first year of the

follow-up, half the patients, selected at random, received maintenance chemotherapy with isoniazid and the other half a placebo.)

The condition of the patients in the SHTW and PH series was similar, both at the time of their initial admission to treatment and at the start of the period of follow-up. One patient (PH) died of tuberculosis in the fifteenth month, having had a bacteriological relapse in the fourteenth month. Nine others (five SHTW, four PH) died of non-tuberculous causes. The radiographic progress over the four-year period was similar in the SHTW and the PH series.

On average, 42 cultures per patient were examined during the four-year period. A bacteriological relapse occurred in eight SHTW and eight PH patients; however, retreatment became necessary in only three (5 %) SHTW and five (10 %) PH patients, the others having had a spontaneous sputum conversion. Most of the relapses occurred with drug-sensitive cultures.

It is concluded that bacteriological quiescence attained with a year of twice-weekly isoniazid plus streptomycin is at least as stable, over a four-year period of follow-up, as that attained with a year of daily isoniazid plus PAS.

Bull. World Health Org. 1970, 43, 143-206

A Controlled Comparison of a Twice-Weekly and Three Once-Weekly Regimens in the Initial Treatment of Pulmonary Tuberculosis

Tuberculosis Chemotherapy Centre, Madras

A previous report from the Tuberculosis Chemotherapy Centre, Madras, demonstrated the value of a fully supervised twice-weekly regimen of high-dosage isoniazid plus streptomycin in the treatment of newly diagnosed tuberculous patients with drug-sensitive cultures. A logical consequence of this finding was an investigation of regimens with a longer interval between successive doses. The present report describes the findings of a controlled study of 3 once-weekly regimens and the twice-weekly regimen. The results confirm that the twice-weekly regimen is highly effective and demonstrate that its efficacy is not influenced by the rate of inactivation of isoniazid or by a reduction (by one-fourth) in the dosage of streptomycin. The results also show that once-weekly chemotherapy from the beginning, whether with high-dosage isoniazid plus streptomycin or high-dosage isoniazid plus streptomycin plus high-dosage pyrazinamide, gives unsatisfactory results. However, when an initial daily phase of 4 weeks with a moderate dosage of isoniazid plus streptomycin preceded the once-weekly phase of high-dosage isoniazid plus streptomycin, the response was highly satisfactory in slow inactivators of isoniazid (as good as with the

twice-weekly regimen) but was considerably less satisfactory in rapid inactivators. These findings suggest that if a method of compensating for the insufficiency of this regimen in rapid inactivators of isoniazid can be found, the prospects for evolving a highly satisfactory once-weekly regimen are bright.

Bull. World Health Org. 1970, 42, 337-351

Attack rate of tuberculosis in a 5-year period among close family contacts of tuberculous patients under domiciliary treatment with isoniazid plus PAS or isoniazid alone

**S. Devadatta, J. J. Y. Dawson, Wallace Fox, B. Janardhanam,
S. Radhakrishna, C. V. Ramakrishnan & S. Velu**

This report from the Tuberculosis Chemotherapy Centre, Madras, considers the risk, over a 5-year period, to close family contacts of sputum-positive patients treated at home for 1 year with a standard regimen of isoniazid plus PAS or one of 3 regimens of isoniazid alone. The attack rate of tuberculosis in the contacts did not appear to be influenced by the treatment received by the patients in the first year or by the duration in the 5-year period for which the patients had (1) positive sputum smears, (2) positive cultures, or (3) isoniazid-resistant cultures. Further, over half the cases of tuberculosis developed in the first year, many of these being in the first 3 months. These findings confirm the conclusions reached from an earlier study, namely, that the major risk to the contacts is from exposure to the infectious patient before diagnosis, and that the risks from the other possible sources of infection (the patient during treatment and the urban environment of Madras) are, in comparison, small.

Bull. World Health Org. 1971, 45, 603-615

Two controlled studies of the efficacy of isoniazid alone in preventing relapse in patients with bacteriologically quiescent pulmonary tuberculosis at the end of one year of chemotherapy

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D. Rajappa, C. V. Ramakrishnan, P. R. Somasundaram, H. Stott,
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An earlier report showed that, in patients with bacteriologically quiescent pulmonary tuberculosis at the end of 1 year of chemotherapy, isoniazid alone in a single daily dose of 150-200 mg, given as maintenance therapy in the second year, did not markedly prevent relapse over a 4-year period of follow-up in patients who had had residual cavitation (the "

open-negative " syndrome) at 1 year, but was highly effective in patients who had no cavitation.

