

## **Chapter 2**

### **Dietrich W. Lübbers**

#### **Celebration of a Life Dedicated to Research into Oxygen Transport to Tissue**

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Dietrich Werner Lübbers: 1917–2005.

### **2.1 Biography**

It was with great sadness that members of the International Society on Oxygen Transport to Tissue heard of the death on 15th November 2005 of Dietrich Werner Lübbers, one of its most distinguished and long-standing members.

He was born on 12th May 1917 in the Harburg district of Hamburg. He attended the Landesschule Pforta, a celebrated German public boarding school

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near Naumburg on the Saale river, where he completed his “Abitur” (the school qualification for entry to university) in 1935. He completed his 6 months compulsory labour service before being called up for compulsory military service.

As early as his last years at high school, and throughout his medical course, he developed the ambition to pursue a career in scientific research applied to medicine. From 1937 to 1939 he studied medicine at the University of Heidelberg (5 semesters). However, in order to gain a basic scientific education that had been missing from the curriculum at school, in addition to his medical course, he studied chemistry for 4 semesters. At the outbreak of the second world war he was conscripted for active service, but was able to continue his study of medicine, but not chemistry (with interruptions for active service) in Halle, Leipzig and Berlin.

Dietrich’s scientific career began in 1941 with the research project for his medical dissertation in the Institute of Physiology at the University of Berlin under Professor Kurt Kramer. Kramer had demonstrated that near infrared light penetrated deep into tissue so that spectral changes could be detected from the outside. Dietrich’s project was to investigate the oxygen supply in the frog heart and, to this end, using haemoglobin as the indicator, applied near infrared spectroscopy to measure oxygen. The first problem he encountered was that the frequency response of the existing manometers was too low to measure the pulsatile pressure. In order to overcome this problem he began the first of his technical developments. Together with Professor Gerlach of the Institute of Physics, University of Berlin, he built a glass plate manometer, which used the capacitance principle, and this enabled him to successfully complete his dissertation in 1944. His thesis “A method for measurement of the O<sub>2</sub> consumption and dynamics of the isolated cold blooded animal heart” clearly set the theme for much of his future research. In the meantime he had passed his final medical examinations in 1943 and was working in the army medical corps.

In December 1944 he found himself a prisoner of war in France where, from time to time, he acted as the camp doctor. He was not released until June 1948. From 1948 to 1950 he held a clinical post at the Borstel Tuberculosis Research Institute near Hamburg

On the basis of the experimental experience gained during his Dr.med. studies he was awarded a post with Professor Erich Opitz in Kiel in 1950. Opitz’s field of research was the exchange processes between oxygen in capillary blood and mitochondria. Dietrich’s research project was to investigate the time course of the oxygen supply and oxygen consumption in the beating mammalian heart. Since his study would involve measurements of the oxygenation of haemoglobin, myoglobin and the redox state of cytochromes, he decided on a spectrophotometric approach to the problem. However, this could clearly only be achieved with a very fast measuring instrument that scanned a wide range of wavelengths, and multi-component analysis of the absorption spectra. After intensive discussions with Dr Köhler, a physicist, he set about with Walter Niesel to develop the so-called short-time spectral analyser, which was completed in 1957. This was further developed by the Howaldtswerke in Kiel as the “Rapidspektroskop” (see below). He completed his Habilitation whilst at Kiel

and in 1956/57 was the guest of Briton Chance at The Johnson Foundation, University of Pennsylvania, where they were investigating the redox state of cytochrome c using spectrophotometry. At Kiel, Dietrich also started other research in the field of electrodes and blood gas measurement (see below).

From 1959 to 1961 he was a supernumerary assistant professor, at the Institute of Physiology, University of Cologne where the Director was Max Schneider.

In 1961 he was appointed to a Personal Chair at the Institute for Applied Physiology and Occupational Physiology, University of Marburg and in 1965 was appointed Professor of Applied Physiology and Director of the Institute in Marburg after turning down a chair in Hanover. In Marburg Dietrich continued his development of oxygen electrodes and, together with Albert and Renate Huch, started to develop the concept of the transcutaneous  $pO_2$  for monitoring neonates. Horst Baumgärtl joined Dietrich in Marburg and together they went on to build the multiwire surface  $pO_2$  electrode and the finest of needle electrodes for quantitative measurements of  $pO_2$  in tissue. Manfred Kessler completed his Habilitation with Dietrich in Marburg.

