1925 - 2005 Evolution and current status of leprosy chemotherapy*

*1925 - 2005 Evolução e estado atual da quimioterapia da hanseníase**

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INTRODUCTION

In the first number of volume two of the *Annaes Brasileiros de Dermatologia e Syphilographia* (Brazilian Annals of Dermatology and Syphilography), J. Ramos e Silva, in an article entitled "Chemotherapy of leprosy; its current status", wrote: "Many have been the valuable findings over the past years that have brought great advances to chemotherapy of leprosy; it seems, however, that the cycle of minute questions which will undoubtedly lead to optimal amelioration of the means currently known or bring about strictly specific novel means is not yet closed".[1]

The discussion on this subject is as current now as it was at that time. Leprosy is still a relevant public health problem in Brazil, one of the nine countries listed by the World Health Organization (WHO) as important endemic areas in the world.[2] In 2003, 49,206 new cases were diagnosed (detection rate of 2.86/10,000 inhabitants), and the country had 79,908 cases recorded (rate of 4.6/10,000 inhabitants).[2] The prevalence is above the target proposed by the WHO, which is less than one case per 10,000 inhabitants, and the detection is at levels of high endemicity, according to the parameters adopted by the Ministry of Health (MH).[3]

If, on the one hand, multi-drug therapy (MDT) is available as the official therapeutic regimen, associated with a broad coverage of public healthcare services, on the other hand, 2,696 new cases were diagnosed with grade 2 physical disabilities, that is, with established sequelae. The MDT recommended by the WHO in 1981[4] is considered efficient, having solved the problem of secondary resistance to dapsone, reduced the duration of treatment, and increased patient compliance.

The development of the treatment since the beginning of last century is undeniable. Nevertheless, leprosy reactions in a significant percentage of patients, the possibility of recurrences in multibacillary cases with high bacilloscopic index (BI),[5] and the decreased but not removed stigma still occur.

THE CHAULMOOGRA ERA

The utilization of chaulmoogra oils in the ancient Hindu and Chinese pharmacopeia was recommended for skin diseases, especially for leprosy.[6] Their utilization in the Ayurvedic Medicine in India dates back to more than 2000 years and is related to the legend telling about the cure of Prince Rama (of Benares) and Princess Piya's leprosy with the fruits of *kalav* tree.[7] The oils became known in the West by means of accounts by Mouat, in 1854[6,*] and started to be used by the end of the 19th century for the treatment of several diseases including tuberculosis and leprosy.[6,8] Chaulmoogra oil is obtained from fruit seeds of plants of the family *Flacourtiaceae*. Initially it was thought to be originated from plants of the genus *Gynocardia* but it was later confirmed to be originated from *Hydnocarpus kurzii*.[1,7] Plants producing this oil are found in Asian rainforests, in India, Sri Lanka, Indochina Peninsula, in the Philippines and Indonesia.[6] In Brazil, the species

* Mouat FJ. Notes on native remedies. Indian Ann Med Sci.1854;1:646-652. *Apud* [6]

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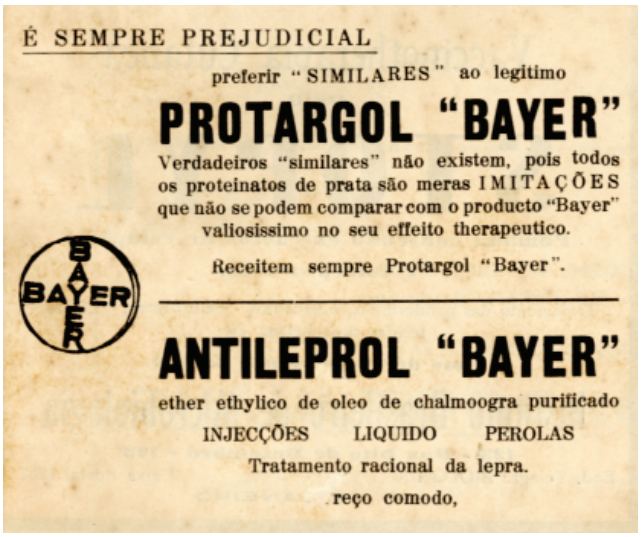


Carpotroche braziliensis, known as '*sapucainha*' was identified.[7]