As a result of these findings, two controlled studies, reported here, were undertaken. The first study was undertaken in patients with bacteriologically quiescent disease and residual cavitation at 1 year, and investigated the value of isoniazid in a higher daily dose (400 mg) throughout the second year; this is known to be the optimum therapeutic dose when isoniazid is prescribed alone for 1 year in the initial treatment of the disease. The second study was carried out in patients with bacteriologically quiescent disease and no residual cavitation at 1 year, and sought to determine the value of a shorter duration (6 months) of chemotherapy in the second year with a daily dose of 300 mg of isoniazid. Neither of the two isoniazid regimens was highly satisfactory, although both appeared to have had some effect in preventing relapse during the 4-year period of follow-up.

British Medical Journal, 1973, 2, 7-11

Controlled Comparison of Oral Twice-weekly and Oral Daily Isoniazid plus PAS in Newly Diagnosed Pulmonary Tuberculosis

Tuberculosis Chemotherapy Centre, Madras

A controlled clinical trial was undertaken in 247 patients with newly diagnosed pulmonary tuberculosis to assess the relative efficacies of a fully supervised twice-weekly oral regimen of isoniazid plus PAS (para-aminosalicylic acid) and a standard self-administered daily regimen of the same drugs following an initial intensive phase of two weeks of daily streptomycin, PAS, and isoniazid. Among patients who had isoniazid-sensitive cultures initially and who attended the clinic regularly the numbers with a favourable bacteriological response at the end of the year of chemotherapy were 79 (88%) out of 90 for the twice-weekly regimen and 72 (87%) out of 83 for the daily regimen; the numbers of patients with considerable radiographic improvement were 54 (60%) and 53 (64%) respectively. Complaints of vomiting or diarrhoea that did not require a reduction of the PAS dosage were made on one or two occasions by 23 (21 %) out of 109 twice-weekly and 25 (23%) out of 108 daily patients, and on at least three occasions by 4 (4%) and 12 (11%) respectively. Finally, all five patients who had chemotherapy changed on account of hypersensitivity to PAS had been receiving the daily regimen, as also had one patient who died of agranulocytosis.

Tubercle, 1973, 54, 23-45

A controlled comparison of two fully supervised once-weekly regimens in the treatment of newly diagnosed pulmonary tuberculosis

Tuberculosis Chemotherapy Centre, Madras

Four hundred and fifteen patients with pulmonary tuberculosis were admitted to a controlled study of a year's treatment, on an out-patient basis, with one of the following two fully supervised regimens:

SH/SHOW. Streptomycin 1 g or 0.75 g plus isoniazid 400 mg administered daily for the first four weeks, followed by streptomycin in the same dosage plus isoniazid 13 mg/kg or 17 mg/kg body-weight, administered once a week for the rest of the year. Pyridoxine 6 mg was incorporated in every dose of isoniazid. SPH/SPHOW. Streptomycin, isoniazid and pyridoxine in the same dosages as in the SH/SHOW regimen, plus sodium PAS 6 g throughout the year, all the drugs being administered daily for the first four weeks and once a week for the rest of the year.

The regimen, the streptomycin dosage and the once-weekly isoniazid dosage were allocated at random for each patient. The main analyses in this report concern 359 newly-diagnosed patients (181 SH/SHOW, 178 SPH/SPHOW) with cultures sensitive to isoniazid and streptomycin on admission. About 90 per cent of the patients had cavitated disease and a positive sputum smear on admission, and 40 per cent were rapid inactivators of isoniazid. The condition on admission was similar for the two series.

Two patients (both SH/SHOW) died of tuberculosis and four (all SH/SHOW) had their chemotherapy changed on account of radiographic or clinical deterioration in the presence of a positive sputum. At one year, 85 per cent of the SH/SHOW and 87 per cent of the SPH/SPHOW patients were classified as having a favourable response, mainly on the basis of culture results at 10, 11 and 12 months. Among those who had an unfavourable response, approximately half had responded well initially but had a bacteriological relapse by one year. Considerable or exceptional radiographic improvement was shown by about three-fourths of the patients in each series, and cavitation had disappeared in about half.

