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Review Article

A Pre-history of the Morphological Index

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The article deals with an over-looked period in the modern history of leprosy, namely the first decades of the 20th Century. The introduction of soluble derivatives of traditional chaulmoogra and hydnocarpus oils for parenteral treatment was received with optimism by physicians working independently in American Hawaii and by Leonard Rogers in colonial India. They reported similar after-treatment clinical and bacteriological phenomena, but stopped short of meaningful investigation of the latter. The pioneering studies of Froilano de Melo in Portuguese Goa on quantification and interpretation of changes in bacterial morphology in stained slides are described, as also the conflict with Rogers's ideas. de Melo's three-fold 'HMG" morphological classification presaged Ridley's 'SFG' Index of five decades later. That ambiguities regarding bacterial viability based solely on morphology in stained smears, which were pointed out by de Melo, were later confirmed in the mouse foot-pad model.

Key words : Chaulmoograte Parenteral Therapeutics 1910-1925; American results in Hawaii; Leonard Rogers in Bengal; Bacillary Morphology; Classification of Froilano de Melo in Goa; Interpretation; Ridley 'SFG' Index; Ambiguities Mouse Foot-pad Inoculation.

Introduction

An "Interpretive Chronology of Leprosy Concept and Practice" appeared in 1973 in the late, lamented International Journal of Leprosy at the time edited by Skinsness (1973). It presented a hundred-year flow of scientific observation and interpretation, from Hansen's discovery of the bacillus in 1873, to 1973 when T and B lymphocytes were found to be differently implicated in lepromatous leprosy.

The instructive "Chronology" had an unfortunate lacuna – there was no mention of the heyday (*circa* 1910-1925) of the injectable derivatives of chaulmoogra and hydnocarpus oils as leprosy therapies. The plant oils had been used orally and externally since pre-historic times in India and adjacent countries. Their reputation for efficacy survived the centuries, despite the severe nausea and vomiting induced by oral administration.

The present article presents an overview of the period 1910-1925 in the history of leprosy, and draws attention to a now forgotten, yet prescient laboratory technique introduced at the time for assessing the effect of the oil-based treatments.

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Overview

Physicians and organic chemists of two early 20th Century colonial powers, the United States of America and Britain, followed dissimilar yet parallel paths and successfully developed injectable soluble chaulmoogra oil derivatives which were then deployed for leprosy treatment in their respective spheres of influence. The compounds used in the U.S. territory of Hawaii, and later in the Philippines and in Latin America were ethyl esters of the fatty acids of chaulmoogra oil, namely ethyl chaulmoograte (McDonald 1920, Dean & Wrenshall 1922). In British India, Sir Leonard Rogers (1868-1062) pathologist at the Medical College and Hospital, Calcutta (Kolkata), energetically promoted parenteral administration of the sodium salts of the oil, namely sodium chaulmoograte and sodium hydnocarpate (Rogers 1916, 1917, 1920). By 1924, culminating in the founding of the British Empire Leprosy Relief Association, Rogers had single-mindedly and almost single-handedly succeeded in 'sodium-chaulmoograting' leprosy treatment in British colonies (BELRA 1924).

Results of Treatments

Despite the difference in the composition of the derivatives, the respective investigators working in Bengal and Hawaii encountered two similar treatment-related phenomena, and expressed similar views on the significance.

(a) **"Reaction" :** *Acute febrile constitutional symptoms of varying severity, accompanied by increased erythema and oedema of infiltrated skin.*

Rogers reported that after subsidence of the reaction "... the diseased tissues were decidedly softer and less indurate than before, while nodules on the face, not showing the local reaction, were also diminished in size" (Rogers 1916, 1917, 1920).

McDonald and co-workers in Hawaii "...[Had] learned by experience that the patient not only sooner or later recovers from his acute illness, but shows a remarkably improved condition and a far more active progress toward recovery than before" (McDonald 1920). In other words, both groups of investigators regarded "leprosy fever" resulting from chaulmoograte treatment as a precursor of improvement.

(b) Alterations in Bacillary Morphology during Reaction

In the stained slide of the serous discharge from a post-treatment lesion in reaction, Rogers found "innumerable minute red dots in rows and clumps" which greatly outnumbered the "few typical rod-shaped bacilli". He regarded this as a specific bactericidal action of sodium chaulmoograte on intact rod-shaped, presumed living, bacilli. (Rogers 1920).

The corresponding description of post-treatment bacteriology by American researchers was more vivid and revealed a nascent attempt at classifying the alterations in the morphology of the organism.

