OBITUARY
Lodewijk A. Sandkuijl, M.D. (July 31, 1953–December 4, 2002)

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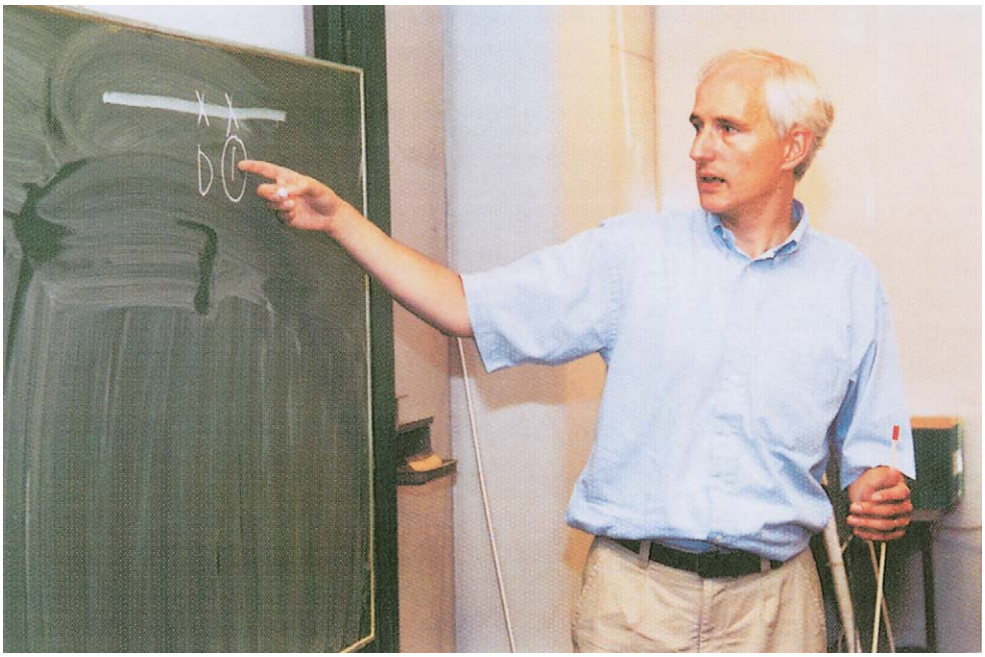

In Memoriam: Lodewijk A. Sandkuijl, M.D. (July 31, 1953–December 4, 2002)

We are sad to report that Lodewijk Sandkuijl died suddenly on December 4, 2002, after a very brief illness, leaving a huge hole in statistical genetics, genetic epidemiology, and the genetic investigation of complex diseases. He was a collaborator, consultant, and guide to more than 20 research groups throughout Europe and North America. He also played a key role in setting up databases for registration of DNA samples and diagnostics in the Netherlands.

Lodewijk was the son of a general practitioner, and, although his first love was mathematics, he trained as a physician at Leiden University. Although he had little liking for the highly structured world of medicine, he formed a clinical intuition that profoundly influenced his approach to research. He became a clinical geneticist, and, early in his career, he became interested in the use of DNA markers for prenatal diagnosis and carrier detection. He contributed to one of the first studies applying DNA markers to the diagnosis of Duchenne muscular dystrophy (Bakker et al. 1985). His interest in statistical genetics grew out of his efforts to solve the problem of calculating genetic risks for mapped Mendelian disorders, using the sparse genetic marker data then available. This interest led him, in the late 1980s, to pursue postdoctoral training with Jurg Ott at Columbia University. While at Columbia, he began to assemble the extraordinarily large collection of collaborators that he maintained for most of his career; this group does not include the numerous investigators, students, and companies for whom he provided consultation. Indeed, as a fellow he showed his brilliance as a consultant; he could rapidly pick out the essence of a project, had extraordinary intuition about how to proceed, and could communicate this intuition in clear terms that gave a road map for molecular geneticists and clinical investigators alike.

