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OBITUARY

Lymphoma 'type K.'—in memory of Karl Lennert (1921–2012)

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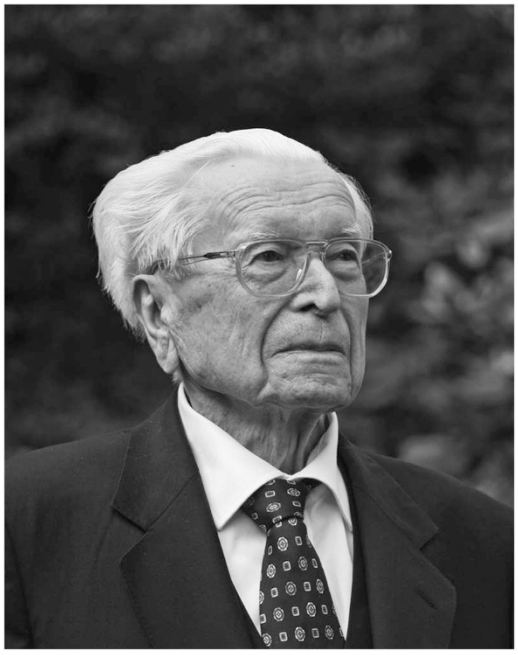

Prof. Dr. med. Dr. h. c. mult. Karl Lennert (1921 – 2012)

On 27 August 2012, Karl Lennert, emeritus Professor of Pathology at the Christian-Albrechts-University of Kiel and one of the most influential und sustainable pioneers in the field of malignant lymphoma biology and classification, died at the age of 91 (photograph above).

Back in 1942, while as medical student attending a course of haematology, he developed his interest in microscopical morphology—and started his first collection of slides, which he retained throughout his life. During his training and postdoctoral stages in Erlangen, Göttingen, Frankfurt and Heidelberg he increasingly focused his interest in haematopathology based on a broad patho- morphologic background. Having been appointed as Full Professor and Chair of Pathology and Head of the Department of Pathology at the Kiel University in 1963, Lennert founded the first German Reference Center for the diagnosis of lymphatic diseases following the example of the Armed Forces Institute of Pathology in the United States.[1] The 'Lymph Node Registry Kiel' was a success story, not only as the birthplace of the Kiel classification,[2] the first lymphoma classification that incorporated immunological findings, but also as the starting point for the careers of a whole generation of scientists who have influenced this field of pathology for decades and continue to do so. The European Lymphoma Club that Lennert initiated gave rise to the European Association of Haematopathology.

Instead of continuing here with naming all of Lennert's outstanding scientific achievements or with listing all the awards and honorary doctorates he received, we would like to give a rather 'private' insight into an unpublished research (hi)story, which documents Lennert's pre-eminent ability to structure his daily observations and to pull them together into a biology-based classificiation. In addition to establishing the archives of the Lymph Node Registry, Lennert began early on to sort a subset of microscopic slides into his 'personal archives'. He placed the stained histological slides in paper envelopes on which he wrote the clinical features of the patient and the follow-up information. As soon as new findings became available, Lennert revised his former diagnoses and indicated the revisions on the paper envelopes and even arranged the cases in new categories within the drawers in which he had placed the envelopes. Thus, his personal archives represented the 'extracts' of most informative cases and a 'tool box' for his research, focusing primarily on the identification and definition (classification) of lymphoma entities.

A remarkable example of this way of structuring is a series of lymphomas starting with a lymph-node biopsy from a 63-year-old male patient (named 'K.') that was resected in 1968. The lymph node showed a small cell infiltrate replacing the entire lymph node architecture. Lennert diagnosed an 'unusual immature lymphatic neoplasia'. In 1971, he analyzed a second biopsy specimen from this patient and another 1 year later in 1972, just before the patient died of the disease, as noted in Lennert's handwriting. Lennert changed the diagnosis several times, named the disease 'small cell lymphosarcoma' and finally classified it as a 'germinocytoma'. In the Kiel classification this latter name was changed to the term 'centrocytic lymphoma'. This renaming can be observed on the paper envelopes containing the case (Figure 1). Interestingly, several lymphomas diagnosed in 1972 and 1973 were placed on the same shelf adjacent to the specimens from the patient 'K.' and labeled by Lennert as 'type K.'. This observation indicates that Lennert had identified the case 'K.' as a prototype of a lymphoma to which he assigned lymphomas with similar features under the working term 'lymphoma type K.' (Figure 2). All the above-mentioned cases were identified within a part of the archives that Lennert reorganized at some time after 1974 following the concepts of the Kiel classification. The case 'K.' is the earliest biopsy specimen in the subcategory that he labeled as 'centrocytic lymphoma'. Thus, patient 'K.'s lymphoma must have been the starting point from which Lennert generated the concept of 'centrocytic' lymphoma.

