How Pharmacometrics Started in Australasia - The Early Years

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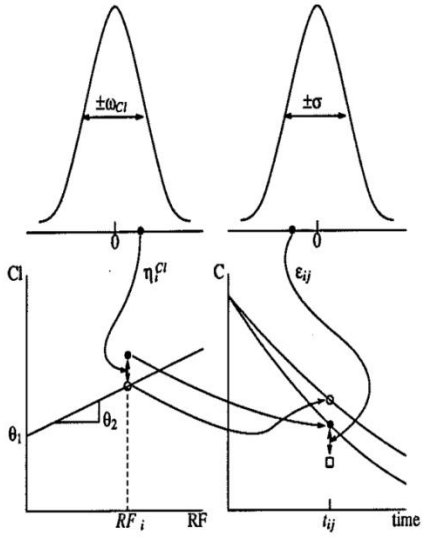
In the beginning…Nick Holford from the University of Auckland Medical School (Department of Pharmacology & Clinical Pharmacology) had regularly presented at the annual ASCEPT meetings (Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists) from the 1980s on. His presentations frequently involved PK and/or PD data in which the analyses were performed using the so-called "population" or "mixed effects" modelling approach – I doubt that few, if any, in those audiences really appreciated what this was all about as evidenced by the standard of questions and comments (below right). To be sure, Nick is a very knowledgeable and entertaining speaker, but at that time he was certainly not preaching to the converted, and was not helped much by the use of slides such as this beauty (below left) lifted from one of the early NONMEM Users Guides (also a first-line therapy for severe insomnia).



Typical audience member in early 1990s

For me the penny dropped when I began to grasp the power of mixed-effects modelling with "difficult/inaccessible" patients who mostly were very ill, and often at best could often only provide sparse observational data from frequently unbalanced and unstructured study designs. More importantly, it could be used to quantify sources of variability in the parameters describing and predicting drug response under actual clinical conditions – This was what the figure (above left) was trying to tell me, but I didn't realise it at the time! My "difficult" patients were often very premature newborn infants from 2 of the largest and best tertiary care neonatal units in the southern hemisphere – Mater Mothers' Hospital, and Royal Women's Hospital in Brisbane.

But seek and ye shall find – At an early 1990s ASCEPT meeting in Melbourne I button-holed Nick at lunch one day to give me a heads-up on what population modelling as implemented in NONMEM was all about. He graciously and enthusiastically obliged, and the lunchbreak extended to more than 2 hours – A Road to Damascus event! He then suggested that if I could get a critical mass of at least 6 interested people, he would run a basic course in population PK using NONMEM. Furthermore, we should bring our own data if possible, as this is a good way to learn NONMEM. Later back in Brisbane I did a ring-around to lobby some "likely suspects" who might be interested in such a course. The eventual attendees included myself, Ted Triggs, Jagdev Sidhu, Joanne Brien, Sue Tett, Annette Gross, plus a couple of individuals from Nick's department (apologies if I have forgotten anyone).

That course was run in May 1993 at the Department of Pharmacology & Clinical Pharmacology, University of Auckland Medical School. The agenda included the following topics: Background and rationale to a NONMEM population analysis; Differences between 2-stage, naïve pooled data, mixed-effects approaches; Conceptualisation of variability and its analysis, especially in clinical data (IIV, BSV, RUV, but nothing on IOV as this was before Mats Karlsson's seminal work); Techniques for screening influential covariates (continuous, categorical); Data file structure; NMTRAN control streams; Diagnostics (ΔOFV, SEE, scatterplots, posthoc parameter estimates and plots; Running NONMEM including using our own data (NH was very busy!). Later we walked over to the Domain gardens for informal discussion on why each of us was interested in population PK, and what we expected from it given the time and effort involved. Discussion also was centred on precautions and limitation using TDM data as several attendees were from clinical pharmacology units attached to teaching hospitals, and this was the data they typically dealt with. At the conclusion of the course Nick offered us the use of his HP system until we got set up in our own. Back at UQ, I expended some futile and expensive effort in trying to get NONMEM going on a central UQ mainframe system with the "assistance" of university computer scientists who proved somewhat less than helpful, especially with the peculiarities and cryptic messages produced during installation, compilation and execution. But this all changed when I moved to a PC platform (under Microsoft Fortran 77 PowerStation compiler) with valuable assistance in implementation and troubleshooting from Steven Shafer (Stanford University), Alison Boeckmann and Lewis Sheiner (UCSF). Regrettably, I never got to meet any of these geniuses but am forever grateful to them. I presume that the School of Pharmacy at UQ was the first site in Australia to actually get NONMEM running – We used theophylline serum concentration TDM data from very premature neonates at Mater Mothers' Neonatal Intensive Care Unit in Brisbane.