In 1968 he was appointed Director of the Max Planck Institute for Occupational Physiology in Dortmund. In 1973 the Institute was renamed the Max Planck Institute for Systems Physiology reflecting Dietrich's approach to the investigation of biological systems. The renaming of the Institute caused great local controversy as the original institute was seen as one that carried out scientific research for the benefit of the ordinary worker. Dietrich had to weather a fierce barrage of criticism in the local press [1]. This was quite unfair as he had been instrumental, along with the state of North Rhein Westphalia, for the founding of an Institute for Occupational Physiology at the University of Dortmund, and of which he was the acting Director initially [2]. In 1985 he "Retired" and became Emeritus director of the Institute, which moved to a new building and was renamed the Institute for Molecular Physiology in 1994. Dietrich retained a laboratory in the Institute until 2003.

Amongst those who went with Dietrich to Dortmund were Manfred Kessler and Horst Baumgärtl. There, of course, with scientists such as Elfriede Leninger-Follert, Helmut Acker, Wolfgang Grünewald, Renate Huch, Sebastian Schuchhardt and Reinhard Wodick – to mention but a few – his institute was enormously productive and unravelled many of the mysteries of local regulation of oxygen supply to tissue.

It was in 1977 that I first met Dietrich – and not through oxygen. My PhD project was the development of a pH electrode for use in human skin and he had organized a symposium on the Theory and Application of Ion-Selective Electrodes in Physiology and Medicine at the Dortmund Institute. That was the first time, too, that I met my good friend and colleague, the late Jens Höper and of course Manfred Kessler whom I worked for in Erlangen from 1981 to 1990. I had, of course, come to know of Dietrich's work as soon as I started my project in 1974. My colleague, Vance Spence had started two years earlier on a project to develop a skin  $pO_2$  electrode and had been the guest of Dietrich who introduced

Vance to the art of making needle electrodes. Enough of my biography. Suffice it to say that it was at this time that Dietrich's philosophy of the systems approach to physiology had a huge influence on me and has remained with me throughout my scientific career.

## 2.2 The Inventions

"The biological problem was always the basic drive for him. If it turned out that the known methods were not good enough to enable him to solve it, he undertook the laborious task of developing the necessary tools himself", Gerhard Thews [3].

Below is the ranking Dietrich himself put to his inventions when he was awarded the Diesel Gold Medal in 1997 of the German Institute for Inventions[4]:

- Photometry at the surfaces of scattering media such as on live organs (6 Patents)
- Blood gas analysis (electrochemical sensors) (3 Patents)
- $pO_2$  and  $pCO_2$  measurements in situ (6 Patents)
- Optical sensors with absorbent and fluorescent optical indicators (optodes) (22 Patents).

As mentioned earlier, by 1957 Dietrich Lübbers, along with Walter Niesel, had built their first fast spectrophotometer in the Institute workshop in Kiel. In collaboration with the Instrumentation Department of the Hohwaldtwerke shipyard the spectrometer was further developed and marketed as the T 13/3 Rapspektroskop [5]. This instrument could record 100 spectra (25,000 measurements) per second, and was the fastest commercially available instrument of its kind in 1964. It was a dual beam spectrometer which relied, of course, at that time on analogue electronics. Depending on the diffraction grating used, it had a wavelength range of 230–600 nm or 350–700 nm. Use of the full spectral range allowed the use of multicomponent analysis to deconvolute the spectra of individual pigments such as oxy- and deoxyhaemoglobin, myoglobin and cytochromes. This was further facilitated after he moved to Dortmund by the rapid evolution of the digital computer and software for the evaluation of the spectra which was developed by Hoffmann. By now the spectrophotometer and dedicated computer hardware was so large that for clinical research, the patients had to go to the laboratory at Max Planck Institute for the measurements. In order to get round this, together with Wodick and Pieroth, he developed a "portable" lightguide spectrophotometer that later was marketed by Sigma as the Oxyscan (see, for example, Merschbrock et al. [6]).

The aim of Dietrich Lübbers' research was to understand the entire pathway and regulation of oxygen transport from the blood into the mitochondria. To do this he needed to be able to measure the  $pO_2$  in the tissue itself. Until the late 1950s polarographic measurements in tissue were fraught with difficulties and interferences. However, the invention of the fully integrated  $pO_2$  electrode by

Leland Clark [7] changed all that and opened up a whole new realm of inventiveness for Dietrich. One of the earliest electrodes Dietrich developed was for *in vitro* measurements. However, his development of electrodes was not limited to oxygen. His team also constructed pH and  $p\text{CO}_2$  electrodes so that they could carry out blood gas analysis during their physiological experiments. Later on he developed electrodes for other ions. As a result of these developments, the company Eschweiler, also based in Kiel, produced one of the first blood gas analysers to appear on the market – the Combi-Analyser U in 1961. Its successor is available nowadays as the Combi Line.

