Vincent C. Barry
Vincent Barry (1908-1975)

- Vincent Barry originally from Cork; studied Chemistry at University College Dublin (UCD); graduated in 1928.
- 1929, Assistant to Thomas Dillon, Professor of Chemistry at University College Galway.
- Originally working on sugars, he established an industry based on seaweeds.
- Barry became famous for his work on the degradation of laminarin, involving hydrolysis and oxidative degradation; technique became known as "Barry Degradation"; later extended to starch, cellulose, and the glycans
- Dr. Barry was appointed to a Fellowship in Organic Chemistry in UCD to carry out investigations into the chemotherapy of tuberculosis.
- 1950, appointed as Director of the new laboratories for medical research established by the Medical Research Council of Ireland (MRCI) at Trinity College Dublin.
- Barry and his team had much success in synthesising and testing hundreds of new compounds against *mycobacteria*. A number of these were found to be effective against experimental tuberculosis. Others proved more successful against leprosy but were costly to produce. Nonetheless, it is now established as one of the three first-line drugs in the treatment of leprosy.
- Dr. Barry also initiated research on chemotherapy of cancer.
- This work is being continued by the MRCI research team, now based in the Chemistry Department of Trinity College.
“I have fought the good fight, I have finished the race, I have kept the faith. Henceforth, there is laid up for me the crown of righteousness” 2nd letter of Paul to Timothy

Long-time eminent scholar, teacher, administrator at Trinity College; adventurer, naturalist, rockclimber, citizen, and family man

I was privileged to be Frank’s first Ph.D. student when I joined him in Vincent Barry’s MRCI unit in 1962. He and Vincent Barry had a profound effect on me personally and professionally
Scientist who helped discover new drug to treat leprosy

• An Irish scientist, Sean O'Sullivan, who helped develop one of the world's most important anti-leprosy drugs has died at the age of 75.

• Dr John F (Séan) O'Sullivan was a member of a team working in the former Medical Research Council of Ireland laboratory at Trinity College Dublin in the years immediately following the second World War.

• With J.G. Belton, M.L. Conalty and Dermot Twomey he was part of a group led by Vincent Barry, whose actual goal was the discovery of new drugs for use in the fight against TB.
Clofazimine (B663; Lamprene)

- [3-p-chloranilino)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino) phenazine]
- Tissue selectivity (adipose; RES)
- Targets DNA – binds to guanine at base sequences; inhibits transcription?
- Reversibly reduced; pro-drug; oxidized form is active species?
- Resistance? None/little

FIG. 19. Structure of clofazimine.

[3-p-chloranilino)-10-(p-chlorophenyl)-2,10-dihydro-2-(isopropylimino) phenazine]
A NEW SERIES OF PHENAZINES (RIMINO-COMPOUNDS) WITH HIGH ANTITUBERCULOSIS ACTIVITY

By VINCENT C. BARRY, J. G. BELTON, MICHAEL L. CONALTY, JOAN M. DENNENY, DEIRDRE W. EDWARD, J. F. O'SULLIVAN, DERMOT TWOMEY and FRANK WINDER

Laboratories of the Medical Research Council of Ireland, Trinity College, Dublin
<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of screening</th>
<th>Daily intake of drug (mgm./kgm.)</th>
<th>Increase in median survival time over controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B.663</strong></td>
<td>Protective screening</td>
<td>119</td>
<td>+ &gt; 241</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>20</td>
<td>+ &gt; 210</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>8</td>
<td>+ &gt; 210</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>5</td>
<td>+ 220</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>2</td>
<td>+ 95</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>1</td>
<td>+ 1</td>
</tr>
<tr>
<td></td>
<td>Established disease screening</td>
<td>180</td>
<td>+ &gt; 250</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>60</td>
<td>+ 200</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>11</td>
<td>+ &gt; 80</td>
</tr>
<tr>
<td></td>
<td>Protective screening using the isoniazid-resistant variant</td>
<td>3.3</td>
<td>+ &gt; 133</td>
</tr>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Protective screening</td>
<td>25</td>
<td>+ 150</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; &quot;</td>
<td>3.7</td>
<td>+ 7</td>
</tr>
<tr>
<td></td>
<td>Established disease screening</td>
<td>39</td>
<td>+ 67</td>
</tr>
</tbody>
</table>
However, the phenazines/rimino compounds, specifically B.663, were disappointing in human tuberculosis, probably due to the highly selective distribution of the drug in the tissues of the body (adipose, RES) not coinciding with the distribution of *Mycobacterium tuberculosis* in human disease (pulmonary cavity).

