In Memoriam: Olli S. Miettinen (1936-2021)

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Olli Miettinen was a native of Finland, but he spent his academic life in North American institutions: University of Minnesota, Harvard University and McGill University. Still, he kept a longstanding and intensive relationship with European universities, in particular through very influential courses he taught in Scandinavia and The Netherlands. This In Memoriam remembers both the European and the North American impact of Miettinen, by two of his close colleagues.

Dr. Jacobus Lubsen writes:

That Olli S Miettinen (1936–2021) had passed away came as a great shock to all who have known him. I met him for the first time in the early nineteen seventies, still a student in medical school. Over the years, he acquired many followers who admired his visionary ideas and the way he talked and wrote about these. That he was sometimes controversial too is just the other side of the same coin.

Miettinen’s ideas and the way he interrogated intellectually any “Fragestellung” (a favourite term used by OSM in a conversation about medicine) has always guided my own work in cardiovascular clinical trials.

In my inaugural lecture in 1986 when I was appointed professor of clinical epidemiology at Erasmus University in Rotterdam (NL) I have called Miettinen the Leibniz of epidemiology. Why did Miettinen amply deserve this accolade already then?

The answer follows from Miettinen’s probably most influential publication: Estimability and Estimation in Case-Referent Studies, published in 1976 (Am J Epidemiol 1976;103:226–235). I was at the Harvard School of Public Health in the early seventies. At the time we were still being taught in Epidemiology textbooks that the exposure odds ratio calculated from a 2×2 table comparing exposure among cases to controls (“referents” as Miettinen liked to call them) approximates the relative risk provided that the disease is rare. In his 1976 paper, Miettinen introduced the concept of stable but dynamic candidate populations “at
risk” of exposed and non-exposed respectively from which incident cases are ascertained. He then shows that the odds ratio is equal to the rate ratio, with the rates (called incidence densities in the paper) for exposed and non-exposed respectively thought of as number of incident cases divided by the population-time “at risk”. Miettinen emphasised that his argument did not depend on any assumption about the frequency of the disease concerned. Out went the rare disease assumption.

The reason that this paper is so important is also that it leads to the fundamental distinction between a rate and a risk. A rate is a measure of occurrence of disease in a population, defined as number of cases divided by the population-time “at risk” of becoming a case. A risk on the other hand is the probability that an individual develops disease during a defined time interval. Note that a rate can take any value above zero, while a risk can only take a value between zero and one. Note also, and this is important as Miettinen would point out, that a rate has 1/time as dimension, while a risk (interpreted as a probability) is dimensionless.

Now why does this remind us of Leibniz? Gottfried Wilhelm Leibniz (1646–1716) was a German mathematician, philosopher and theologian. He is considered one of the founding fathers of differential and integral calculus. A (dimensionless) risk is the integral over a defined time span of a rate with dimension 1/time. Admittedly, this is not something that can be attributed to Miettinen only. But what we must to a large extent attribute to him is how to obtain rate estimates in epidemiologic studies, in concept and in study design. Of note, the terms “rate” and “risk” as defined here are not universally used in this manner. A rate may also be called incidence, incidence density, instantaneous risk, or hazard. A risk on the other hand may be called also cumulative incidence. Miettinen himself has also used different terms, but leaves the reader never in doubt what is meant. That can’t be said of many publications even today. In particular, when a risk or odds ratio is reported, it may in fact very well be a rate ratio.

Miettinen emigrated to the USA from his Finnish fatherland (to what extent did political tensions in post-World War II Northern Europe play a role?) after first studying physics, and then medicine (BMJ Evidence-Based Medicine 2022;27:A18–A19). Hence, he had a thorough understanding of the role of theoretical concepts in physics, and saw that such concepts were lacking in public health and clinical medicine. Because of this he was eminently suited to advance a general theory of medicine, relevant to all of health care.

In textbooks as on the internet, epidemiology is loosely defined by sentences such as “the study of the distribution of health-related states and events in specified populations”. Both in writing and in spoken word Miettinen has made it eloquently clear that this notion of the nature of epidemiology is inappropriate, and therefore impairing progress. According to him, the goal of any field of research must be defined in terms of its object of inquiry. From here Miettinen went on to define the object of inquiry of epidemiology as the relationship between the occurrence of a phenomenon relevant to health and the determinants of that occurrence: in short the occurrence relation. It is the purpose of epidemiology to provide a theoretical framework, as Miettinen wrote, for the practice of studying etiognostic, diagnostic and prognostic occurrence relations relevant to all health-related fields.