Tubercle, 1976, 57, 115-121

Studies of immediate adverse reactions to different doses of a slow-release preparation of isoniazid

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'Double-blind' studies were carried out to assess the incidence of immediate adverse reactions to different doses of a slow-release preparation of isoniazid (matrix isoniazid). Individual doses of 30 mg/kg matrix isoniazid were well-tolerated but higher doses resulted in giddiness, the incidence being dose-related. The giddiness was characterized by a late onset and was usually present even at 24 hours. A few patients complained of gastro-intestinal symptoms. It is concluded that matrix isoniazid can be given to Madras patients in doses of 30-40 mg/kg without risk of an undue incidence of immediate adverse reactions.

Tubercle. 1976, 57, 123-130

Study of adverse reactions to a once-weekly regimen of streptomycin plus a slow-release preparation of isoniazid in high dosage for six months

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**Tuberculosis Chemotherapy Centre (Indian Council of Medical Research),
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A once-weekly regimen of streptomycin (1 g) plus a slow-release preparation of isoniazid (matrix isoniazid) in high dosage, namely 50 mg/kg body-weight for rapid inactivators of isoniazid and 35 mg/kg for slow inactivators, was prescribed for 6 months to 64 tuberculous patients (27 rapid, 37 slow). The regimen was tolerated by most of the patients. However, 4 rapid and 3 slow inactivators had a modification of the regimen, mainly for giddiness. There were no cases of peripheral neuropathy. No adverse effects on haemopoiesis or hepatic or renal functions were observed in any of the patients. It is concluded that it is feasible to administer matrix isoniazid in dosages considerably higher than ordinary isoniazid, in once-weekly chemotherapy.

Address card for obtaining accurate addresses of clinic patients

**K.V. Krishnaswami, M.C. Satagopan, P.R. Somasundaram, S.P. Tripathy,
S. Radhakrishna and Wallace Fox**

In developing countries sufficient attention is not usually paid to recording complete and accurate addresses of clinic patients, since active follow-up is rare. A major problem also in routine tuberculosis treatment is the very high rate of drop-out, much of it in the first three months. When a patient fails to attend a clinic on a due date in India it is the national policy to send a reminder postcard, a measure which can be successful only if the patient's address is recorded accurately. We report on the accuracy of addresses obtained with an "address card," a new approach.

In a tuberculosis clinic in Madras City we compared the accuracy of addresses of 355 patients obtained by (1) a registry clerk at the patient's first attendance; (2) a health visitor, with good knowledge of the area, at the second attendance-in about half the cases she knew whether a letter posted to the address recorded by the clerk had reached the patient; (3) an address card given to the patient at the second attendance to be completed by the postman or any literate neighbour, friend, or relative. This novel approach was employed because about half the patients were known to be illiterate. The address card was collected at the third clinic attendance, usually two or three days later. (If the address on it differed from that obtained by the health visitor earlier she carefully re-interrogated the patient.) The health visitor then visited the homes to verify the accuracy of the addresses obtained. When these were incorrect she tried to locate and record the correct address. The address that was finally confirmed by a home visit was used to assess the relative efficiencies of the three approaches.

Out of the 355 patients included in the study (table) the registry clerk recorded the correct address for only 66 % and a nearly correct address for 10% more, in efficiency of 76 %. The health visitor improved the efficiency to 85% ($P < 0.001$). The address card was returned by 320 (90 %) patients.

Tubercle, 1979, 60, 1-11

An investigation of the accuracy of the home address given by patients in an urban community in South India

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Studies were undertaken in three tuberculosis clinics in Madras, a large Indian city with a good civic organization, to assess the accuracy of address recorded routinely by registry clerks at the patient's first clinic attendance. The accuracy was poor, with 20 % to 30 % of the letters posted not reaching the patients. It was appreciably improved, by 10 % to 20 %, by supplementing the clerk's efforts with questioning by a motivated, experienced health visitor. An address card, a card on which the patient's address was recorded by the local postman or a literate neighbour, relative or friend, was returned by 90 % to 94 % of the patients, and the accuracy of addresses was found to be at least as good as that obtained with the health visitor. Even when all three sources of information were considered, the patient's home could not be traced in 3 % of cases and was found with difficulty in 4 %.

Tubercle 1979, 60, 151-157

**Efficiency of address cards, experienced health visitors and motivated registry clerks
in obtaining the home address of urban patients in South India**

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The address card, a card on which the patient's home address is asked to be recorded by the local postman, or by a knowledgeable and literate neighbour, relative or friend, was investigated for acceptability and efficiency in 4 tuberculosis outpatient clinics, in an urban community with substantial levels of illiteracy in Madras City. In the 4 clinics combined, 96% of the patients who re-attended returned the completed card. Letters posted to the address on the card were received by 85 % of 419 patients, while 5 % were returned by the post office as undelivered and a further 4 % were, in all probability, not delivered; no information was available about the remaining 6 %. A formal comparison in 392 of the above patients demonstrated the address card method to be significantly more efficient than interrogation by experienced health visitors.

