

AUTHOR COMMENTARIES - From Special Topics

Tuberculosis - January 2009

Interview Date: July 2009



Paul van Helden

From the Special Topic of **Tuberculosis**

According to our Special Topics analysis on tuberculosis (TB) over the past decade, the work of Professor Paul van Helden ranks at #4 by number of papers, based on 95 papers cited a total of 1,754 times. Two of these papers also appear on the lists of the top 20 papers over the past decade and over the past two years. In addition, these two papers are designated as Highly Cited Papers in Essential Science IndicatorsSM from Thomson Reuters.

Professor van Helden is the Director of the South African Medical Research Council's Center for Molecular and Cellular Biology and Co-Director, DST/NRF Centre of Excellence for Biomedical TB Research, which operates out of the Department of Biomedical Science, part of the Faculty of Health Science at Stellenbosch University.

Below, he talks with ScienceWatch.com about his TB research.

SW: Would you tell us a bit about your educational background and research experiences?

I was born in Cape Town of rather humble beginnings. My parents, not wealthy, saved and sacrificed and sent me to a local junior school, but then determined to send me to a good government boys-only high school (SACS) some distance from our home, which I attended from 1964-1969. Education was not free in South Africa in those days. If I had attended the local high school in the area where we lived, I doubt that I would be where I am today. My parents could not advise me on a direction, other than to get a good qualification.

I have been fascinated by science and scientists since early junior school. From high school days that interest became more directed towards biological science, although I was concerned that career options in the more ecological/zoological sciences were not that good. I was quite keen to be a game ranger, but realized that opportunities were very limited and that one should at least have a four-year degree for this. Thus, I determined that I should at least have four years of university training.

For my undergraduate studies in South Africa, I started with basic courses with the intention to major in chemistry and physics. However, by the end of my first year, I became aware of a "new" subject, namely biochemistry. I therefore changed direction slightly and majored in chemistry, microbiology, and biochemistry for my bachelor's degree. In South Africa, to continue with post-grad studies, one must take another degree, called Honours. I did this one-year course in biochemistry, and discovered that science was a lot more interesting at higher levels, compared to undergrad! None of my known family had ever had a university qualification and thus after this four-year qualification, I searched for a job and was

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- [Inside This Month...](#)
- [Interviews](#)

- [Featured Interviews](#)
- [Author Commentaries](#)
- [Institutional Interviews](#)
- [Journal Interviews](#)
- [Podcasts](#)

Analyses

- [Featured Analyses](#)
- [What's Hot In...](#)
- [Special Topics](#)

Data & Rankings

- [Sci-Bytes](#)
- [Fast Breaking Papers](#)
- [New Hot Papers](#)
- [Emerging Research Fronts](#)
- [Fast Moving Fronts](#)
- [Corporate Research Fronts](#)
- [Research Front Maps](#)
- [Current Classics](#)
- [Top Topics](#)
- [Rising Stars](#)
- [New Entrants](#)
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offered one as a QC chemist in a local municipality.

On the way home from my interview and job offer and just before I signed acceptance, I stopped over at my university teaching department and wandered into the professor's office to tell him what I had decided to do. He (Prof. Claus von Holt) told me that I had more in me than that and that if I would change my mind, he would accept me as a Ph.D. student. I went home to discuss this with my parents, who were not particularly pleased with this turn of events. I think their reaction is easy to understand with the wisdom of hindsight. They grew up in the Depression years and my father was a soldier in WWII for six years, returning home with nothing. Turning down a "good" job offer was just not in their realm of thinking. Fortunately, I decided that research was more interesting than being a QC chemist. So, I went back to being a student and completed my Ph.D. in protein (histone) sequencing at the end of 1978.

After this, I accepted a job based in the Health Science Faculty of Stellenbosch University in Cape Town, where I have been ever since, with the exception of a post-doc period at the Roche Institute in New Jersey, USA, during 1981-2. This was an important experience, for while it did not equip me for the details of research projects back home in South Africa, my thinking was influenced, and learning new ways to do science, as well as learning new techniques and being exposed to a different culture was extremely important.

SW: What influenced your decision to research tuberculosis?

Being associated with—and later employed (1990) by—the South African Medical Research Council, I came into contact with scientists specializing in fields that I had never heard of as a molecular biologist/biochemist. These included fields such as epidemiology, health systems research, and the like. Some of these people introduced me to concepts such as the "burden of disease."

Since I was in a medical environment, I began to question what I was doing and what relevance it may have in a developing country. I began to think that we had some responsibility to use our limited finances carefully and to perhaps apply them to our most pressing problems. I gave thought to how we might do this, using new molecular biology tools. At that time, PCR had just recently hit the news and was the new kid on the block.