After his move to Marburg, together with Horst Baumgärtl and Manfred Kessler, Dietrich continued to develop electrodes for measurements in tissue. The multiwire surface electrode (MDO) was one of the trusty tools of the physiological investigation of oxygen transport to tissue. He also applied the polarographic principal to the measurement of blood flow using hydrogen clearance – a technique that I also became very involved in during the 1980s. The advantages of the MDO were that it was non-invasive and had a high resolution: 98% catchment depth of each wire approx. 60  $\mu\text{m}$ . The random distribution of its 8 wires meant that 13 small rotations of the electrode gave a statistical distribution of  $p\text{O}_2$  consisting of more than 100 values – a process that took only 3 or 4 minutes. Assessment of  $p\text{O}_2$  histograms on most organs, revealed a remarkable similarity under physiological conditions: a Gaussian distribution always with less than 5% of values less than 5mmHg. The histogram brought life to the Krogh model of oxygen supply from the capillaries to the tissue and demonstrated that, again under physiological conditions, a highly efficient regulation of blood flow prevents anoxia occurring in the so-called lethal corner – the cells at the venous end of the capillaries.

Dietrich always questioned his own methods, and he wanted to test how representative the  $p\text{O}_2$  histograms measured using the multiwire electrode were. He and Horst Baumgärtl therefore produced what I think must be the finest tipped Clark type needle electrode ever made in order to carry out measurements within tissue. He presented their results at his last ISOTT meeting in Nijmegen in 2000 [8]. He was able to show that with increasing distances between  $p\text{O}_2$  histogram measurement points, the histogram remained unchanged thus showing that measurements of histograms with the MDO, which encompass several capillary supply units, do indeed represent the distribution within a single unit.

The citation for the award of the Diesel Gold Metal stated: “Of particular significance, then, is the fact that not only did he invent things that were highly innovative – at the same time he endeavoured to put his ideas into clinical practice” [2]. An excellent example of this is the development of the transcutaneous  $p\text{O}_2$  electrode which he continued after his move to Dortmund. He, along with the Huchs, discovered that the blood supply of the skin of newborn babies is so high that it was possible to effectively measure arterial  $p\text{O}_2$  across the skin. It was important, however, that the hyperaemia, which was induced by heating the skin, always remained sufficient for the  $p\text{O}_2$  to remain independent of changes in

blood flow. How this was achieved was the subject of yet another of Dietrich's patents and the transcutaneous  $pO_2$  electrode [9] was adopted throughout the world in neonatal intensive care units for many years as an indispensable monitoring device until it was eventually superseded by the pulse oximeter.

Dietrich became interested in fluorescence lifetime measurements of  $pO_2$  in the early 1970s whilst trying to study angiogenesis and oxygen supply in the dorsal skin fold chamber in the rat. Measuring  $pO_2$  was a problem because they had to open the chamber to do so. He decided that this new optical technique would be suitable and with Norbert Opitz developed so-called optodes (optical electrodes) [10]. They found, however, that the fluorescence- $pO_2$  calibration was unstable when the indicator was placed directly in the tissue. His trick was to sandwich the optical sensor between an oxygen-permeable and an oxygen-impermeable membrane. In a further development, the indicator itself was bound into a membrane. pH and  $pCO_2$  optodes followed and, in collaboration with a number of commercial companies, the technology has been incorporated into blood gas analysers, single use flow-through devices and catheter devices for continuous monitoring.

In typical fashion, Dietrich used his inventiveness to apply his fluorescence sensor technology to another physiological question. Some years earlier, his group had discovered, using  $pO_2$  microelectrodes, that the  $pO_2$  in the upper layers of skin is a function of depth. He wanted to know to what extent atmospheric air was the source of oxygen supply to the skin, and what clinical implications this might have. He therefore adapted the fluorescence sensor to measure the oxygen flux across the skin. In collaboration with Markus Stücker at the Dermatological Clinic in Bochum they carried out a number of investigations and were able to demonstrate that cutaneous blood flow contributes little to the oxygen supply of the upper layers of skin [11]. Recognising the clinical importance of the discovery – particularly for the treatment of diabetic, venous and ischaemic skin diseases – in collaboration with Dr Paul Hartmann of AVL (later to become part of Roche Diagnostics) an oxygen flux imaging system was developed [12].