A retrospective comparison suggested that the efficiency of experienced health visitors was slightly better than that of highly motivated registry clerks, the proportions of letters received being 72 % and 65 % respectively.

Lancet, 1979, *i*, 1361 - 1363

Sputum-smear-negative pulmonary Tuberculosis :
Controlled trial of 3-month and 2-month regimens of chemotherapy
First Report

Hong Kong Chest Service, Tuberculosis Research Centre, Madras, India,
and British Medical Research Council

Of 1072 Chinese patients with radiographically active pulmonary tuberculosis and no microscopic evidence of acid-fast bacilli in sputum examinations, only 691 (64%) were sputum-culture negative. All patients were randomly allocated to selective chemotherapy (antituberculosis chemotherapy not being started until the activity of the disease had been confirmed), to daily streptomycin, isoniazid, rifampicin, and pyrazinimide for 2 months or 3 months, or to a standard 12-month control regimen. During the subsequent 12 months, 64% of the patients in the selective chemotherapy series started antituberculosis chemotherapy. Both 2-month and 3-month regimens were inadequate for patients whose pretreatment sputum cultures were positive (relapse-rates 14% and 7%, respectively, in

patients with drug-sensitive strains) but in the patients whose first cultures were negative the relapse-rate was only 1% after both short-term regimens.

Tubercle, 1980, 61, 197-206

A study of the accuracy, and factors influencing accuracy, of home addresses of patients obtained by registry clerks and address cards in four large towns in South India

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In 4 large towns in South India with illiteracy levels of 26 % to 40 %, the efficiency of registry clerks in eliciting the home addresses of 1338 out-patients was assessed, by verifying receipt of a letter posted to the patients. The efficiency was found to be very poor, namely 66 %. Moreover, the accuracy of address was substantially poorer for illiterate patients and for patients living for relatively short durations at their present address.

Our innovation, the address card, on which the home address was recorded by a knowledgeable literate person of the patient's choice, was returned by 98% of the patients, and the addresses were found accurate in 84 %; the findings were similar in the 4 towns and were unaffected by any patient characteristic. The substantially better results with the address card were found in both illiterate and literate patients. These findings establish the address card as a simple, inexpensive and efficient device for obtaining accurate addresses.

Am Rev Respir Dis 1981, 124(2), 138-142

A Controlled Trial of 2-Month, 3-Month, and 12-Month Regimens of Chemotherapy for Sputum Smear-Negative Pulmonary Tuberculosis: The Results at 30 Months

**Hong Kong Chest Service/Tuberculosis Research Centre, Madras/
British Medical Research Council**

Of 1,033 Chinese patients with radiologically active pulmonary tuberculosis but with sputum negative for acid-fast bacilli on 5 initial microscopic examinations, 370 (36%) had 1 or more initial sputum cultures that yielded tubercle bacilli. All patients were randomly allocated to (1) selective chemotherapy, anti-tuberculosis chemotherapy not being started until active disease had been confirmed, or to (2) daily streptomycin, isoniazid, rifampin, and pyrazinamide for 2 months or (3) the same 4 drugs daily for 3 months, or to (4) a 12-month control regimen. In patients with 1 or more of their initial sputum cultures positive, the short-course regimens were inadequate, being followed by bacteriologic relapse rates of 15 and 9%, respectively, during 30 months, compared with 0% in the control series. In patients with all their initial cultures negative, the corresponding relapse rates were 4, 2, and 0%, and in the selective chemotherapy series, 53% of the patients had treatment started during the 30 months because active disease was confirmed (bacteriologically in 40%). It is important to continue studying short-course chemotherapy for smear-negative patients because in many countries they represent a high proportion of those treated.