This framework of “gnosis” meaning knowledge relevant to health allows us to highlight several other fundamental concepts that must be attributed to Miettinen. Traditionally, epidemiologists have been concerned with the question whether the comparison between cases and referents in a 2 × 2 table is distorted by some other factor. This is what is called confounding. Also already in 1976 Miettinen introduced the multivariate confounder score (Am J Epidemiol 1976;104:609–620) as a basis for uni-variate stratification to achieve comparability within strata. At first sight this seems like a nice trick. It isn’t. Generations of researchers are likely to have really understood what confounding means only after reflecting on the theoretical basis of Miettinen’s confounder score. One reason for this is the question how to derive the multivariate function used to calculate the score for each subject. Miettinen emphasised that confounding is a property of the data. Hence, the purpose is to control for it, not to conclude about the relevance of one or more other determinants that may also be confounders. Because of this the confounder score modeller is concerned about the magnitude of the coefficients in the model, not about their statistical significance. Similarly, the modeller is concerned about interaction terms with the indicator of exposure variable in the model. The beauty of the argument is to set the indicator variable of exposure for all subjects to non-exposed before calculating the score. I have really only finally learnt how to think about multivariate modelling after reading Miettinen’s publications on this topic, listening to his teachings, and putting his ideas in practice in my own work.

Another fundamental concept that follows from the occurrence relation as central theme concerns diagnosis. When I was in medical school in the nineteen seventies, disease was either absent or present. If one wasn’t sure, the chance was 50/50. No opinion leader in clinical medicine talked during lectures about the concepts of prior probability of disease, the sensitivity and specificity of diagnostic tests, and about Bayes’ rule for how to obtain the posterior probability when a test result becomes available. Miettinen has extensively written about diagnosis, and is for theoretical reasons critical of ‘Bayesian thinking’ in this context (Stat Med 1994;13:201–209).

Coming to determinants of outcome in clinical medicine, a further seminal idea that Miettinen proposed is the notion of confounding by indication. That treatment is a determinant
of outcome, and that the randomised clinical trial is therefore epidemiology too, follows directly from Miettinen’s thinking about the central role of the occurrence relation in a theory of medicine. What has always been a matter of debate is the question when randomisation is essential. In this context Miettinen introduced in 1983 the distinction between intended and unintended effects of treatment (Stat Med 1983;2:267–271). To illustrate, prevention of stroke by daily aspirin use requires a randomised placebo controlled trial to assess efficacy as this is an intended effect of treatment. When comparing aspirin users with non-users one cannot measure, and thus control for, the intuition of the prescribing physician that in a particular subject aspirin may have the intended effect of preventing a stroke. Stomach bleeding on the other hand is not an intended effect of aspirin use as it relates to its potential toxicity. Hence, Miettinen argues, aspirin as a cause of stomach bleeding may very well be studied by a non-randomised (i.e. non-experimental) study.

The distinction between intended and unintended effects of treatment plays a central role in any discussion about why and when to randomise. Regrettably, Miettinen has otherwise not taken much interest in the scientific basis and in the practice of randomised clinical trials, which he has left (on purpose?) to statisticians who do not seem to pay much attention to the distinction between a risk and a rate, competition between events in what by nature are comparisons between closed cohorts of assigned treatment followed over an often variable arbitrary time interval, etc. Randomised trials are the basis of much of Evidence Based Medicine, which Miettinen has called in his 2011 book a “fallacy” and a “cult”. Because of the uncritical manner in which odds ratios, risk ratios and hazard ratios are treated as somehow essentially similar, and because in meta-analysis relative effects of treatment are often considered constant over the range of absolute risks observed in different trials, he has a point. Characteristically, Miettinen was well known for criticising statisticians by, for example, playing down the p-values and reflect on their careers, their professional influences, and the future of epidemiology. I expanded the list and had the previous 15 years, so I saw it as an opportunity for them, had not had wide exposure to McGill University students in the 20 years after the first one. On the first page Miettinen quotes the following lines written by Francis Bacon in 1597:

Read not to contradict and confute, but to weigh and consider.

Miettinen’s legacy should be weighed and considered in gratitude, and will live on like Leibniz’s calculus does.

Dr. James Hanley writes:

In 2011, the Editor of Epidemiology asked me to interview Olli Miettinen for its Voices project [1, 2]. In Voices, distinguished ‘seniors’ answer a standard list of questions and reflect on their careers, their professional influences, and the future of epidemiology. I expanded the list and had the 2-h interview professionally videotaped [3]. Miettinen had not had wide exposure to McGill University students in the previous 15 years, so I saw it as an opportunity for them, and trainee epidemiologists elsewhere, to see and hear him for themselves. His writings can be difficult to read, and an interview was a chance to help “translate” some of them, and to encourage ‘young people’ (a favourite phrase of his) to consider his ideas. I had often joked to him, that whereas most books are better than the movie, in his case one needed to see the movie first, and not just once, before attempting the book.
Olli was not keen on posthumous ‘tributes’ [4], so I will avoid this format.