Chaulmoogra derivatives appeared as an alternative to antimonials, arsenicals, iodine, and other treatments.[1,7] The plants producing this oil started to be cultivated in several regions worldwide, including Brazil. Further identification of *C. braziliensis* enable this species to become the main supplier of the active substance in the country.[7] Chaulmoogra oil was obtained by pressing the seeds and further saponification with sodium hydroxide. Among the fatty acids obtained are the chaulmoogra acid and the hydnocarpic acid, whose chemical compositions and power of optical deviation of polarized light are slightly different.[6,7] The oil was used in magisterial formulations, such as Brocq and Pomaret formula, mentioned by Ramos e Silva:[1]

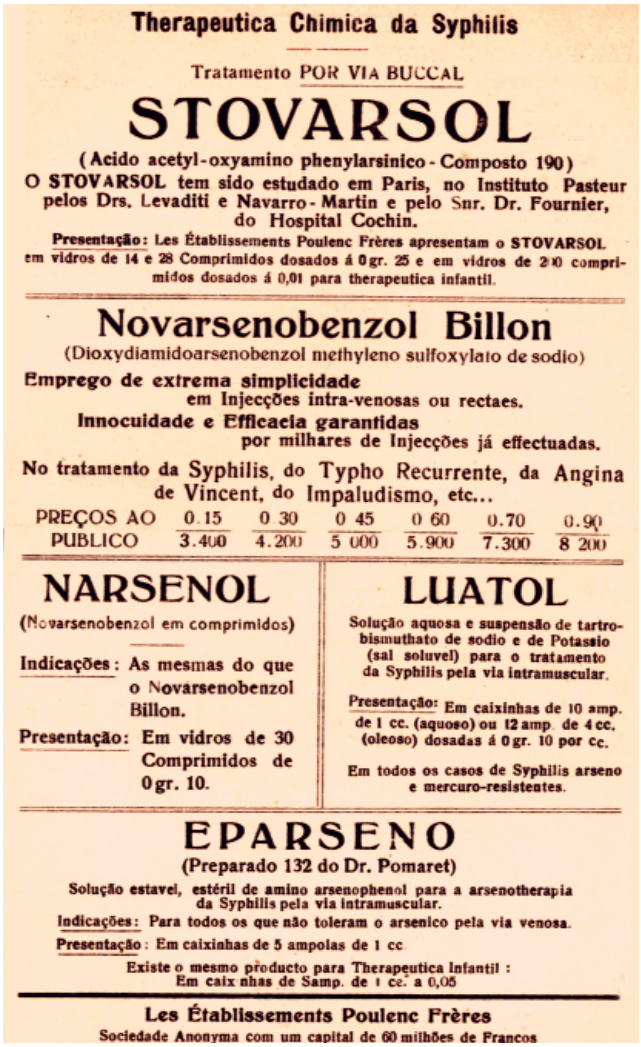
Chaulmoogra oil.....70cc
Eucalyptol.....30cc
For intramuscular use.

The local pharmaceutical industry developed various products and multinational companies produced Alepol®, Moogrol® (Burroughs-Welcome),[6] Antileprol® (Bayer) among others. Actually, the chaulmoogra treatment represented the first concrete possibility for the therapeutic armamentarium of leprosy. It was used orally - and then abandoned because of the irritant effects on the gastrointestinal tract, parenterally (intramuscularly or intravenously), and as intralesional applications known as *plancha*. The latter had many supporters and was considered efficient in the resolution of paucibacillary lesions.[7,9,10] Its mechanism of action was not known. The oil was believed to stimulate the activity of serum lipases on the bacterial wall, thus facilitating the lysis of the organism.[1,8,11] De Mello, in 1925, also considered a possible immunostimulatory effect[11] and some authors suggested that, in the case of intralesional treatment, mechanical injury would be responsible for this stimulation.[9]

Although chaulmoogra derivatives had been largely used, many questions were asked since they were introduced in the therapeutic armamentarium of leprosy. In 1951, Bechelli, Rotberg showed a considerable disagreement among several authors as to the results obtained with this treatment and stated that there were no studies methodologically adequate that could confirm its efficacy. However, they admitted its local effect in the improvement of many lesions and its role in the control of the disease by encouraging or making it easier for patients who hired themselves to search for treatment.[10]

The introduction of sulfones in the treatment of leprosy based on Faget´s observations, in 1941[12,*] marked the decline of chaulmoogra oils. The implementation of an outpatient-based leprosy control policy by the end of the 1950´s led to an end of this stage in treatment of leprosy.[13]

[*] Faget GH, Pogge RC, Johansen FA, Dinan JF, Prejean BM, Eccles CG. The promin treatment of leprosy. Public Health Rep.1943;58:1729. *Apud* [12]



Therapeutica Chimica da Syphilis

Tratamento POR VIA BUCCAL

STOVARSOL

(Acido acetyl-oxyamino phenylarsinico - Composto 190)

O STOVARSOL tem sido estudado em Paris, no Instituto Pasteur pelos Drs. Levaditi e Navarro-Martin e pelo Snr. Dr. Fournier, do Hospital Cochin.