Because he had so many collaborators, Lodewijk was able, after his fellowship, to set up a life that many envied. He became an independently employed consultant, working from his home, in an attic room jammed with boxes holding the files of his many projects and with several computers, one of which was continuously

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running linkage analyses. It looked chaotic, but it was completely systematic, and he could find any of his meticulous notes in minutes. Some of these projects belonged to separate research groups working on the same problem, often in intense competition with each other. Yet such was Lodewijk's integrity and discretion that none of his collaborators minded this arrangement. Students and collaborators came from all over the world to spend long days in this attic, overlooking a canal in the old city of Delft. These days invariably ended over a beer in a nearby café. His hospitality to students was invariable and remarkable. He was an excellent teacher and organized well-attended courses throughout the world. He was especially committed to the genetic epidemiology program at Erasmus University, Rotterdam, and to the linkage courses organized by Jurg Ott. Teaching alongside him was a great deal of fun and always included several good dinners with excellent wine.

Students come to the field of human genetics with great excitement and enthusiasm but also with naiveté. Lodewijk's great ability was that he could encourage enthusiasm in students and colleagues while at the same time injecting caution. He revealed to all of us who worked with him the many pitfalls that one can blunder into with linkage and association analyses. His teaching did not focus on complicated formulae, with which he himself was not terribly comfortable. Rather, he dissected the problems to be analyzed to clarify what exactly was being tested, step by step showing why particular choices were made.

He served as an ideal sparring partner for new ideas and would challenge them. This was not just passing time; weeks later he often came back to the topic with new arguments to continue the discussion. This was typical for Lodewijk in that he was always ready to help and to spend time to resolve problems that might be simple for him but that were a big hurdle to students and collaborators alike. The most important thing that he tried to convey was to plan the experiment with future analysis in mind and to design "what if" scenarios in case the outcomes were not what was initially expected. He was acutely aware of the strengths and limitations of the experimental design used for each project. When results needed to be analyzed, he was there as well, studying results with meticulous care and showing attention to all details.

His collaborators came to know him as a continuous source of new ideas. These ideas did not form from quantitative theory; rather, they came from data, from his experience poring over the results of the numerous mapping studies for which he was performing the analysis. Therefore, his ideas never had to search far to find an application. He contributed to the successful mapping of at least 30 Mendelian disorders. As an example, he was instrumental in identification of the facioscapulohumeral muscular dystrophy (FSHD) mutation. Identifying this mutation depended on Lodewijk's statistical analysis showing that an unusual distribution of bands on a Southern blot represented de novo deletion fragments in a number of patients with sporadic FSHD (Wijmenga et al. 1992). He had a long-standing interest in identifying modifier genes for a wide range of disorders. He was an early leader in efforts to map complex disorders, focusing in particular on bipolar disorder, schizophrenia, diabetes mellitus (types I and II), multiple sclerosis, and migraine. Lodewijk was the linchpin for the International Genetics Consortium for Tourette Syndrome (TS). Mapping studies of TS were fragmented, and little progress was made. Lodewijk then spearheaded the development of an affected sib-pair study of this disorder, bringing together the efforts of several research groups from North America and northern Europe. The analysis of this sib-pair data set identified promising candidate regions for TS and showed the utility of such a consortium for mapping complex traits (TSAICG 1999).

The incredible web of connections that tied Lodewijk to so many scientists is illustrated by the following anecdote. Lodewijk had been discussing with one of us (N.F.) the possibility of mapping complex traits in population isolates using genomewide linkage disequilibrium (LD) analysis. We agreed that it was first necessary to test this idea on a simple trait. During the party following the thesis defense of another of us (C.W.), Lodewijk came in contact with a clinician who had collected a sample of three remotely related patients with a rare liver disease who were from an isolated Dutch fishing village. Lodewijk had the idea that this disease could be mapped by searching for genome segments shared by the patients in a genome screen. The strategy proved successful (Houwen et al. 1994), and this simple demonstration of the power of haplotype-based mapping was one of Lodewijk's biggest achievements and contributed to the current widespread interest in using such approaches to map complex traits. Indeed, he played a major role in the design of some of the first genomewide LD studies of such traits (Ophoff et al. 2002; Vassen et al. 2002).