Barry *et al*. *Bull. Int. Union against Tuberculosis* 29 (1959), 582-593
B.663 and Leprosy

Key Studies in Adoption of Clofazamine as Part of the WHO MDT

• Chang, Y.T. Story behind the clinical trial of B.663 in leprosy. Int. J. Lepr. 1967. 35: 78-80
• Jamet et al. Short-term trial of clofazamine in previously untreated lepromatous leprosy. Int. J. Leprosy 60 (1992) 542 -548
Clofazamine, WHO-TDR-THELEP and MDT

• 1960/1970s: Prevalence ~8,000,000 cases; rampant Dapsone resistance; no alternatives; no diagnostics

• 1962: Shepard, Mouse Footpad Model

• 1972: Kircheimer/Storrs; Armadillo → M. leprae

• 1975: UNDP/World Bank/Special Programme for Research and Training in Tropical Diseases (TDR) – Tore Godal

• 1976: TDR-IMMLEP – Barry Bloom - leprosy vaccine; instead, the great successes of IMMLEP were antigenic definition of M. leprae, LAM, r-proteins, definition of T-cell immunity, MAb definition, PGL-I & its serology

• 1976: TDR-THELEP – Jacques Grosset; its great success was MDT, based on RIF from TB studies; CLO from mouse foot pad studies; and retention of DAP; perfected and introduced by WHO in 1982; prevalence now at ~250,000

MDT Blister Pack (Novartis/WHO; 3 Drugs: Dapsone; Rifampin; Clofazimine)
Dear Dr Noto,

I refer to Dr Warren’s message dated LML Sept. 29th, 2010. I am not aware of any other report of clofazimine resistant leprosy in a patient apart from the one published by Titia Warndorff in an Ethiopian patient in 1982. This was published as a case report in the International Journal of Leprosy:


In that case (which I was privileged to see), there was only the clinical evidence to go by.

Best regards,

H Joseph Kawuma
GLRA, Uganda
B663 and ENL

Dear Dr Noto,

Thank you very much for bringing the issue of chronic ENL and steroid dependent ENL. Thank you very much also to the experts that have commented about this important issue. I remember one senior dermatologist saying that these are among the most difficult problems in treating leprosy patient.

In Indonesia for steroid dependent ENL, we used prednisolone tapering off and substituted with clofazimine high dose 3 x100 mg for 2 months and continued 2 x 100 mg for 2 months and 1 x 100 mg for 2 months. It should be noted that the effect of clofazimine will be evident after 1 month of therapy; so we should think (of it) for prednisolone when tapering off. Prednisolone is still needed for at least a month, in our protocol for adult case, we start 40 mg and tapering off every two week. In Papua, Indonesia, many triggered factors for ENL are present like malaria, dental problems, psychological problems, anaemia, under-nutrition.
Dear Salvatore,

In addition to the valuable comments of Pieter Schreuders and Ben Naafs (LML Sept. 2nd 2010): I fully agree on their comments. Perhaps a word of caution in those cases of chronic recurrent ENL when a prolonged regime of Clofazamine needs to be combined with corticosteroids. In that situation there is definitely an increased risk of drug induced gastro-intestinal bleeding. This risk is further increased when analgetics are added. These patients should be carefully monitored for this potential life threatening complication.

With best regards,

Willem Theuvenet
Ref.: Clofazimine in high dosage used for the treatment of late ENL reaction in leprosy: could it mask a relapse?

From: Maria Leide W. de Oliveira, Rio de Janeiro, Brazil

Dear Dr Noto,

I have been following all the discussion regarding clofazimine with my colleagues in LML and the following is my point of view:

1- As reported by some Leprosy Control Program managers, Brazil too has been receiving loose clofazimine (100mg and 50mg capsules) for the past years from WHO Geneva free of charge. However, it is not a regular allocation and the total delivered has been inferior to our requests. For this reason, the National Hansen’s Disease Control Program has manifested the desire to buy loose clofazimine. Another reason is to avoid the misusing of MDT blister-packs by extracting the 50 mg clofazimine capsules from the MB blister-packs and discarding the DDS and rifampicine or using it for other purposes.

2- In field work I used to prescribe clofazimine in many leprosy cases. As in Brazil we have Thalidomide available and its dramatic effect in type 2 reaction is undoubtedly superior to the action of clofazimine, I only use it in a high doses to treat recurrent type 2 reactions, usually in late reaction after polychemotherapy or in some young women. However, after my latest experience with relapse cases I started wondering if clofazimine is not masking relapse development and also, creating a risk of clofazimine resistance due to its mono-therapy. We must protect this wonderful drug from now on. Therefore, I am avoiding giving clofazimine in late type 2 reactions and have started observing those cases where clofazimine was given previously.