Presentação: Les Établissements Poulenc Frères apresentam o STOVARSOL em vidros de 14 e 28 Comprimidos dosados á 0 gr. 25 e em vidros de 200 comprimidos dosados á 0,01 para therapeutica infantil.

Novarsenobenzol Billon

(Dioxydiamidoarsenobenzol methyleno sulfoxylato de sodio)

Emprego de extrema simplicidade em Injecções intra-venosas ou rectaes.

Innocuidade e Efficacia garantidas por milhares de Injecções já effectuadas.

No tratamento da Syphilis, do Typho Recurrente, da Angina de Vincent, do Impaludismo, etc...

PREÇOS AO PUBLICO	0.15	0.30	0.45	0.60	0.70	0.90
	3.400	4.200	5.000	5.900	7.300	8.200

NARSENOL

(Novarsenobenzol em comprimidos)

Indicações: As mesmas do que o Novarsenobenzol Billon.

Presentação: Em vidros de 30 Comprimidos de 0 gr. 10.

LUATOL

Solução aquosa e suspensão de tartro-bismuthato de sodio e de Potassio (sal soluvel) para o tratamento da Syphilis pela via intramuscular.

Presentação: Em caixinhas de 10 amp. de 1 cc. (aquoso) ou 12 amp. de 4 cc. (oleoso) dosadas á 0 gr. 10 por cc.

Em todos os casos de Syphilis arseno e mercuro-resistentes.

EPARSENO

(Preparado 132 do Dr. Pomaret)

Solução estavel, estéril de amino arsenophenol para a arsenotherapia da Syphilis pela via intramuscular.

Indicações: Para todos os que não toleram o arsenico pela via venosa.

Presentação: Em caixinhas de 5 ampolas de 1 cc

Existe o mesmo producto para Therapeutica Infantil: Em caixinhas de Samp. de 1 cc. a 0,05

Les Établissements Poulenc Frères

Sociedade Anonyma com um capital de 60 milhões de Francos

CURRENT CHEMOTHERAPY

In 1981, the WHO recommended the treatment of leprosy with (MDT). The regimens proposed comprised several drugs with different mechanisms of action, aiming to prevent emergence of bacterial resistance, and they were efficient even in the presence of dapsone-resistant *M. leprae* The reduced duration of MDT when compared to treatment with sulfones, which was maintained for the whole life of the patients, had the purpose of increasing patients´ compliance to treatment. To this end, the association of bactericidal drugs was recommended.[4] Standard regimens actually have a highly bactericidal drug - rifampicin - and two drugs considered bacteriostatic or mildly bactericidal - dapsone and clofazimine.[14]

Of the regimens officially recommended by the WHO, Brazil currently adopts MDT-PB, which is recommended for the paucibacillary forms of leprosy - indeterminate and turberculoid forms, and MDT-MB, for the multibacillary forms of the disease - borderline and lepromatous forms.[3] Both regimens recommend rifampicin as a drug to be administered under supervision in monthly doses. The MDT-PB establishes daily self-administration of dapsone and must be concluded after six supervised doses in up to nine months. The MDT-MB establishes the administration of the supervised dose of clofazimine, in addition to rifampicin, and daily self-administered doses of dapsone and clofazimine. The duration of the treatment was initially of 24 doses, and further accepted as 12 doses in up to 18 months.[3] There is also a third alternative regimen, recommended for PB forms with a single skin lesion and named ROM - rifampicin, ofloxacin and minocycline, administered in a single dose.

The standard regimens have already been used by 14 million patients worldwide,[2] and their safety and acceptation for use in the field have been confirmed. Recurrence rates of approximately 0.1% per year among multibacillary forms take into account the 24-dose regimen.[14] However, recurrences at levels considered unacceptable for specific multibacillary groups with high BI have been reported.[5,15] The search for regimens that could combine highly bactericidal drugs continues, with promising prospects from the demonstration, in laboratory animals, of the superiority of rifampentine and moxifloxacin over rifampicin and ofloxacin, and of their association with minocycline (PMM), which is regarded as superior to ROM.[14,16]

MDT brought the premise of patient's multidisciplinary care, a closer relationship between patients and healthcare services, thus improving the levels of compliance to treatment and enabling early diagnoses and interventions in reactional states, as well as continuous work in the prevention of physical disabilities.