Am Rev Respir Dis 1981; 124: 138-142

Tubercle, 1981, 62, 155-167

A study of the characteristics and course of sputum smear-negative pulmonary tuberculosis

**Hong Kong Chest Service/Tuberculosis Research Centre, Madras/
British Medical Research Council***

A total of 302 Chinese patients were diagnosed on clinical and radiographic grounds by chest physicians from the Hong Kong Chest Service as having radiographically active pulmonary tuberculosis, but had sputum negative for acid-fast bacilli on 5 recent microscopical examinations. They were not given anti-tuberculosis chemotherapy until active disease had been confirmed by positive bacteriological findings, or by radiographic or clinical deterioration during close observation. Of the 283 patients assessed up to 30 months, 200 (71 %) had active disease confirmed and had chemotherapy started during the 30 months. A further 42 (15 %) had evidence of changing lesions on serial chest radiography, and hence of recently active disease.

A number of characteristics of the patients and of their bacteriological and radio-graphic status were tested singly and in combination for association with the presence of active disease confirmed on admission or at any time during the 30 months. Patients with radiographic lesions which were larger and classified as “active” on independent radiological assessment, and with a history of blood-streaked sputum or frank haemoptysis were more likely to have unquestionably active disease on admission or at sometime during the 30 months, than patients without these characteristics.

Tubercle, 1981, 61, 103-112

A randomised study of two policies for managing default in out-patients collecting supplies of drugs for pulmonary tuberculosis in a large city in South India

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A randomized controlled study was undertaken to compare 2 policies of default management in out-patients with smear-negative pulmonary tuberculosis attending a large chest clinic in Madras city. All the patients were due to collect monthly supplies of drugs for a year, for daily self-administration at home. In the routine (R) policy, if a patient failed to collect the drug supply on a due date, a reminder letter was posted on the fourth day and, if necessary, a health visitor visited the home a week later. In the intensive (I) policy, a health visitor visited the home on the 4th day and, if necessary, a week later and at 1 and at 2 months.

The main analyses concern 150 patients (75 R, 75 I), of whom 16 R and 15 I patients had a positive culture. A total of 29 patients (11 R, 18 I) did not default at any time. For the remaining 64 R and 57 I patients, the mean numbers of defaults were 3.0 and 2.3, and the mean numbers of defaulter retrieval actions were 4.3 and 3.8, respectively. The home visit as the first action (I series) was successful in retrieving defaulters on 65 % of 132 occasions, while the reminder letter (R series) was successful in 56 % of 193 occasions (P=0.1). Following the second action, which was a home visit in both the series, these

proportions became 80 % and 84 %, respectively. In the I series, 22 third and 18 fourth actions were taken, but the patient was retrieved in only 4 and 0 instances respectively.

The mean number of drug collections during the year was significantly higher in the I series (9.8) than in the R series (8.6). Finally, the proportions of patients who made 12 collections in a 15-month period, a satisfactory target under Indian Programme conditions, were 69 % and 52 %, respectively (P=0.07).

Lancet, 1982, 2 (8296), 483 – 486

**STUDY OF A POLICY TO MINIMISE THE
PRESCRIPTION OF MEDICAMENTS AT FIRST
ATTENDANCE AT CHEST CLINICS**

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Summary In chest clinics in Madras, south India, medicaments are prescribed to many patients at the first clinic attendance, whether necessary on medical grounds or not, in the belief that this practice will increase the likelihood of the patients subsequently reattending the clinic. This study of 2608 patients in four chest clinics showed that the proportion prescribed medicaments ranged from 50% to 75%. Subsequently, a modified policy of prescribing medicaments only when they were medically essential was investigated in 956 patients in the largest of these clinics. The policy was found to be practicable, and it did not have any adverse consequences such as an increased rate of default or an unacceptable level of patient dissatisfaction. The advantages of the new policy are savings in money, man-power, and time and the potential for a reduction in the incidence of side-effects.

Ind. J. Tub., 1983, 30 – 39

Tubercle 1984, 65, 41-45

A novel system to obtain addresses of out-patients-assessment in routine clinic practice in Madras

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A novel method of obtaining accurate home addresses from out-patients was introduced as a routine procedure in 6 chest clinics of Madras City, following highly satisfactory results under study conditions. In this method, the patient is given a card (the Address card), and asked to get his exact address entered on it by any knowledgeable person of his choice such as the landlord or a literate neighbour. An assessment of the system was undertaken after it had been in operation for about 8 months. A complete and legible address was available for 82 % of 3956 patients, the range in the 6 clinics being 74% to 91%. The main causes for failure were: not giving Address card to patient (7 %), patient not re-attending the clinic (6%), and patient re-attending but not returning the Address card (3 %). Corrective measures have now been introduced, and a re-assessment will be undertaken in due course.

