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Editorial

Qua vadis leprosy?

We have come a long way in our fight against leprosy. The skeletal evidence of leprosy from 2000 B.C. in Rajasthan, India, predates similar evidence from the other parts of the world[1]. From these ancient times to the beginning of 2023, the fight against leprosy has been hard and relentless, the pace accelerating rapidly at the turn of the 21st century. However, India still holds the undesirable distinction of being the leading nation harbouring human leprosy[2]. Reflections on the future of leprosy must hence consider the enormous work done in the past, often unrecognized through scientific publications. It would be impossible to generate a comprehensive list of all those who served in the field of leprosy, but it will not be amiss to cite a few – Mohandas Karamchand Gandhi, Manohar Dewan, Baba Raghav Das, Abdul Kalam, Robert Cochrane, Dharmendra, H. Srinivasan and Charles K. Job. Although there is a worldwide decline in the various statistics of leprosy, increasing new cases, childhood cases and grade 2 deformity (G2D) in 2021 compared to 2020, in the time of the COVID-19 pandemic when much of leprosy surveillance was reduced, is a cause for concern[2]. In India, new cases of leprosy increased from 65,147 in 2020 to 75,394 in 2021 and G2D increased from 1572 to 1863[2]. In southeast Asia, new child cases were 5664 in 2020 as compared to 5380 in 2021[2].

Leprosy misdiagnosis

All aspects of leprosy, including epidemiological data, depend on the accurate diagnosis of the disease. Leprosy symptoms are often ambiguous, and apart from diseases that closely mimic leprosy, replacing the Ridley-Jopling classification with the WHO Paucibacillary (PB) - Multibacillary (MB) classification, necessary for employing large-scale treatment with multidrug therapy (MDT), has resulted in the unintended consequence of an increase in misdiagnosis[3]. In Brazil, among 574,181 new leprosy cases, 7477 (1.3%) were misdiagnosed, more common among females, children, PB and indeterminate forms, and in neural leprosy without skin lesions[4]. The consequences of misdiagnosis are serious and can impact treatment, physical and mental circumstances and ruin the economic productivity of individuals and families.

Therefore, finding solutions to reduce the level of misdiagnosis should be a top priority. To end this, experienced leprologists should be retained in tertiary institutions where laboratory facilities exist to evaluate uncertain cases. Their comprehensive knowledge in diagnosing and treating leprosy should be passed on to the next generation. Educational material should be freely and easily accessible. Translating these into local languages is important. Furthermore, adding interactive blogs that relate to these leprosy digital textbooks will be helpful.

Tele-leprology

The doctrine of early diagnosis, effective treatment and monitoring has not changed over the years and rapidly evolving technologies hold possibilities of preventing damage from the disease. Over the past several decades, telemedicine has gained popularity in several disciplines and the COVID-19 pandemic has solidified its use further[5]. With widespread internet coverage and smartphones, tele-dermatology is an effective tool even in remote rural areas with inadequate health care. Establishing remote reading centres for diagnosing and monitoring leprosy should be a top priority. These centres could be a part of tertiary leprosy hospitals staffed with experienced leprologists or act as conduits between the field and the leprologists wherever and whenever available. Ideally, image evaluation would require stations with similar computers and calibrated monitors under regulated ambient lighting. A crucial aspect of this system is training workers to take good, gradable images of leprosy lesions. An imaging protocol

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giving guidelines for standardizing the imaging (magnification, distance from the smartphone and lighting parameters (natural daylight outside the dwellings) should be made available to all workers. Training should include methods of safely and securely transferring uniquely labelled images and patient data to the central reading centre. Certifying the imagers by requesting sample images and giving feedback on the quality of images would make the system more robust. These images would be a permanent record over time and can be evaluated retrospectively as well as be a repository amenable to artificial intelligence investigations[6,7].

Biomarkers for early diagnosis

Predicting the development of the disease or its reactions can mitigate its subsequent deleterious consequences. Some intriguing reports on biomarkers have been published recently including. One on the transcriptional risk signature for predicting the development of leprosy using blood 4-61 months before the actual clinical diagnosis[8]. Other biomarkers for detecting leprosy include the repetitive element RLEP which is a highly specific target for detecting *Mycobacterium leprae*, a recombinant multi-epitope antigen and a multiplex real-time quantitative PCR assay[9,10]. A five gene signature has been reported to predict type 1 reactions at least two weeks before the actual onset of the disease/symptoms[11]. Anti-LID-1 serology at diagnosis has been shown to have prognostic value for type 2 reaction in *M. leprae* positive patients[12]. In the future, more biomarkers may be discovered and once these undergo further evaluations for repeatability and economic feasibility, these will become ready for transfer from laboratory to field.

Newer drugs for treating leprosy and its reactions

Treatment efficacy and safety of newer drugs to treat the disease, newer combinations of drugs and the myriad periods of interventions that have reported the need for careful investigations for validity and repeatability. The specter of dangerous amounts of drug resistance to *M. leprae* is of concern and there is a constant need for innovative drugs and drug combinations to successfully kill the bacilli. Newer anti-inflammatory drugs used in other diseases may hence be explored particularly for recalcitrant type 1 and type 2 reactions. Some drugs, such as cyclosporin A, infliximab and methotrexate, have been used in controlling reactions in leprosy, but their efficacy needs to be replicated in larger studies.