However, never reliant on the results provided by a single methodology, it was at this time (2001) that I was recruited to the Dortmund team – albeit for just 2 weeks – to apply the transcutaneous hydrogen clearance technique that I had developed based on his transcutaneous  $pO_2$  electrode. The idea was to test the reverse hypothesis, i.e. that if the blood flow contributed significantly to the oxygen supply at the surface of the skin at normal skin temperature, the freely diffusible, biologically inert hydrogen carried by the blood would be detected at the surface of the skin. Although we were unable to complete a full series of experiments at the time, for Dietrich our preliminary results provided further confirmation of the important role of atmospheric oxygen supply to the skin [13].

I have just used the example of skin, but through Dietrich's long scientific career he was a prolific publisher of some 450 papers reporting studies involving the oxygen supply of all of these organs, cells and organelles: heart, brain, liver,

carotid body, kidney, eye, tumours, inner ear, lymphatics, olfactory lobe, placenta, capillaries, mitochondria, erythrocytes and many more.

On a personal note, Horst Baumgärtl [1] told me that it was always difficult for Dietrich to get away from the Institute to go on holiday with his family. With almost predictable regularity some sort of calamity occurred just before he was due to go on leave. On one occasion the garage door fell down on his head; on another he damaged his leg; on another he injured his wrist. In the end the members of the Institute assumed that these events had nothing to do with chance or accidents, but an unconscious reluctance to leave his scientific endeavours.

## 2.3 Honours and Awards

Dietrich Lübbers' achievements were recognised with a host of honours and awards: Member of the New York Academy of Science; Honorary Professor, Ruhr University, Bochum; Corresponding member of the Mainz Academy of Science and Literature, 1975; President of ISOTT, 1981–2; President of the German Physiological Society, 1984; Honorary member of the German Physiological Society 1986; Honorary member of the German Microcirculation Society, 1985 Honorary member of the Association for Occupational Physiology and Occupational Safety, 1977. He was awarded the Ratschow Medal of the German Society of Angiology in 1985 and, as mentioned above, the Diesel Gold Medal of the Diesel Trust at the German Institute for Inventions in 1997. The first Dietrich W Lübbers Award was awarded by ISOTT in 1994.

## 2.4 ISOTT

Dietrich was a member of the first International Committee of ISOTT [14] and attended almost every meeting until 2000. Indeed it was the workshop organised at the Max Planck Institute in Dortmund in July 1971 that was probably the inspiration for Duane Bruley to organise, with Melvin Knisely, what turned out to be the first ISOTT meeting in April 1973 in Charleston, South Carolina [14]. My first ISOTT meeting was in Dortmund in 1982 and as a young scientist I was in awe of Dietrich who always had a challenging question for the discussion. However, as I got to know him well, I learnt that it was simply a passionate searching for the scientific truth that inspired his questions.

Dietrich was usually accompanied by his wife Angela to the meetings and together they were very much part of the ISOTT "Family". In 1996 I had the honour of welcoming him to the ISOTT meeting I organised in Dundee. Manfred Kessler used to refer to Dietrich as his "scientific father" and my "scientific grandfather". It was a term I think that Dietrich himself didn't really

approve of, mainly, I believe, because it made him feel old. His health started to make it difficult for him to travel long distances, and the Nijmegen meeting in 2000 was the last ISOTT he attended.

Many of us remember Dietrich as a dedicated scientist with a sharp mind, always ready to discuss new ideas and concepts. As someone who was always seeking after the scientific truth, it may be a surprise to learn that he was a shameless story-teller. He used to tell all sort of tall stories to his children about strange goings on in a castle they were passing, or the wildest tales about the river they were walking alongside [15]. He was also a religious man. Although professing to be unmusical, he and his family often sang together a particular song in German by Matthias Claudius "The moon has risen" (Tr. Catherine Winkworth, 1855) that begins:

Look up; the moon tonight  
Shows us but half her light,  
And yet we know her round and fair.  
At other things how oft  
We in our blindness scoffed  
Because we saw not what was there.

The words of the whole song reveal that Dietrich was fascinated by the beauty and mysteries of God's creation – and this is clearly reflected in his scientific endeavours to understand it.

Dietrich felt greatly honoured by the Society's decision to present an annual award to young scientists bearing his name and it is indeed very fitting that through the Dietrich Lübbers Award, members of ISOTT will continue to recognise and celebrate his enormous contribution to research in the field of oxygen transport to tissue.

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