2019 is a special year. It commemorates the journey of Stanley Browne Lab (SBL) through the past 25 years. SBL celebrated this significant event by organizing a symposium. Eminent leprologists gathered together to deliberate on the current leprosy scenario in the post elimination era and to discuss the way forward. Research in leprosy has been slow, deterred by lack of funding. Transmission studies are funded and everyone is suddenly discussing ways and means to stop transmission. I guess, this is pertinent when our goal and ambition is zero leprosy. However, somewhere along the way, the leprosy fraternity seems to have forgotten that people affected by leprosy are living with disability and that research is needed to alleviate the pains associated with it. We are concerned with zero grade 2 disability, but not worried about the another 30% who develop impairment along the course of their treatment and beyond. Many a time, they go undetected and untreated till irreversible deformity happens. The national program does not have provision to detect such impairments after MDT. Its our prerogative to undertake issues related to disability and make lives easier for those living with disability.

We have come a long way and still have miles to go…. let us run our race well.

Joydeepa Darlong

Will Prophylactic Single Dose Rifampicin (SDR) fulfill its preventive potential in contacts Of Leprosy Patients? Perspectives from the Phenomenon Of Bacterial Persistence

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There has been intense debate with regard to a recent policy decision to use Single Dose Rifampicin (SDR) among contacts of leprosy as chemoprophylaxis (1). The SDR is promoted because it is considered to be an easier and convenient intervention. The main study reporting the efficacy of SDR was the double blind, cluster randomised, placebo-controlled trial conducted in Bangladesh by Moit et al (2). In this six year follow-up study it was concluded that SDR gives 57%, protection against development of all types leprosy for a period of 2 years. Some of the notable findings were that household contacts who took SDR did not have significant protection, it only protected second level neighbors. SDR did not protect against development of MB leprosy suggesting that SDR is only effective when patients have a low mycobacterial load. With respect to cost-effectiveness; to prevent the occurrence of one case of leprosy, 1556 persons have to be treated. Citing the findings from nude mouse model it was further opined by Lockwood et al (3) that multiple doses of Rifampicin might be required for effective prophylaxis, moreover it cannot be assumed that the index case is the only source of infection.

We wish to draw attention to the well-established phenomenon of dormant (living but non-dividing) Mycobacteria in lesions prior to antibacterial treatment and even at the subclinical stage (4). We opine that SDR in contacts of leprosy, may at best result in postponement of clinical disease as SDR will not have any effect on the dormant bacilli.

Some facts about ‘dormant’ also termed ‘persister’ bacilli:
Persisters cannot be identified in a bacterial population by presently available techniques but their presence may be inferred. The term persister was first coined by Bigger in 1944 (5). It was shown that the persister state could be induced in normal staphylococci by changing the environment e.g. by cooling. Subsequently various factors which could influence the survival of organisms in the host were hypothesized and tested. The evidence from in vitro and in vivo studies suggested that factors that are unfavorable for bacterial multiplication and growth trigger the conversion of the organism to dormant forms. Such factors could be ageing, crowded populations, populations inside old necrotic lesions, poorly vascularized sites with low pO2 and intracellular locations within macrophages where pH is acidic. Persistence may thus be an adaptation to an adverse environment. Theoretically therefore the bacterial cells have the potential to resume normal multiplication when favorable conditions return. Since the bacillary metabolism is altered during the state of persistence, the usually effective drugs fail to act on such cells.
In TB the outcome of exposure to infection and progression of the disease is well documented and serves as an illustrative point (6,7). Following close contact 30% of individuals become infected, of whom 40% develop primary active TB and 60% latent infection. Of this 60%, 2.23% may show disease symptoms in one’s life time with intact immune-competence. However with states of immuno-compromise, the rate of disease may be as high as 5% to 10%. Persistence is detected even at a post treatment stage though over all figures to describe its extent are not available. A similar phenomena may occur in leprosy.

Persisters are a heterogeneous population:
Induction by environment: A model of ‘persisters’ was created for M. tuberculosis using anaerobic culture conditions. As opposed to exponentially growing cultures, the non-replicating forms (NRFs) showed resistance to ciprofloxacin and sensitivity to metronidazole. The NRFs therefore displayed differential DNA coiling and accumulation of activated metronidazole. Whether this is a phenotypic adaptation or not is not known but it is possible that actively growing tubercle bacilli adapt to the administration of antimicrobial drugs by moving into a persistent state associated with increased antibiotic resistance (7). Therefore it is envisaged that the drugs developed for use in multi-drug resistant disease should be designed also with a focus on targets of non-replicating mycobacteria.

Induction by chemotherapy: Another form of dormancy is that which occurs during chemotherapy of clinically overt disease. Whether these persisters are identical in nature to those present in the latent phase between primary and post primary disease is not at all clear. Persister models created with INH and pyrazinamide may not be relevant to all forms of dormancy. For example, bacilli persisting during chemotherapy are not killed by INH, whereas those targeted for chemoprophylaxis seemingly are. The differential action of the drugs could be due to the differing immune status of the patient before symptomatic disease and nearing completion of treatment (COPT) and in that case the use of immunomodulators or use of Vaccine candidates would be most efficacious in the COPT phase.

