

“Colorado Responds to MDR-TB”

A meeting to Foster Collaborative Research on the Front Range

Thursday, August 2, 2007

Radisson Hotel and Conference Center - Longmont, CO

A Summation from Patrick Brennan

The assignment for the other wrinkled gray-beard, in the room, is to come up with some concluding remarks and identify joint research programs. However, the break-out groups have done a marvelous job in the latter context. Therefore, I will confine myself to some observations and comments, and a bit of a summary.

Firstly, this has been a very successful, even a brilliant event in the context of what has been tried before as a regional group or individually. In the past we have had the Vail National Jewish conferences in the 1990s organized by Dr. Jim Cook; we had the CSU Pingree Park Campus conferences in the context of the Rocky Mountain Immunology, Microbiology, and Biochemistry Groups and all of these have had a substantial TB component. However, they were all more in the “show and tell” format which was appropriate for the times when TB research was in its infancy. For the success of this meeting and the genius in its construction we owe a special thanks to the Planning Committee of “Colorado Responds to MDR-TB”, namely Mary Ann De Groote, Chuck Daley, Bob Horsburgh, Ed Janoff, Chuck Peloquin, Martin Voskuil, and Amy Livingston.

It is most appropriate that the Keynote Speaker be Michael Iseman. If you have not been impressed with what Bill Burman had to say about Mike, there is a wonderful portrait of him in the *P&S Journal Vol 12, No 2, 1997* of the Columbia College of Physicians and Surgeons, referring to Mike’s athletic prowess (“he mastered every sport to which he ever applied his mind and body”), in baseball, varsity football, track, rowing, rugby, and basketball, all while at Princeton, where incidentally he majored in history. After his medical training at Columbia College of Physicians and Surgeons in New York, he came to Denver, where he came under the influence of Dr. John Sbarbaro and his practice of “directly observed therapy”. Mike formally joined National Jewish in 1982, although he had long been associated with TB in Colorado at the detection, treatment, research, and education levels, through the University of Colorado School of Medicine and Denver General Hospital.

Indeed, in closing today’s meeting we should pay a special acknowledgement to National Jewish and what it has done for the treatment of TB, research on the topic, and education of countless

physicians, nurses, laboratory personnel, over the years. Drs. Iseman, Hewlitt, Daley, Peloquin, Chan, several of whom were outstanding in dealing with the recent well publicized cases of drug resistant TB in our country, are the most recent of outstanding researchers and practitioners who graced National Jewish, joining some of the “greats” of the past, such as John Saboro, Gardner Middlebrook, Mayer Goren, Paul Davidson, Werner Schaefer, Marian Goble, *etc.*

In fact, almost all of the tuberculosis programs you heard of today and the people you heard from had their origins at National Jewish in one way or another. And I look around at people like David Cohen, Bob Horsburgh, and they all have or had a National Jewish connection. Certainly that can be said of the program at CSU in Fort Collins. I came to National Jewish in 1976 at the invitation of Mayer Goren to take up Werner Schaefer’s program on the chemical definition of the specific antigens of *M. avium* and other non-tuberculosis mycobacteria. It proved to be very successful, fundable research and with the encouragement of Mayer Goren I moved the program and some leprosy research that I had started at National Jewish to Fort Collins in 1980. Subsequently, the people who are here today from CSU joined me, such as Ian Orme, Mike McNeil, Delphi Chatterjee, Dean Crick, and they in turn attracted their own colleagues, such as Anne Lenaerts joining Ian Orme and then developing her own important research. And in some cases, our own graduate students, such as John Belisle, Karen Dobos, Ric Slayden, left CSU and then came back, to develop their own programs. Besides Mary Ann De Groote and myself as National Jewish alumni, John Spencer is now in Fort Collins having worked with Ralph Kubo, Howard Gray, and John Freed at National Jewish during the late 1980s – early 1990s.

So the issue now, is what have we here in Colorado to address this devastating problem of TB, HIV-TB, MDR/XDR-TB and what can we do better as a group rather than individually. The Conference was outstanding in defining for us the available, regional facilities and tools, suitable for a Consortium approach to the problem.

We had the problem defined for us, very clearly, very eloquently, by Mike Iseman, Bill Burman, Ed Janoff, and Chuck Daley, in terms of numbers infected with TB globally, those with TB-HIV co-infection, the extent of MDR and XDR-TB, treatment modalities and the challenges of understanding and treating latent-TB.