The downside of being a consultant was that he had no students of his own and was at the beck and call of his many collaborators. As a one-man operation he couldn't possibly keep up with their expectations, particularly as he found it hard to say "no" to any interesting problem or to any investigator who was clearly in need of his help. Furthermore, he was a perfectionist, and this sometimes made it impossible for him to finish things. His perfectionism is probably one of the reasons he did not publish as much as he could have done. He was not easily satisfied with an answer. He also always tried multiple possibilities just to make sure that he did not do anything wrong. His biggest worry was to publish something that turned out to be scientifically incorrect.

He was not interested in the quick publication of "hot" results that too often occurs in human genetics. Instead, he would not agree to submit manuscripts until he was completely satisfied that he could vouch for the results, down to the smallest detail. Sometimes this characteristic would make all of us jump up and down impatiently; indeed, his many collaborators often shared with each other their frustration at his slow pace in completing analyses and editing manuscripts. But, in retrospect, most of us have never regretted that we waited for him to complete work to his satisfaction. In this respect, he served as our "conscience" in conducting studies and reporting their results. Although he was slow in completing many projects, he was adept at thinking on his feet and took great pride in his ability to program quickly. One of us (N.F.) remembers a site visit for a major grant, during which he demonstrated this ability. Toward the end of the first day of the site visit, the reviewers had expressed doubts about whether a particular experimental strategy would work. Overnight, he programmed and ran simulation analyses that perfectly addressed their concerns. He presented the results in such a confident way that it seemed as though he had anticipated and solved this problem weeks in advance.

Because he was a consultant, rather than a group leader, he was usually in the middle of authorship lists. In his case, the authorship position does not reflect the importance of his contribution to most of these papers but does reflect the fact that he was unconcerned about his curriculum vitae (although he did take satisfaction at the high citation rate of so many of his publications). He also was not interested in academic titles or honors. His lack of self-promotion meant that he did not always get the credit that he deserved. A striking example is the fact that, having done so much teaching, he never obtained a Ph.D. himself. His identity was not dependent on a degree, and he did not need the degree because people respected him for who he was and what he did.

After a few years of "freelancing," Lodewijk took appointments as a consultant at four Dutch medical schools (Leiden, Rotterdam, Groningen, and Utrecht), since, by this time, he was involved in virtually all human genetics projects in the Netherlands. He cut down, but only a little, on his overseas commitments. Then, in May 2001, he made a major change, taking a "real job," as associate professor in the Department of Medical Statistics at Leiden. The computers were moved out of his attic. He scaled back his consulting. Much to the surprise of his friends and collaborators, he loved his new job and didn't seem to miss his former freedom. He was very much looking forward to having students and postdoctoral fellows of his own, after having participated in the training of at least 30 Ph.D. students in the Netherlands. Even more to our surprise, he began to write grants and enjoyed this, too. At the time of his death, he was just beginning to recruit students and postdocs to a huge project for which he was the statistical coordinator, a pan-European twin-pair study funded by the European Union that would require him to analyze >15 million genotypes.

He was devoted to his family: his wife, an elementary school teacher; his teenage daughter; and his mother, who herself earned a Ph.D. in her 70s, a fact of which he was exceptionally proud. He had passionate interests outside of science, including cooking, music of all kinds, and extended road trips on every continent. He was a gracious host and, above all, enjoyed socializing with friends, family, and colleagues. He always made time for asking about the personal lives and well-being of the people he worked with, and he could be counted on for a few new jokes with each meeting. He remained very involved in the development of the careers of his former students. He amazed speakers of American English with his command of their idioms and slang. How and where did he pick these up?

With his death, we have lost a trusted friend with whom we could share both ups and downs. It is striking how much his close collaborators trusted him; as we have shared our reminiscences, we each noted that, for 15 years, we asked his advice on most important decisions about our work, whether he was involved in the work or not. It is hard to believe that he is no longer there to be consulted. In fact, the best remembrance we can give him is for us to continue to ask ourselves, when confronted with a difficult scientific decision, "What would Lodewijk advise me to do?" We suspect that many of his collaborators will continue to employ him as a consultant for many years to come.

Acknowledgments

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