Persisters bacilli have the potential to become genetically resistant
Finding from recent studies suggest that persister’s behave as an evolutionary reservoir from which drug resistant forms can emerge. For example continuous exposure of M. tuberculosis to a lethal dose of rifampicin or moxifloxacin led to the development of persisters (8). Extensive accumulation of hydroxyl ions led to gene mutation, in rpoB, the target of rifampicin, or via the SOS pathway which is involved in the response to DNA damage (9, 10).

Persistence of M. leprae following chemotherapy:
In leprosy persistence of M leprae following chemotherapy is well established. Using the mouse footpad method presence of persister M. leprae was recorded in 9 to 10% of multidrug treated (MDT) multibacillary (MB) cases in two of the major THELEP studies in Chingulput and Bamako (11). These findings were very similar to that observed with DDS Monotherapy (12). It was also noted that the MDT regimen and duration of treatment used made no difference on the incidence of persisters. Further studies showed that persisters probably are the main cause of relapse and treatment failure in leprosy (13,14).

Relevance of bacterial persistence in the usage of SDR among contacts of leprosy
Let us ponder the phenomenon of bacterial persistence in the context of prophylactic SDR among contacts of leprosy to combat subclinical infection and thereby halt disease transmission. Rifampicin, a highly bactericidal drug with a half-life of —3 hrs, acts only on actively dividing bacteria (15).

The mycobacterial species of tuberculosis and leprae have a much slower growth rate (24hrs; and 14 days respectively) than the free-living Mycobacterium smegmatis (3hrs) suggesting that slow growth is not a phylogenetic constraint on all mycobacterial species, but is associated with persistent infection which is a major impediment to control efforts by drugs and vaccines. The sigma factor gene (sigF) responsible for sporulation of Bacillus subtilis, detected almost exclusively in the slow-growing mycobacteria species is a good example of this genetic selectivity. The gene is absent in M. smegmatis, M. cheloni and M. fortuitum but is present in M. leprae, M. kansassi and M. bovis. The transcription of this gene is virtually undetectable in the exponential phase of growth but is induced in the stationary phase and with cold shock and exposure to reactive oxygen intermediates (9,16). A detailed review of clinical studies and observations of the chemotherapy of syphilis, malaria, scrub typhus, tuberculosis and Q-fever show that, when effective chemotherapy was begun shortly after sub-clinical infection, the result was often only the postponement of the onset of clinical disease. However, the same treatment was highly effective when it was begun after illness was manifested clinically or shortly before the manifestations of the illness were expected to appear. It was inferred therefore microbial persistence might occur before antimicrobial therapy has been administered (6). If we envisage a similar scenario in leprosy, usage of SDR in contacts of leprosy at the best, may result in postponement of the onset of clinical disease. In the long run, a worse scenario would be the promotion of microbial resistance (17). This is refuted however by proponents of chemoprophylaxis in TB. The logic might be: if bacteria are in a state of persistence, these drugs designed to act on multiplying bacilli would not have any action on the persisters. If there is no action on the bacteria, then the chances of developing resistance to the drug appear remote.

To conclude we need to remind ourselves that, a disease such as leprosy in slow motion and Mycobacterium leprae is a hard nut to crack. Every known scientific fact that may impact outcomes in the long run needs careful consideration before making policy decisions.

Acknowledgements: Our sincere thanks to Dr Kalpana and Anju Wakade for their help in the preparation of the manuscript.
National Leprosy Eradication Programme (NLEP), India achieved the elimination of leprosy as a public health problem, defined as less than 1 case per 10,000 population, at the National level in 2005. However, through situational analysis of health indicators of NLEP conducted in September, 2015, it was observed that trend of two important indicators of Program i.e. Annual New Case Detection Rate (ANCDR) and Prevalence Rate (PR) are almost static since 2005 – 2006 and Grade II disability (G2D) has increased from 3015 (1.87%) in 2005-06 to 5852 (4.60%) in 2015-16 leading to occurrence of many thousands of G2D due to leprosy which could have been prevented.

In view of the above, Central Leprosy Division (CLD) along with the strengthening of routine activities, has brought following initiatives in the programme during the last three and half years:

1. Leprosy Case Detection Campaign (LCDC)
2. Focused Leprosy Campaign (FLC)
3. Special Plan for Hard To Reach Areas (HTRA)
4. Post Exposure Chemo-prophylaxis (PEP)
5. Sparsh Leprosy Awareness campaign (SLAC)
6. Grade 2 Disability Investigations (G2D Inv)
7. ASHA Based Surveillance for Leprosy Suspects (ABSULS)
8. Nikusthweb based reporting system
9. Mathematical Modeling
10. Antimicrobial Resistance Surveillance system
11. National Trainings
12. Operational Research Projects: Immuno-prophylaxis (MIP Vaccine) and Extended PEP (PEP++)

As an outcome, >80,000 hidden/ early leprosy cases detected in high endemic districts through 14 days house to house search during each Leprosy Case Detection Campaign (LCDC), 2016, 2017 & 2018. It further leads to reduction of percentage of G2D due to leprosy from 4.60% (2015-16) to 3.61% (2017-18) leading to prevention of high number of disability due to leprosy.