I first saw Miettinen at meetings of the Biostatistics Department at the Harvard School of Public Health in the Fall of 1977. He was appointed in both Epidemiology and Biostatistics. Fred Mosteller had just taken over as Chair, and had managed to attract Marvin Zelen, who brought with him a number of younger faculty members. Together, they sought to modernize the department’s doctoral program. Miettinen felt it was necessary to first precisely define biostatistics and its mission, but Mosteller and Zelen pressed on. We had already learned that he did not take kindly to being challenged. He had clashed with one of the newly arrived junior faculty members who, as an examiner in the doctoral defense of one of Miettinen’s students, had insisted on seeing numerical results that Miettinen had told the student not to include in the dissertation.

I moved to a department of “Epidemiology and Health” in the faculty of medicine at McGill in 1980. In 1984, the incoming department chair had the name changed to “Epidemiology and Biostatistics” to recognize the largest concentration of biostatisticians in such a department in Canada. These included Samy Suissa, who would help put McGill on the map for pharmaco-epidemiology; Duncan Thomas, who was the first to link the conditional logistic regression likelihood in what is now called a ‘nested case–control study’ with the likelihood in Cox’s proportional hazards model, and helped expand on the estimation of the incidence-density-ratio introduced by Miettinen in 1976 [5]; and the late Sholom Wacholder, who is still fondly remembered for his short compass in pharmaco-epidemiology; Duncan Thomas, who wrote like the Oracle of Delphi but who seemed to be one that has always stuck with Duncan: “because people believe it!”.

Even before assuming his post, the chairman was working on getting Miettinen to leave Harvard for McGill. He was keen to add lustre and breadth to McGill’s training and research programs, including in pharmaco-epidemiology methods: Miettinen had been a consultant to the Boston Collaborative Drug Surveillance Program since 1970; in the interview [3] he speaks highly of one of its founders Hershel Jick [10].

When some faculty members suggested McGill might do better hiring two younger persons for the same price, the incoming chair admonished them: “I am disappointed in your attitudes. Every great university needs to have at least one Professor whose job is to sit in a room and look out the window and think big thoughts.”

At one of the recruitment visits, the chair was busy one evening, and asked Samy Suissa and his wife to take Miettinen out to dinner. Afterwards Samy showed him the city and they “stopped at midnight at St-Viateur Bagel (the real ones, not what they make in Boston!) where he was greeted by the bagelman as “Professor”. He not only had the CV, but certainly also the aura. He was delighted and loved the bagels.”

I vividly remember Miettinen’s inaugural lecture at McGill, where his topic was the valid selection of subjects in the “case–control” study. [Whenever he was forced to refer to that term, he put it in quotes, or disdainfully referred to it as the ‘so-called’ case–control study]. He had everyone rolling in the aisles with his rendition of the type of case–control study the textbooks of the time would have us use to test the hypothesis that a cause of traveller’s diarrhea is the consumption of tequila [11]. I remember how proud the chair and the dean were of their raid on Harvard.

During his recruitment, Miettinen had been promised that a “McGill Centre for Advanced Studies.” would be established and fashioned as he developed it to be one in the “Theory and Practice of Medicine”, and that he would become its scientific director. It never came to fruition, and that was a major disappointment for him.

His courses were attended (repeatedly) by a small group of students who found his teaching compelling (e.g., Jaime Caro, KS Joseph, Lucie Blais, Brenda Hemmelgarn and Igor Karp, among others), and Miettinen was very gratified to have been selected ‘Teacher of the Year’ for two consecutive years. He also turned to his academic contacts in Europe, where he was better received than in his adopted hometown [12].

He prided himself on his uncompromising principles and high standards, and on challenging the paradigms and the orthodoxies. This style, however, did alienate some people. I asked him many times to simplify his writing style, but he dismissed my suggestions. I believe that this attitude, which I again asked him to address in the interview, cost him a large number of readers.

For his doctoral training and his first two decades as a professor, his academic base was a school of public health. His base in McGill was in a faculty of medicine, and so he naturally turned to the concepts and principles involved in the practice of medicine. He felt that Medicine was a practice without underlying theory and he wanted to fill that...
void. His many published pieces on these topics became the basis of three books [2010, 2014, 2015].

He insisted on distinguishing the two meanings of ‘epidemiology’: the practice of epidemiology (community medicine) and epidemiological research. He also continued his interest in the latter and, again in his last decade, published his final understandings of the concepts and principles in two books [2011, 2012].