Although Lennert's observations were based primarily on his outstanding talent as a morphologist, he realized that the definition and acceptance of disease entities require additional efforts. Already in the 1970s he stimulated his disciples to apply immunological methods,[3] inspired his ordinarius colleague W. Grote from the Institute of Human Genetics to perform (cyto)genetic analyses of lymphomas and started a clinical research group, the Kiel Lymphoma Study Group, to collect data on the clinical outcome.[4] How visionary the implementation of novel techniques and clinical data was can nowadays be judged again in case 'K'. Taking into account clinical, immunophenotypic and genetic data, in the early 1990s,[5,6] almost 20 years after the observation of case 'K.' by Lennert, consensus criteria for the lymphoma represented by this were defined under the new and commonly accepted name of the disease, mantle cell lymphoma

(MCL). The identification and cloning of the translocation t(11;14)[7] proved to be a milestone in the definition of the disease[8] and detection of aberrant cyclin D1 expression caused by the translocation by immunohistochemistry is nowadays standard in the diagnosis of MCL according to the WHO classification. Thanks to the establishment of the Lymph Node Registry by Lennert it is after 50 years still possible to retrieve a paraffin block from patient 'K.' from the files and to analyze this historical material by immunohistochemical and fluorescence *in situ* hybridization techniques that were not available at the time when Lennert did his analysis. And indeed, modern molecular means reveal the typical immunophenotype of MCL with cyclin D1 expression and an underlying t(11;14) confirming that Lennert's lymphoma 'type K.' was MCL with 'case K.' being the proto-type (Figure 2).

Until his very end, Karl Lennert was strongly interested in novel insights in lymphoma biology derived from the application of new molecular techniques. In particular, in times of rapidly developing high-throughput techniques, he continuously reminded us how important a careful morphological analysis still is to make to scientific progress. Indeed, case 'K.' exemplifies how all steps in the discovery of a disease from morphological observation of a single case over a case series up to development of a biological concept of the cell of origin ('centrocytic lymphoma') can be made simply by use of a light microscope.

Finally, we should not forget that Lennert has been involved in a long-lasting scientific controversy about lymphoma classification that preceded the internationally accepted REAL and WHO classification and again case 'K.' makes also reference to this trans-atlantic dispute. Until the 1990 s, the Kiel classification developed by Lennert and his team[2] was used in Europe and Asia, whereas in the United States the Working Formulation [9] largely replaced the Rappaport classification.[10] Moreover, some centers continued to use the Lukes-Collins classification.[11] The different disease definitions in the competing classification schemes made it difficult to compare pathological and clinical results. The paper envelope in which case 'K.' is stored in Lennert's archives includes the brief note 'Chicago' (Figure 1). In Chicago, in June 1973, Lennert demonstrated lymphoma cases at a meeting and the case 'K.' was obviously part of this tutorial. This meeting was the first at which he presented the principles of the Kiel classification to American and European lymphoma experts. The intention of the Chicago meeting was to find a consensus classification for lymphomas on behalf of the WHO. However, it was to take decades and a new generation of pathologists before in 2001 a worldwide consensus WHO classification was published which finally in many aspects followed Lennert's ideas.[12]

Lennert's friends and former fellow workers always mention the discipline he demanded of all, but first of all of himself. They remember him as a person who could inspire and enthrall people. A charismatic and warm personality. A consummate host. A talented pianist. Above all, however, a medical scientist of the highest ethos based on a strong Christian faith. Until his death Karl Lennert avidly followed the new developments in research and in the faculty of medicine. It is with deepest gratitude that physicians