Around 3.5 lakh (60%) & 4.5 lakh (75%) villages observed the village level meetings in Gram Sabhas on the Anti-Leprosy Day, 2017 & 2018 respectively under Sparsh Leprosy Awareness Campaigns (SLAC), wherein messages on theme of early case detection and stop discrimination against leprosy were spread.

Routine case detection is strengthened with introduction of ASHA Based Surveillance for Leprosy Suspects (ABSULS) in community.

It is perfect to be mentioned here that we are moving in right direction to achieve the target of < 1 case of G2D/ million population among new leprosy cases, given by World Health Organisation (WHO), to be achieved by 2020. More efforts and resources are required during last few miles before achieving “Leprosy Free” status.
Reaching the landmark of 25 years of eventful journey has not only been important for those working with or at Stanley Browne Laboratory (SBL-TLM) but also for leprosy research in India and also globally. Its contributions in these 25 years are highly significant and are well recognized by one and all. Research carried out by SBL has covered aspects ranging from fundamental to applied areas. It is significant to note that this laboratory continued to embark on path of growth and productivity even during the period when the fatigue and false euphoria of having conquered leprosy was visible everywhere.

While several international and national agencies like Indian Council of Medical Research (ICMR) showed commitment and priority for leprosy research during those years, the main problem was of human resource and institutional support to leprosy research focused on patient care and public health aspects. SBL provided that valuable resource which planned relevant studies, competed for funds and implemented such research projects. Current scenario shows intense efforts by NLEP Government of India and quite a few non-governmental agencies to break the chain of persistence of leprosy endemicity at low level for more than a decade. Deterioration was also apparent by problems of child cases and rise of disabilities (which has been reversed to some extent by the efforts of NLEP and its partners), mainly due to delayed diagnosis due to various reasons.

Today, our programme needs lot of inputs pertaining to improving the diagnosis and treatment of disease as well as its complications. There are also challenges and opportunities to contribute to better understanding of transmission of disease in different settings. These transmission dynamics need to be investigated in the light of various intense public health efforts which involve leprosy detection campaigns and treatment, diagnosis of atypical cases being missed by current strategy, effects of chemoprophylaxis, immunophylaxis or both. Reasons for re-emergence of drug resistance in certain areas/patients should be properly investigated by in depth studies so that this does not pose a threat to public health programme at a later stage.

Of course basic studies aimed at understanding the structure and function of genome of leprosy bacillus, host parasite relationship etc should continue to receive the attention of scientists of SBL, TLM and other partners. It will also be important to maintain focus on social and other issues, techniques and approaches relevant to lives of people afflicted with leprosy specially after the medical and surgical treatment. While SBL will have limitation of human resource and also funds required to investigate all these aspects of Indian and global importance, it may be advisable to develop partnerships within and outside the SBL-TLM system for making better impact in the immediate as well as distant future.
Published papers (May - Aug. 2019)

1. Social participation of persons affected by leprosy in an endemic district, West Bengal, India. 
   Pitchaimani Govindharaj, Sampathkumar Srinivasan & Joydeepa Darlong 

2. Accessibility of social entitlements by leprosy affected living in different localities: Leprosy Colonies and the general community in 4 states of India. 
   Mathanraj David Monickaraj & Solomon Raju Moturu 

   Pitchaimani Govindharaj & Annammma S. John 

4. Resistance as a cause for chronic steroid dependent ENL - a novel paradigm with potential implications in management. 
   Pooja Arora, Kabir Sardana, Aastha Agarwal & Mallika Lavanja 
   Lepr Rev (2019) 90, 201–205

5. Utility of multiplex PCR for early diagnosis and household contact surveillance for leprosy. 
   Pathak VK, Singh I, Turankar RP, Lavenia M, Ahuja M, Singh V, Sengupta U. 
   doi:10.1016/j.diagmicrobio.2019.06.007


7. Association of non-tuberculous mycobacteria with Mycobacterium leprae in environment of leprosy endemic regions in India. 
   Turankar RP, Singh V, Gupta H, Pathak VK, Ahuja M, Singh I, Lavenia M, Dinda AK, Sengupta U. 

8. Survival of Mycobacterium leprae and association with Acanthamoeba from environmental samples in the inhabitant areas of active leprosy cases: A cross sectional study from endemic pockets of Purulia, West Bengal. 
   Turankar RP, Lavenia M, Darlong J, Siva Sai KSR, Sengupta U, Jadhav RS. 

The midterm Indian Association of Leprologists (IAL) Symposium was held on 17th & 18th August 2019 on the theme ‘Leprosy Scenario post elimination and the way forward’. TLM staff presented oral papers and panel discussions on Transmission, Reactions and Resistance.