We have also heard to some extent on what is being done about the problem at the international level, the various players, such as NIAID, WHO, the Global Alliance, the Bill and Melinda Gates

Foundation, FIND, the Clinton Global Initiative, and the new Eli Lilly Initiative in conjunction with the NIH-Foundation. And in our own presentations, we have heard how our own efforts here in Colorado are complementing those global efforts.

The presentations today can be divided into 3 broad areas: For instance from CSU, the home of more basic research, we heard from Dean Crick, who reflected a considerable body of work being conducted by many of us in parlaying our basic research on the structure, biosynthesis and genetics of the cell wall of *M. tuberculosis* into target identification and validation, assay development and drug screening, and the need to work on the true *in vivo* organism in its various physiological/infectious forms.

At the CSU end, we also heard from Anne Lenaerts on the pre-clinical testing of experimental drugs, through the NIH-TAACF Program, particularly those more topical new drugs such as moxifloxacin, the new quinolones, PA-824, diaryl-*N*-oxides, and the various animal models she has developed to answer the different clinical issues, and the challenges of addressing latent TB, drug tolerance, etc. She ended up with an intriguing story on the form of the bacilli surviving the highly potent John & Johnson R207 drug, as existing in extracellular clusters in the granuloma.

From Ian Orme, we had a lovely talk on, firstly, the global status of prophylactic vaccine development and what are the front-runners and the status of human trials, and the most promising approaches. He presented an altogether very hopeful scenario, but still with great challenges, such as the efficacy of vaccination vs MDR-TB challenge and challenge with the more virulent fit clades of *M. tuberculosis*, and the question of the ability of vaccines to counteract regulatory T-cells. Ian Orme mentioned the promise of post-exposure vaccines, but their failure so far to prolong survival. Perhaps, more intriguing was the new insights Ian Orme provided into TB in the guinea pig; the identification and location of persistent bacilli, in a fibrin matrix; the story of the accumulation of iron; the use of MRI; and the interesting kinetics of immune cell influx.

Then, from Denver we heard about the second aspect of the Conference, more to do with the actual human disease. We heard from Ed Janoff about CFAR and its role in building opportunities for broad infectious disease research, and the fact that the problem of HIV is also one of TB. Dr. Janoff's take home messages were: 1) TB research is HIV/AIDS research; 2) The need for advocacy for these programs; 3) The availability of some seed money for cross-cutting research programs; 4) The availability of clinical sites in Zimbabwe and Uganda.

From Chuck Daley, we had a very powerful review of the need for new diagnostics, particularly as they relate to MDR-TB. Dr. Daley presented an excellent introduction on the epidemiology and demographics of drug sensitive and resistant TB, the two forms of AFB practice, standard drug sensitivity testing, the need to aggressively move towards molecular approaches, a review of what is in the pipeline, and a clear definition of the needs and priorities.

Bob Horsburg - though not physically of Denver, is spiritually so, and, indeed is spending a sabbatical here - gave a very eloquent talk on surrogate marker/end points of disease, progressing from death, radiologic and bacteriologic markers. He cited the example from HIV with viral load and CD4 counts being accepted as the FDA "Accelerated Approval Process". In the case of TB, whatever markers are chosen, we must comply with clinical effectiveness. Prospective candidates will be either microbiological, immunological, or host proteins.

We did not have a formal talk from Bill Burman or David Cohn from Denver Health, but we did learn that within that enterprise are: 1) The Tuberculosis Trials Consortium, Denver being one of the study sites world-wide enrolling patients for randomized clinical trials of new treatments against latent and active TB, and 2) The Tuberculosis Epidemiological Studies Consortium. From the Denver end we also had an excellent presentation by Chris Pelloquin on the application of pharmacodynamics for the treatment of TB and the importance of that exercise.

The third phase of the meeting then, and the most innovative, were the break-out sessions, where the two aspects of TB research within the region, namely basic and human, were brought together to show how we could compliment each aspect to better address the problems. The outcome and action items from these break-out sessions are described below.

As I said this has been the most successful such conference in my experience of 32 years of research on tuberculosis in Colorado. Still the problems and challenges are huge. In order to allow us to take a more integrated approach to these challenges combining our strengths in basic and applied research, I suggest, firstly, circulation of a draft of the minutes of the meeting particularly of the action items emanating from the break-out groups, secondly, immediate action on their implementation and, thirdly, a meeting in the Denver-Longmont-Fort Collins area to discuss follow up and joint projects and applications.