Putting these thoughts together, I realized that TB was a major problem in South Africa and that the diagnostic test being used (microscopy smear) was essentially over 100 years old, and due for a change! Together with Prof. Tommie Victor (my Ph.D. student at that time), we decided that we should try to investigate TB diagnosis by PCR from sputum. We could not afford to purchase any sophisticated equipment (there were all sorts of sanctions in place against South Africa at that time and our funding was very limited), so we got together with our electronics technician to see what we could do. Our electronics technician, Mr. Frank Peiser, is a real MacGyver type of person, and he soon built us what we think was the very first PCR instrument in Africa (see fig. 1). This was based on airflow from four domestic-quality hairdryers bought from a local supermarket! This instrument was the key to unlocking our new research and our first TB papers. It also meant that the lab used to get quite hot!

SW: One of your highly cited papers is the 1999 *NEJM* article, "Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment" (van Rie A, *et al.*, 341[16]: 1174-79, 14 October 1999). Would you tell our readers a little bit about this paper—its goals and conclusions?

At that time, and still today, people talk about "relapse" in TB. This is regarded to be the phenomenon seen when a patient is treated, appears to be cured, and then has a second or subsequent episode of disease. The explanation for this was that some bacilli remained "hidden" within the patient, are not "killed" by treatment and at a later stage reactivate to cause disease.

It seemed to us that this might not be the case, since with such a high incidence and prevalence rate, it was self-evident that individuals would be likely to be exposed to a source case multiple times in their lives. In addition, our people had been vaccinated by Bacille Calmette-Guérin and the high rates of TB suggested no protection from infection. We reasoned that if these ideas were true, then we could expect

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This "PCR" instrument was developed in the lab of Prof. Paul van Helden in 1989. It was made entirely in-house and is based on 4 supermarket hairdryers. The "developers" are shown, from left to right: Prof. Tommie Victor, Prof. Paul van Helden, Rene du Toit (Technologist), Frank Peiser (electronics), Cor Wijtenburg, (metal working).

to see different strain types in some patients experiencing a subsequent TB episode.

By this time, we had quite some experience at using "fingerprinting" or genotyping and had a good collection of TB isolates from a high-incidence community available since 1993. This included a number of individuals who had had TB twice, after cure. We therefore looked at the strain types and noted that in the majority of cases subsequent episodes of TB were associated with a new strain type. The conclusion was simple: reinfection and not relapse was responsible for most cases of subsequent TB in our high-incidence community, provided the patient was treated properly and had no other complicating illness, e. g., diabetes (patient compliant and not drug-resistant or HIV-positive).

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This paper was part of the Ph.D. work of Annelies van Rie, now a professor herself in the USA. I recall some interesting experiences with this paper, one of which was arguing with the editorial staff at the NEJM about the usage of English, which illustrated the differences between UK and South African English and American English!

A further thought regarding this result is that in these patients, an initial episode of TB is not protective. This can be the starting point of hours of conversation and debate amongst TB researchers, particularly epidemiologists, immunologists, and vaccinologists! It also was a major driving force behind a number of other important (in my opinion) papers from our lab, such as those showing that TB patients with a first episode are more likely to have a second episode (Verver S, *et al.*, "Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis," *American Journal of Respiratory and Critical Care Medicine* 171[12]: 1430-5, 15 June 2005) and that many TB patients have mixed infections (Warren RM, *et al.*, "Reinfection and mixed infection cause changing Mycobacterium tuberculosis drug-resistance infections," *American Journal of Respiratory and Critical Care Medicine* 172[5]: 636-42, 1 September 2005). Finally, it triggered some thoughts about mathematical modeling and has driven some efforts of ours along those lines, which I find particularly interesting and stimulating (see papers by P Uys *et al.*).

SW: Another of your highly cited papers is the 2006 *BMC Microbiology* paper, "Mycobacterium tuberculosis complex genetic diversity: mining the fourth international spoligotyping database (SpolDB4) for classification, population genetics and epidemiology" (Brudey K, *et al.*, 6: art. no. 23, 23 March 2006). What types of information can researchers get from this database?

We are not the originators of this database, nor do we maintain it. Our group merely contributed towards it. Any researcher worldwide can access this data, which enables them to identify a strain they have genotyped using this technology and to find out what family of strains their isolate belongs to. This information is very user-friendly, open-access, and a valuable resource.

SW: Many of your papers deal with, unsurprisingly, outbreaks of tuberculosis in South Africa, and WHO has also pointed to sub-Saharan Africa as a region of concern for this disease. Why is this; what makes tuberculosis more common in South Africa than elsewhere?

There is no easy or single answer, but the following factors may play a role:

Genetics and immunology: the population of Africa has not been exposed to TB for centuries like some other parts of the world, thus the people of Africa may be inherently more susceptible.