The impact of MDT was essentially observed in the prevalence of the disease, and no significant decrease in the detection of new cases occurred.[14] Detection rates are estimated to decline, though slowly, so that the adoption of long-term control strategies will be required.[17]

The involvement of the society, and the commitment of governments and healthcare professionals,- especially of dermatologists who play an important role in supporting the healthcare structure - are necessary to address this typically dermatological and neurological disease.

Finally, we can state that Ramos e Silva´s expectations were correctly outlined when he made the prognosis that chemotherapy was an optimal therapeutic method to be achieved, which would lead to the end of compulsory isolation and to the treatment of leprosy on an outpatient basis.[1] The development of chemotherapy over the 20th century allowed these objectives to be achieved, with the cure of the infection. The remaining issues, such as immunological alterations that lead to reactional states. and the stig-

ma that still exists in many societies, are expected to be eradicated with the development of the treatments currently available and the consolidation of the goals for elimination. ❑

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REFERENCES

1. Ramos e Silva J. A chimiotherapia da lepra; seu estado actual. An Bras Dermatol. 1926;2:17-28.
2. World Health Organization. Global leprosy situation, 2004. Week Epidemiol Rec. 2005; 80:118-24.
3. Brasil. Ministério da Saúde. Portaria nº 1073/GM, de 26 de setembro de 2000. Diário Oficial [da] República Federativa do Brasil, Poder Executivo, Brasília, DF, 28 set. 2000. Seção 1, p. 18.
4. World Health Organization Study Group. Chemotherapy of leprosy for control programmes. Geneve: WHO; 1982. p. 675. [WHO Technical Report Serie].
5. Gelber RH, Balagon MVF, Cellona RV.The relapse rate in MB leprosy patients treated with 2 years of WHO-MDT is not low. Int J Lepr Other Mycobact Dis. 2004;72:493-500.
6. Norton AS. Useful plants in dermatology.I. Hydnocarpus and chaulmoogra. J Am Acad Dermatol. 1994;31:683-6.
7. Bechelli LM, Rotberg A, Maurano F. Medicação Chalmúgrica. In: Bechelli LM, Rotberg A, Maurano F. editores. Tratado de Leprologia. Rio de Janeiro: Serviço Nacional de Lepra; 1944.p. 235-314.
8. Urbino G. Le traitement chimiothérapique de la tuberculose et de la lèpre. Presse Med. 1925;33:1332-4.
9. Muir E. Hydnocarpus oil. In: Muir E. editor. Man ual of Leprosy.Edinburgh: E&S Livingstone; 1948. p.117-23.
10. Bechelli LM, Rotberg A. Chaulmugra, outras drogas, medicações em estudo. In: Bechelli LM, Rotberg A. editores. Compêndio de leprologia. São Paulo: Empresa Gráfica da Revista dos Tribunais Ltda; 1951. p.459-77.
11. De Mello F. Ètat actuel de la chimiothérapie antilépreuse. Presse Méd.1925;33:1348-52.
12. Muir E. Sulphone treatment. In: Muir E. Editor. Manual of leprosy. Edinburgh: E&S Livingstone; 1948. p.124-30.
13. Paula ASV. A hanseníase em Minas Gerais (comentários sobre a situação da endemia em 1979). Boletim Informativo SOSP. 1980;65:3-7.
14. Report of the International Leprosy Association technical Fórum. Paris, 2002. Int J Lepr Other Mycobact Dis. 2002;70: 62.
15. Jamet P, Ji B. Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. Marchoux Chemotherapy Study Group. Int J Lepr Other Mycobact Dis.1995; 63:195-201.
16. Consigny S, Bentoucha A, Bonnafous P, Grosset J, Ji B. Bactericidal activities of HMR3647, moxifloxacin, and rifapentine against Mycobacterium leprae in mice. Antimicrob Agents Chemother. 2000;44:2919-21.
17. Meima A,Smith WC, van Oortmarssen GJ, Richardus JH,Habbema JD.The future incidence of leprosy: a scenario analysis. Bull World Health Organ. 2004; 82:373-80.

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