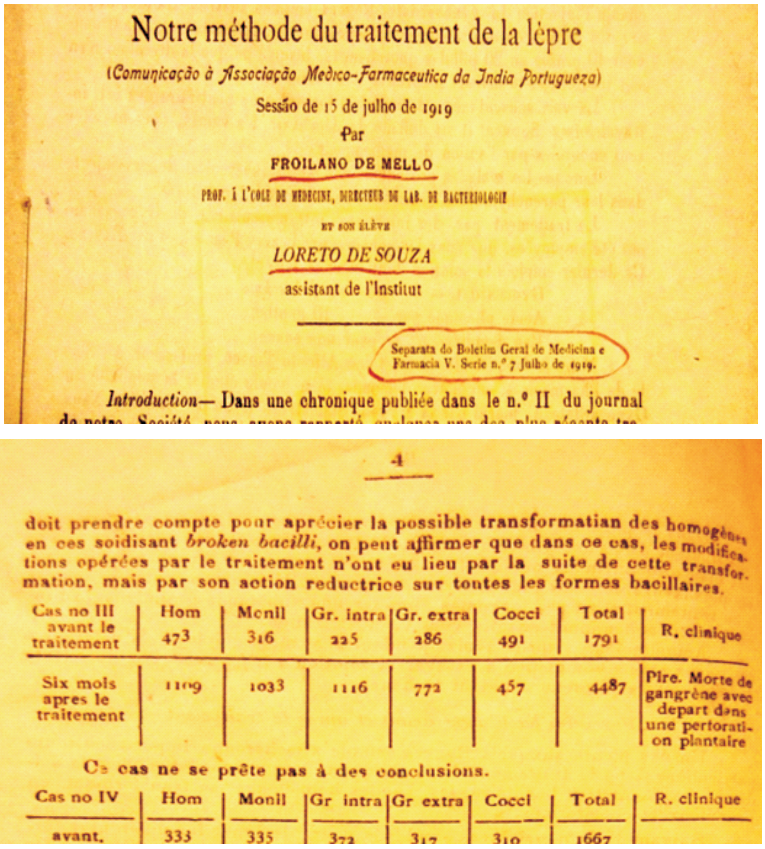
[Slide from a new patient] "Discloses myriads of well-defined bacilli of even, homogeneous stain and of practically even length ... [T]here is scarcely any morphologic difference between the individual bacilli in a microscopic field..."

[Slide from a patient on intensive ethyl ester treatment] "the greater portion of the bacilli to have undergone a distinctive change which causes them to take the stain only in segments, the bacillus becoming simply a row of bright red dots. When a mass of them are crowded together... There is a characteristic granular appearance in which the rod-like aspects are entirely lost, and so we have become accustomed to record such findings as "b. and g."—beaded and granular..." (McDonald 1920).

Neither group of investigators, however, ventured beyond the "here and now" of morphology. The credit for introducing objectivity and a longer term perspective to treatment-related changes belonged to Froilano de Melo (1887-1955), a less widely known, but locally significant researcher from the tiny Portuguese possession of Nova Goa in coastal Western India.

De Melo's Method of Treatment and Assessment of Bacteriological Morphology:

In an obscure publication of 1919, [Fig. 1] de Melo, reported the results obtained by his assistant Loreto de Sousa who carried out total and differential counts of three categories of stained bacilli: "homogenous" ("H" forms), "moniliform" (beaded or "M" forms), and "granular" (cocciform, "G" or "C" forms) in 5 patients treated with sodium chaulmoograte (de Melo 1919). de Sousa painstakingly enumerated organisms in 100 equal microscopic fields at the start and after six months of chaulmoograte therapy. Results were expressed as number of organisms in each category, and as H/M and H/C ratios. Interestingly, granular forms



Notre méthode du traitement de la lèpre

(Comunicação à Associação Medico-Farmaceutica da India Portugueza)

Sessão de 15 de julho de 1919

Par

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doit prendre compte pour aprécier la possible transformatian des homogènes en ces soidisant *broken bacilli*, on peut affirmer que dans ce cas, les modifications opérées par le traitement n'ont eu lieu par la suite de cette transformation, mais par son action reductrice sur toutes les formes bacillaires.

Cas no III	Hom	Monil	Gr. intra	Gr. extra	Cocci	Total	R. clinique
avant le traitement	473	316	225	286	491	1791	
Six mois apres le traitement	1109	1033	1116	772	457	4487	Pire. Morte de gangrène avec depart dans une pertoration plantaire

Ce cas ne se prête pas à des conclusions.