Lessons to be learnt from other diseases that have signs in common with leprosy

The hallmark of leprosy is a decrease or abolition of tactile sensation. Various other conditions cause hypoesthesia, but two important ones, diabetes mellitus, which is a metabolic disease and HIV, which is a viral disease, have both undergone extensive research to prevent hypoesthesia, identify early peripheral nerve dysfunction and regenerate peripheral nerves to restore sensation. Great strides have been made in imaging techniques of peripheral nerves, bioengineering of neural tissue and in deciphering the mechanisms involved in the regeneration of peripheral nerves. Limb prosthesis with robust functions like never before is now becoming available, but few have been used and tested in deformed leprosy patients[13]. Shoes that are prescribed for patients with diabetic neuropathy are highly functional, more effective in preventing ulcers and aesthetically pleasing compared to the footwear offered to leprosy patients.

In the current age of intensive national and global travel, it is important to study the risk and course of MB leprosy with co-existing morbidities such as HIV, tuberculosis, COVID-19 and monkeypox. Both HIV and tuberculosis as co-morbidities with leprosy are of concern because of the resistance the virus and bacteria are acquiring. Surveillance would play a critical role in this context.

Specialized areas that require training

While physicians, physio and occupational therapists receive reasonable training in leprosy, it is generally not the case with paediatrics, nursing, dentistry and nutrition. Childhood leprosy, besides being a marker for recent transmission, warrants accurate, early diagnosis by paediatricians who are generally poorly trained in leprosy[14]. When leprosy patients are admitted to a hospital, nursing becomes the focal point of caregiving. Publications related to leprosy nursing are scarce. Gingival recession, tooth loss, chronic pulpitis, periodontitis and dental caries, fissuring and atrophic glossitis, fibrosis and loss of uvula are commonly seen in patients belonging to the pre-MDT era and a substantial number of them have limb deformities[15,16]. Can leprosy patients with deformed hands maintain oral hygiene? This is an area lacking important information. Malnutrition is common in children of leprosy contacts as well as adults with leprosy, but only a few studies focus on nutrition in leprosy patients in the post-MDT era[17]. Modifying

curriculum in dentistry, paediatrics and nursing must hence be undertaken to remedy these shortcomings. Nurses trained in specialized care of patients with deformity and acute reactions will be better prepared to learn on the job in caring for leprosy patients.

Zero leprosy

M. leprae has been detected in a wide variety of wild animals. Leprosy-like lesions have been reported in wild chimpanzees and sooty mangabey monkeys (Cercocebus atys)[18,19]. Armadillos infected with *M. leprae* are found in the southern United States and in South American countries and play a small role as reservoirs for the transmission of leprosy to humans[20]. As long as, this type of transmission exists, a world with zero leprosy is unlikely.

However, infection of *M. leprae* in laboratory animals has opened up opportunities for in-depth investigations on the bacilli. *M. leprae*-infected armadillos have become extremely useful in leprosy neuropathy research, providing insights into the reprogramming and fate of Schwann cells when denervation occurs, thereby granting opportunities to discover novel therapeutic targets for delaying or preventing nerve destruction[21,22].

Leprosy stigma

Leprosy stigma remains a problem in several parts of India. There have been plenty of reports on stigma and ways to measure it, but reports on successful outcomes are few[23]. Future focus should be on investigating and promoting factors that have proved useful in bringing down the level of stigma. Poverty, illiteracy, ageing and visible deformities enhance stigma[24]. Integrating leprosy into the general healthcare system appears to have brought down the level of stigma[25]. Integration appears to have worked more successfully in a relatively poor and illiterate state than in an affluent and literate state[26]. Stigma reduction that is a byproduct in specialized hospitals of excellence where service is sought by wealthier populations and where discounted care is provided to leprosy patients needs reporting.

Leprosy prophylaxis

The WHO advocates administering a single dose of rifampicin to reduce the risk of leprosy, in contacts of leprosy patients, after excluding leprosy and tuberculosis in them[27]. It is an attractive concept, especially when the risk of inducing resistance in *Mycobacterium tuberculosis* is small[28]. Reports on long-term microbiological consequences of a single-dose antibiotic are scarce. A short-term study on the effects of a single-dose antibiotic prophylaxis on normal oral microflora reported that it can induce selection of resistant strains[29]. In the recent past, antimicrobial resistance to leprosy and tuberculosis has been growing[30-32]. It is critical to continue to evaluate the long-term beneficial effect of this chemoprophylaxis against the risk of microbiological consequences. However, it may not be wise to extend this chemoprophylaxis to other populations where comorbidity with tuberculosis and HIV is substantial.

***M. leprae*, armadillos and liver regeneration**

M. leprae has some amazing properties – it is the only bacillus that selectively invades human peripheral nervous tissue, it has an extraordinarily lengthy doubling time, a long incubation period and it defies culture in a laboratory medium. It has added one more surprising property in conjunction with 9-banded armadillos. It regenerates liver tissue. *M. leprae* induces hepatocyte proliferation and a proportionate increase of vasculature, and the biliary system. It does so without accompanying fibrosis or tumorigenesis. This hepatogenesis, if it can be replicated in human beings, holds promise for patients with liver destruction awaiting organ transplants, conditions such as cirrhosis[33].

Conclusions

An excerpt from Dr. Abdul Kalam, a wise ex-President of India, addressing a national conference on the elimination of leprosy gives the ultimate solution in eliminating leprosy – 'Real cure for the elimination of leprosy lies in the development of the region, that means developing the district, and the State. The development approach would provide for the people better amenities, clean drinking water, better hygiene and sanitation, better education and awareness, better healthcare and nutritious food resulting in a livable environment. This holistic approach is the vital need for eliminating leprosy in endemic regions'[34]. The proof that this has worked can be found in the developed nations of the world. The current Prime Minister of India envisions that India would become a developed nation in 25 years and once that vision is realized, the end to leprosy in India would become a reality.

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