Tubercle, 1983, 64, 73-91

Study of chemotherapy regimens of 5 and 7 months' duration and the role of Corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India

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A controlled clinical trial of 3 short-course chemotherapy regimens was undertaken in patients with bacteriologically positive, newly diagnosed pulmonary tuberculosis. The patients were allocated at random to receive one of 3 regimens: rifampicin, streptomycin, isoniazid and pyrazinamide daily for 2 months, followed by streptomycin, isoniazid and pyrazinamide twice weekly for 3 months (R/5) or for 5 months (R/7), and the same regimen as R/7 but without rifampicin (Z/7). Further, half the patients in each series, selected at random, were prescribed daily prednisolone for the first 8 weeks. Of the 509 patients admitted to this phase of the trial, 390 had pre-treatment sputum cultures sensitive to isoniazid and streptomycin. At 2 months, in 92 % of R/5 and R/7 patients (combined) and in 72% of Z/7 patients all cultures were negative. After follow up for 24 months from the time of admission a bacteriological relapse requiring retreatment was observed in 5.4

% of R/5, 0.0 % of R/7 and 3.9 % of Z/7 patients. The differences between R/7 and each of the other 2 series were significant ($P \leq 0.03$).

Am Rev Respir Dis 1984, 130, 23–28

A Controlled Trial of 2-Month, 3-Month, and 12-Month Regimens of Chemotherapy for Sputum-Smear-Negative Pulmonary Tuberculosis Results at 60 Months

**Hong Kong Chest service/Tuberculosis Research Centre, Madras/
British Medical Research Council**

Of 1,019 Chinese patients with radiologically active pulmonary tuberculosis but with sputum negative for acid-fast bacilli on 5 initial microscopic examinations who were studied for 5 yr, 364 (36%) had 1 or more initial sputum cultures positive for *Mycobacterium tuberculosis*. All 1,019 patients were randomly allocated to (1) selective chemotherapy (anti-tuberculosis chemotherapy not being started until the disease had been confirmed to be active); or to (2) daily streptomycin, Isoniazid, rifampin, and pyrazinamide for 2 months; or (3) for 3 months; or to (4) a standard 12-month control regimen. In the 364 patients with 1 or more of their initial sputum cultures positive, the short-course regimens were inadequate, being followed by relapse rates of 32 and 13%, respectively, during 60 months, compared with 5% in the control series. In the 655 patients with all their initial cultures negative, the corresponding relapse rates were 11, 7, and 2%. In the selective chemotherapy series, 57% of the patients had treatment started during the 60 months because their disease was confirmed to be active.

Am Rev Respir Dis 1986, 134, 27-33

A Controlled Clinical Trial of 3- and 5-Month Regimens in the Treatment of Sputum-Positive Pulmonary Tuberculosis in South India

**Tuberculosis Research Centre, Madras and National Tuberculosis Institute,
Bangalore**

A controlled comparison of 3 short-course regimens was undertaken in patients with newly diagnosed, sputum-positive, pulmonary tuberculosis in South India. The regimens were: (1) R3: rifampin plus streptomycin plus isoniazid plus pyrazinamide daily for 3 months; (2) R5: the same as regimen R3 followed by streptomycin plus isoniazid plus pyrazinamide twice weekly for 2 months; (3) Z5: the same as regimen R5 but without rifampin. The distributions of various pretreatment characteristics were similar in the 3 series. At the end of treatment, 6 patients (3 R3, 3 Z5) of 694 (228 R3, 230 R5, 236 Z5) with drug-sensitive organisms initially were classified as having an unfavourable response. By 24 months (21 months of follow-up for the R3 regimen and 19 months for the R5 and Z5 regimens), a bacteriologic relapse requiring treatment occurred in 20% of 200 R3, 4%

of 187 R5, and 13% of 199 Z5 patients, the difference between the R3 and R5 series being highly significant ($p = 0.00001$). Considering patients with cultures initially resistant to isoniazid, 4 of 57 in the R3 and R5 series combined had an unfavorable response to treatment compared with 13 of 26 in the Z5 series ($p < 0.0001$). Of the 4 patients with an unfavorable response in the R3 and R5 series combined, resistance to rifampin emerged in 2. Complaints of arthralgia were made by 45% of the R3 and R5 patients combined and 70% of the Z5 patients ($p < 0.00001$). However, chemotherapy was modified in only 5 and 12%, respectively. Jaundice occurred in 7% of the R3 and R5 patients and 1% of the Z5 patients ($p < 0.00001$).