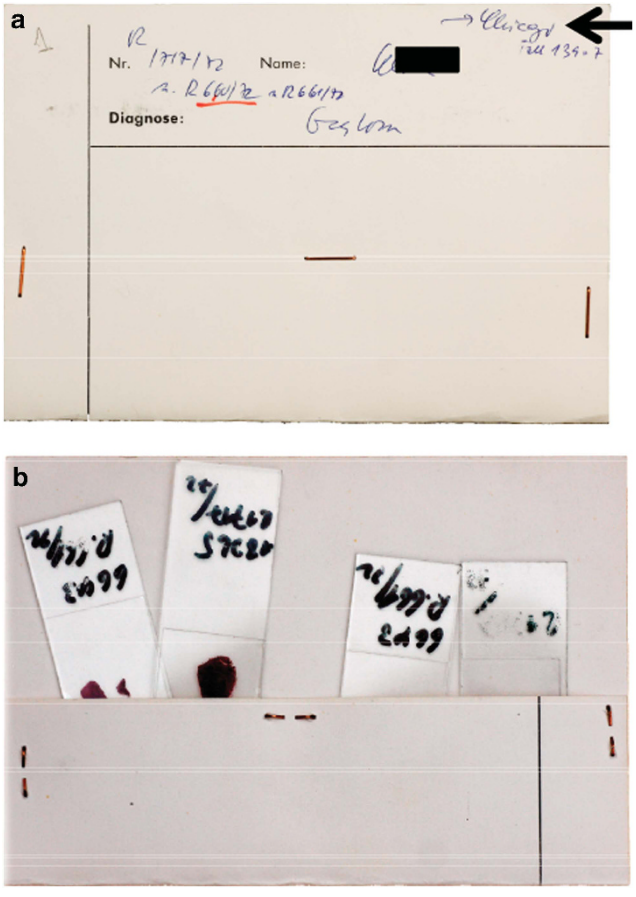

Figure 1. Paper envelope of the case 'K' from Karl Lennerts personal archive in front view (**a**) with the note 'Chicago' (arrow) indicating that the case was shown on a tutorial in Chicago 1973. The back view of a paper envelope showing the storage of stained slides in the archive (**b**).

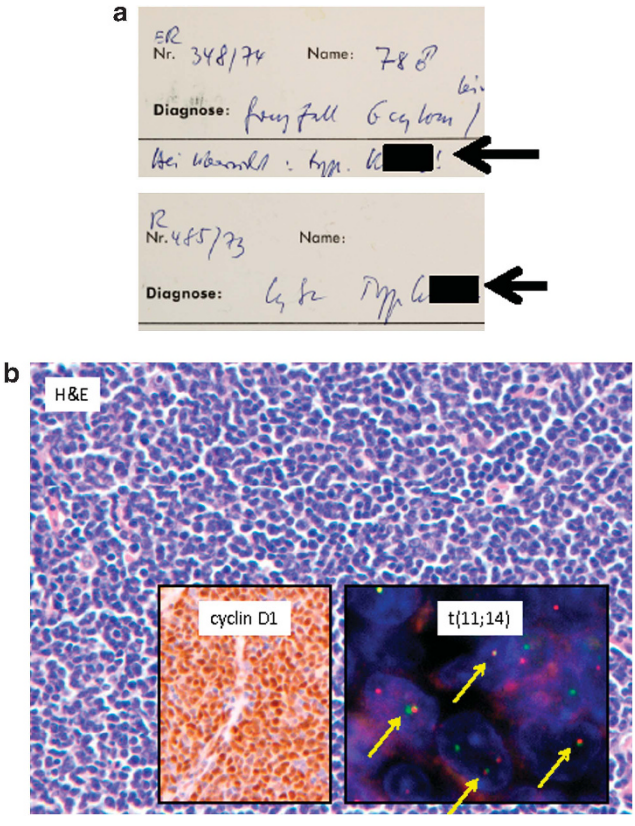

Figure 2. (**a**) Details of further paper envelopes adjacent to the case 'K' in the archive with biopsies from different patients labeled 'type K' (**b**, arrows) indicating that the case 'K' was the starting point of the concept for a lymphoma entity by Lennert. (**b**) Histology of the case 'K' shows a typical mantle cell lymphoma stained for hematoxin and eosin (H&E) with detection of t(11;14) by fluorescence *in situ* hybridisation using a fusion assay (Abbott, Abbott Park, Illinois, U.S.A.) and expression of cyclin D1 (inserts).

and scientists all over the world pay their respects to this great personality.

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