Even now, as I write this, I am conscious of how adamant Olli was about the accurate use and meaning of terms and words. A month before he died, I expect he took issue with the statement that announced the award of the Nobel Prize in economics: “natural experiments help answer important questions for society.” I was also reminded of Hofman’s telling of Dimitri Trichopoulos’s response concerning the use of this term in the title of a classic paper on the Athens earthquake. Hofman told Trichopoulos that Miettinen emphatically told his students that there was no such thing as “natural experiments,” which he called a contradiction in terms and utter nonsense. Trichopoulos replied that “as a lifelong epidemiologist, it is important to be principled but not dogmatic.” [13] [One colleague of mine, known for his one-liners, used to deflect Miettinen by saying “I’m not anti-semantic.”].

When Samy Suissa first gave his talk on immortal time bias in our department in the early 2000s, Miettinen came up to him afterwards and said: “Professor Suissa, time is not immortal, people are!” Samy replied that this is indeed true, but the term is intended to be simply a catchy label, instead of the more awkward ‘person-time-during-which-there-is-no-death bias.’

In his final book [2019], he addressed patient-oriented clinical research, where the goal is to produce the knowledge bases for dia-, etio- and pro-gnosis. For each of these three missions he provides his understanding of the essence and the core concepts, and distinguishes the traditional ‘methods’ design from the usually-ignored ‘objects’ design. Indeed, despite his life-long efforts to draw attention to this latter element, he lamented that it was still “not even in the common vocabulary of epidemiological research.” [2012, Chapter 7].

His 2001 article [14] drawing attention to the delayed mortality deficits produced by cancer screening was an important intervention. [Just like his still-poorly-understood formula for population attributable fraction [15], it was “obvious” to him, but for others only in retrospect]. If the benefits of cancer screening are to be properly measured, the delay-principle must be heeded [16, 17].

Miettinen strongly opposed the randomized trials of low-dose CT screening for lung cancer. When the results arrived, the large mortality reductions he and colleagues expected had not materialized: the actual reductions ended up being much more modest.

The interval between his being diagnosed with cancer and dying from it was mercifully short, but it made the news of his death all the more of a shock, especially for those who had seen how vigorous he had been. Given his larger than life aura, a young collaborator of his remarked to me that, “somehow I even thought he might outlive all of us.”

When asked in the 2011 interview [3] which of his contributions to the field he would most like to be remembered for, he told me he was not one of those people “who think about how they are thought of posthumously.”, Instead, “I am here and now, and I don’t care what is thought or said afterwards.” But, “if there is any attention to the man when he is gone,” his wish was that it focus on his recent books. “These books represent a synopsis of the understandings that I have come to, through concentrated efforts over 5 decades, as for what ultimately matters, namely the elementary.”

My last contact with him was in 2018, when he asked me for the URL for the casebase package[18] in R, which implemented the sampling scheme set out in our 2008 paper [19]. He cited the package in Chapter 19 of his book, ‘Clinical Research Transformed.’ He also asked me to provide an endorsement that Springer might use for that last book. Although Springer did not end up using it, he was happy with the ‘pithy’ blurb I supplied.

This book presents well-thought-out precepts for establishing the probabilities doctors should ‘know.’ The emphasis is on first principles, relevance, and the unifying role of logistic regression functions. It makes a strong case, and supplies clear principles, for improving clinical research. Readers new to the unique writing style in it will find the journey through it arduous but the destination worthwhile.

To him, it represented his best thinking and understanding, and he considered it his ‘magnum opus.’ It completed the lifelong mission that began “as a medical student in Helsinki, where, around 1960, I was involved in cardiological research. I was headed for an academic career in cardiology, but became uncomfortable with the lack of any theoretical framework for the research” [20].

Just as he did through his life, the end of the video, Miettinen specifically addressed ‘young people.’ To appreciate his earlier theoretical developments, they might consult his written [2, 20] and oral [3] accounts, or Greenland’s annotated collection [21], or Rothman’s commentary [22]. For a sense of his more recent work, they might wish to dip into Miettinen’s mini-dictionary of epidemiologic concepts and terms: since definitions don’t need full or long sentences, the dictionary format is more concise and easier to follow. And for a sense of his final book, prospective readers might wish to sample Chapter 19 (Example: Research on ‘Hormone Replacement Therapy’). In it, he also uses a hand-worked example to illustrate the casebase approach. His fervent
hope, strongly expressed in the interview, was that today's
students will finally leave behind the separate 'cohort' and
'case–control' terminology of 60 years ago, and instead
adopt the unifying concept of the etiologic study [23].

My own hope is that those young people listen to him,
and be inspired to continue his mission.

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