Cas no IV	Hom	Monil	Gr intra	Gr extra	Cocci	Total	R. clinique
avant.	333	335	372	317	310	1667	

Fig 1 : de Melo and de Sousa communication of 1919 (Ref. 4) on their method of classification of bacillary morphology in stained slides, and quantification of serial changes resulting from chaulmoograte treatment. The paper was appreciated by American workers in Hawaii in 1920. Wellcome Institute Library, London. Shelfmark : WC335 1919M52n

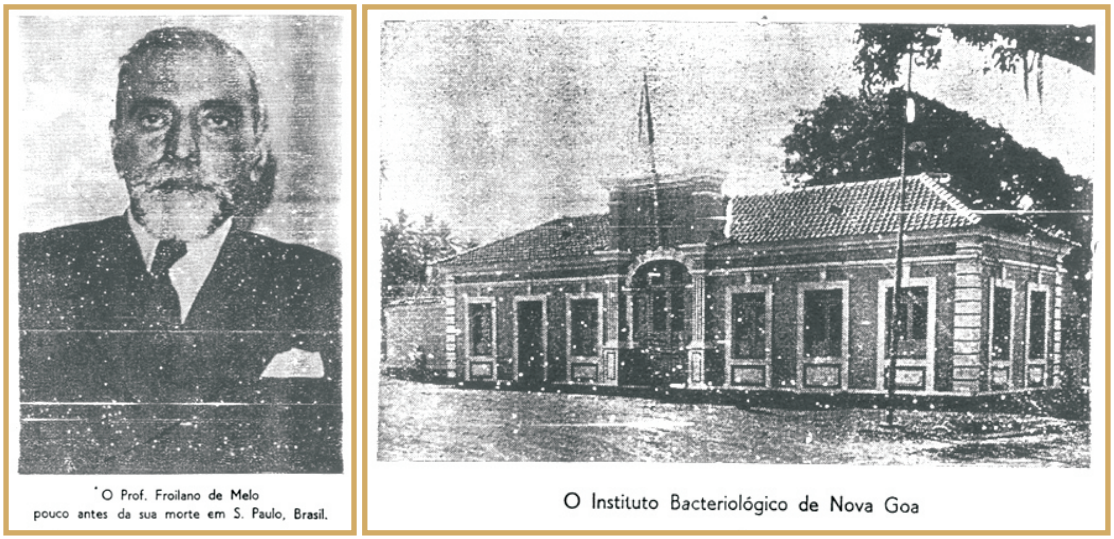

Fig 2 : Frolano de Melo and the Institute of Bacteriology in Panjim where the leprosy study was carried out. Source : *Arquivos da Escola Médico-Cirurgica de Goa, Serie A, Fasc. 28, 1955.*

were detected even before start of therapy. After six months' treatment, bacillary numbers were indeed reduced, but H/M and H/C ratios were largely unchanged. The unchanged H/M and H/C ratios pre- and post- treatment, in de Melo's view indicated a proportionate decline in all bacillary forms, not mainly the homogenously stained rods. There was thus no rationale to regard the granulated form of the bacilli per se as degeneration, or as bacteriological proof of the improvement (de Melo 1921). The 1919 study of de Melo was noticed as “meritorious” by American workers in Hawaii (McDonald 1920).

However de Melo's views were at odds with those of Rogers who characterised uniformly stained bacilli as living, and other forms as degenerate. de Melo was ignored by Rogers in numerous pronouncements and reports on the efficacy of Sodium Chaulmoograte. Neither did the Goan medical researcher feature in Rogers and Muir's 3-edition text-book Leprosy. De Melo's work was also referred to by workers from Colombia at the Third International Leprosy Conference held at Strasbourg (France) in 1923. Parra & Santos (1924) confirmed that varied morphologies of the leprosy bacillus might co-exist in stained slides of untreated patients but whether the technique proved that only homogenously stained bacilli were viable, was, in their view, debatable.

Froilano de Melo (1887-1955)

De Melo [Fig. 2] was a Lisbon-educated Goan medical polymath who was pre-eminent in public health administration, tropical medicine, medical education, research and medical politics in colonial Goa before his emigration to Brazil in the early 1950s on account of political differences with the regime in Portugal. He established the leprosy hospital at Macazana in the 1930s. His leprosy studies reported in this article were conducted at the Institute of Bacteriology established by him at “Nova Goa” (Panjim). His multifarious activities have interested medical and social historians of Portuguese colonialism (Bastos 2008). Regrettably, nothing significant is

known about de Melo's diligent assistant Loreto de Sousa.

Concluding Remarks

Bacillary morphology continued to draw attention during the Dapsone chemotherapeutic era. An "Index" advocated by Ridley was calculated from enumeration of three types of bacillary morphology ("Solid", "Fragmented" and "Granular") encountered in skin smears of patients under sulphone treatment (Ridley 1971). This categorisation was strongly reminiscent of "H", "M", "G" of de Melo and de Sousa five decades earlier. The "SFG" Index for Bacterial Morphology was also proposed as a useful semi-quantitative method for assessing bactericidal therapies after the mouse foot-pad technique had suggested that uniformly-stained bacilli were viable while fragmented and granular forms were non-viable (Boerrigter & Ponnighaus 1981). However, the foot-pad technique produced contrary conclusions in the hands of other researchers who detected bacillary multiplication even with inocula of Morphological Index of zero, *i.e.,* no homogenously stained forms (Karat et al 1973, Desikan 1976, Odinsen et al 1986).

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