Poverty and nutrition: TB is a disease of poverty and poor nutrition. The poorest continent on earth is Africa; therefore it is not surprising that TB is at high levels there.

Health systems (related to poverty): if we do not have a good health care delivery system that will catch, hold, and treat all (or at least 85%+) TB patients in a timely fashion and properly, we cannot win. There is probably no country in Africa that can claim that their system fulfills this level of delivery.

Diagnosis: we still do not have a good, simple, cheap, PoC (point of care) effective diagnostic. Even in communities around Cape Town, which are quite aware of TB, we lose up to 20% of potential TB cases between the first appearance at a TB clinic and the subsequent visits to confirm diagnosis. We do not have the resources to follow up with these people. How can one win under these conditions? Delay or failure to treat implies that transmission will continue and the epidemic will persist.

Why does South Africa in particular have such a high incidence rate? I do not know what the definitive answer is. One can speculate. Firstly, factors such as those listed above play an important role. Secondly, I question that the statistics and figures from all African countries are correct or accurate. Other countries may have even higher rates of TB, but lack the resources to measure them accurately.

Even in South Africa, which is regarded as a resource-rich sub-Saharan country, we regularly question figures such as those used as denominators in epidemiology estimates.

South Africa also has a relatively high population density. Yes, of course, countries such as Rwanda also have a very high population density, but this is somewhat more rural (hence better outdoor living and ventilation conditions?) and evenly spread. In South Africa, in contrast, we have had very high densities of underprivileged people living in urban environments for decades. The same has not been the case in other African cities for as long. This is equivalent to the tenement slums/ghettos seen in European cities at the start of the industrial revolution around the late 1700s, where TB rates were the same as we see here now. Once those living conditions (and nutrition) started to improve, TB rates dropped in Europe. We have also had a lot of migration within the country, and disease could easily have used this social factor to spread.

Finally, in early colonial times (and remember, South Africa was settled by Europeans from 1652), South Africa was regarded as the perfect place for TB sufferers from Europe to effect the "solar cure." The climate is largely hot and dry, with lots of sunshine. In addition, over most of the country, we do not have the other tropical diseases, such as schistosomiasis, malaria, yellow fever, etc., making it a healthy place in general. The result was fairly large-scale importation of TB from Europe and from the East, via trade and limited slavery in very early years. Thus, it is likely that TB gained a foothold in South Africa far earlier and at much higher levels than elsewhere. Perhaps this is the main original driver for the disease to have gained a stronghold.

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SW: Have you observed any appreciable changes in the trends of tuberculosis incidence in the past decade?

Yes. Sadly, the incidence rate has not really declined at all. Of course, much of this is ascribed to the HIV epidemic sweeping the country.

SW: What would you like the "take-away lesson" about your research to be?

The more we research TB, the worse it gets! No, more seriously, I would like to make the following observations:

No man is an island. My successes are not only a reflection of myself as an individual. I have been fortunate and privileged to have some wonderful colleagues, such as my wife Eileen Hoal (who has worked with me since 1983), and Tommie Victor, Rob Warren, Ian Wiid, Gerhard Walzl, Peter Donald, Nulda Beyers, and many others, as well as long-lasting support from the MRC (South Africa) and the University of Stellenbosch. Some funding from GlaxoSmithKline really helped to kick-start our research in 1993 and helped to leverage funding from other sources.

We have tried to constantly challenge dogma and to live with the idea that research is not just a "job." One must be driven and passionate to succeed.

I think that there is a real danger that research done, particularly on disease trends, in developed or relatively developed countries lead to generic policy guidelines being developed, which are slavishly implemented or adopted worldwide. There is a very real danger in my opinion, that such information is not necessarily correct or applicable for different environments. Thus we need research in every environment, with tailor-made solutions where relevant. Yes, maybe it is more expensive, but if we carry on as we have, we will continue to get what we've got. I have nothing against developing generic guidelines, but these should be a starting point, not seen as the final one-size-fits-all solution.

The new trend by funding agencies towards funding only very large multinational consortia has its place and can be very important. However, in the process, I think we will destroy much of the creative individual or small-group research, which is usually where breakthroughs are made. The reason is simple: the consortia frequently run projects on a large scale, e.g., recruit patients for some measurement. Thus, everyone must follow an exact protocol in order to minimize deviation and make results valid. There is no or little room for individuality and creativity. Much of the funding is spent on administration and process control, rather than research. The small but creative individual or small times are being left behind in this rush to obtain large grants and should not be left out in the cold. ■

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Paul van Helden's current most-cited paper in *Essential Science Indicators*, with 249 cites:

van Rie A, *et al.*, "Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment," *N. Engl. J. Med.* 341(16): 1174-9, 14 October 1999. Source: *Essential Science Indicators* from Thomson Reuters.

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