The years between 1993 and 1998 saw developments which significantly accelerated PM activity in Australia. Several people took up or returned to positions in universities and hospitals following PhD or postdoctoral training overseas, e.g. Steve Duffull (to School of Pharmacy, Qld Uni) and Andrew McLachlan (to School of

Pharmacy, Sydney Uni), both of whom had studied under Leon Aarons at Manchester, and there were a few others including some clinicians who subsequently dropped by the wayside with respect to serious PM research. The stayers developed their own research in PM, and supervised PhD students who upon graduation took up positions in academia, industry and hospitals. The regulators also began showing interest. A Drug Information Association (DIA) sponsored meeting was convened in Canberra in December 1997 at the request of the Australian Drug Evaluation Committee (ADEC) to discuss the role of population pharmacokinetics and pharmacodynamics in drug evaluation and development ("Population_Pharmacokinetics_and_Pharmacodynamics:_An_Underutilized_Resou rce") - ADEC was particularly interested in the registration of drugs in children, and the potential of the population approach to play a role in this. This burst of activity in population modelling research initially was centred in Brisbane and Sydney, spreading later to other centres in Australia and New Zealand. By the late nineties it had become apparent that we would benefit by having a local association consisting of individuals working in PM in our own corner of the world. A major incentive for this was the tyranny of distance and the cost associated with regularly attending annual northern hemisphere meetings such as PAGE (Population Approach Group in Europe). Furthermore, PAGE meetings were typically held in June which is an awkward time for many Australian academics because of clashes with examinations and organising semester 2 teaching, although several of us managed to attend these meetings consistently over the years. Various PAGE "heavies" were lobbied at times to consider our situation and, while sympathetic, could not really do much (this also was the case for some PM meetings in North America). So it was about this time that Nick Holford grasped the initiative for the establishment of our own regional association to be known as PAGANZ (Population Approach Group of Australia & New Zealand). Meetings were to be run annually (typically January/February) in an Australian or New Zealand city in which PM research was active. Thus the organisation was born, although the witty acronym raised a few eyebrows, and got a few giggles.

The inaugural PAGANZ meeting was held in January 1999 at the University of Auckland Medical School (Department of Pharmacology & Clinical Pharmacology). The agenda was in 2 parts; a practical training module PAWS (Population Analysis WorkShop) run over the first half of the meeting, followed by the PAGANZ section comprising oral/poster presentations including some by invited speakers (see website for details of all PAWS-PAGANZ programs). Nick Holford was the local organizer, major speaker, chief cook and bottle washer. In the early years, the meetings were organised by locals from the host institution, and were run on the smell of an oily rag with registration fees kept to a bare minimum especially with respect to encouraging student attendance. When convinced that these were non-profit educational meetings, some universities (e.g. UQ) did not charge for the use of lecture theatres and other facilities, and this assisted us greatly. A number of international PM luminaries were invited who generously gave of their time sometimes on several occasions. These included Mats Karlsson, Janet Wade, Diane

Mould, Paul Williams, France Mentre, Yusuke Tanigawara, and Roger Jelliffe. I fondly remember Roger Jelliffe who was about to leave Los Angeles for Vienna changing his itinerary and diverting down to Brisbane at the last minute in response to my invitation to speak at the 2nd PAGANZ meeting in 2000. The least I could do was to invite him and a few others to our home in Brookfield (wife Kathy put on a sumptuous dinner at short notice) on the eve of that meeting…. and to help carry his incredibly heavy suitcases to the University taxi rank (what on earth could have been in them?)

Attendances in these early meetings were typically 20-25, but this increased steadily in subsequent years, and there was a smattering of international researchers (including an American guy based in Guam of all places). There was a mixture of those with no knowledge of population modelling/NONMEM (Beginners PAWS attendees), and those with some knowledge/experience (Intermediate PAWS attendees). It was encouraging that increasing numbers of research higher degree students attended, as well as a few clinicians, hospital scientists, and a few regulatory and pharmaceutical industry personnel. The topics covered in these early meetings included (among others): Background, rationale and current status of NONMEM for population approaches; Linking PK and PD data during population PK/PD analysis; Covariate model building; Disease progress modelling; Nonparametric population modeling; Using NONMEM for clinical trial simulation; Bayesian philosophy and hierarchical modelling; Comparison of NONMEM and WinBUGS/PKBUGS; Opportunities and applications for population modelling in the specialized patient groups (e.g. very premature babies). It should be acknowledged here that warfarin data published in *Journal of Clinical Investigation* and *Circulation* by O'Reilly et al in the 1960s was first introduced to PAWS at the 2005 Brisbane meeting, and has been a mainstay of the NONMEM basic PAWS course since then. There was also an AGM held at each PAGANZ meeting which comprised an open forum at which brief reports were presented on the previous meeting (attendance, financial details, etc). After the first few meetings it was decided that any "profits" from the previous meeting should be made available to the organisers of the next meeting. An important aspect of each AGM was to decide on the venue, local organisers, and program for the following meeting, including invited speakers and instructors. The rapid development of PAGANZ over the next few years after the 1999 Auckland meeting is evidenced by the number of different institutions who came on board to host PAGANZ meetings: Brisbane (2000), Christchurch (2001), Melbourne (2002), Sydney (2003), Adelaide (2004), Singapore (2007). Importantly, joint meetings with other population approach organisations were established, notably the 1st PAGANZ-PAGJA (Population Approach Group in Japan) meeting in 2006 in Brisbane.

Pharmacometrics in Australasia was on its way, greatly boosted by the nurturing of the embryonic PAGANZ way back when!.

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