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Horst Otto Stoeckel: Clinician, Administrator, Researcher☆,☆☆,☆☆☆

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ABSTRACT

Horst Otto Stoeckel was born September 26, 1930, in Lodz, Poland, which was part of the newly founded Second Republic of Poland until it was occupied by Nazi Germany in 1939. After World War II, his family immigrated to Meiningen, Germany, where he obtained his primary and secondary education. He attended Humboldt University and the University Hospital Charité of Berlin for his medical degree. Profs Theodor Brugsch, Karl Lohmann, and Friedrich Dost were important individuals who helped develop his interest in quantitative clinical pharmacology and pharmacokinetics. Prior to anesthesiology, Stoeckel trained in surgery, internal medicine, and obstetrics and gynecology in addition to clinical anesthesiology at a community hospital in East Germany. He completed 2 years of obligatory training to become an anesthesia specialist at the Teaching Hospital Hufeland and the Research Institute for Lung Diseases at Berlin-Buch. He also received training in anesthesia at the Humboldt University of Berlin. After escaping East Berlin through the Brandenburg Gate in August 1961, he obtained a position at the University of Heidelberg and obtained his West German board certification in anesthesiology in 1962. In the following 12-year period, Stoeckel was married, was promoted, passed his "habilitation" or lectureship period, started a family, and was granted the title of "Professor." His administrative career began in February 1974 when he was selected as the first Chair of Anesthesiology at the University of Bonn, a position he held for 22 years. He also served as Dean of the medical school from 1980 to 1981. As Chair, he developed three areas: patient care, teaching, and research. He developed a long-term research program in the field of "Quantitative Clinical Pharmacology in Anesthesia and the Quantitative Modeling and Control in Anesthesia," which required an interdisciplinary team of specialists in biochemistry, physics, and modern analytical methods. Over 20 years, the group's research program led to the discovery of basic algorithms providing the foundation of the automatic regulation of dosing control by the closed-loop feedback system, which is a concept important to the target-controlled infusion of intravenous and inhalation anesthetics. Following his career as a clinician, administrator, and researcher, he pursued a second career as a collector and museum founder.

Family Ancestry: Historical Perspective

The area in Germany known as the *Rhineland* was part of the Kingdom of Prussia from 1815 to 1871 until the foundation of Deutsche Reich by Otto von Bismarck (1815-1899). As a consequence of the peace treaty of Tilsit in 1807, the Dukedom of Warsaw became the Kingdom of Poland. Following the defeat of Napoleon at Waterloo in 1815, the victorious powers of Russia, Austria, and Prussia reorganized the political landscape of Europe at the Congress of Vienna. The expanded Dukedom of Warsaw was also called *Russian Poland* or *Congress Poland*. During the years 1824-1949, in the area of Eastern Europe which is now Poland, four generations of Horst Stoeckel's ancestors underwent three changes of citizenship.

The recorded ancestry of the Stoeckel family begins in 1824 when they immigrated east from the Vogtland (Saxonia) and Rhineland areas of Germany to Lodz, which was then Russia and is now Poland. In this time period, the village of Lodz thrived as a new settlement as the Russian Tsar granted land and exemption from taxes for farmers from German textile centers such as the Rhineland and Saxony to develop the textile manufacturing industry. Both Horst Stoeckel's paternal great-great-grandfather (Gotthelf Stokel, born 1810)—who immigrated to Poland in 1826—and paternal great-grandfather (August Frydrick Stokel, born 1848) had white collar occupations working as merchants in the textile and watch manufacturing industries. From

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the long period of 1824 to 1918, his ancestors improved their economic and social standing from being experts in "blue collar" craftsmanship occupations to moving into the "white collar" middle class "bourgeoisie" before World War I (WW1), as Lodz grew to one of the biggest centers of the textile industry. Karl Reich (1881-1916), Stoeckel's maternal grandfather, was a soldier in the Russian army and was wounded during WW1. He was sent to a military hospital in Armenia and died in 1916 at the age of 35 from a secondary infection. Stoeckel's paternal grandfather (Emil Stoeckel, born 1884) worked as a weaver in the textile industry. He later became a successful businessman who introduced the first mechanical mill for the production of plush, a textile similar to velvet, and owned a cotton farm in Andijan, Uzbekistan. Awareness of their native language and cultural identity was a value that helped his ancestral family stay together and prosper. However, the rapid rise of economic progress was driven by Jewish and German "industrial barons" and would lead to growing social tensions in the area.

The Republic of Poland gained independence in 1918 following WW1, and Stoeckel's grandparents' citizenship was Polish from 1918 to 1939. Lodz grew to be one of the largest Polish cities and one of the most international and industrial centers of Europe. However, citizens of the three ethnic groups (German, Jewish, and Polish) aimed to preserve each of their own cultural identities, mainly expressed through language and religion (Lutheran and Catholic Christians and Orthodox Judaism). Although the German minority was a closely knit community which founded social services and built their own churches, schools, and hospitals, they were also largely conservative, shutting their eyes to the social and economic inequality and misery in the rapidly developing multicultural society. In hindsight, Stoeckel feels the isolation in this minority shaped his behaviors and led him to focus on family and career, individualism, self-reliant problem solving, and careful selection of friendships.

The Stoeckel family stayed in Lodz for 120 years, where four generations had to change their citizenship three times. The first generation (Stoeckel's great-great-grandparents) came as Germans in 1824 to Lodz and took on Russian citizenship until 1918. From 1919 to 1939, they were citizens of the newly founded Second Republic of Poland. Living in Poland, the rise of the Nazi regime in Germany seemed far away. When Hitler occupied Poland in September 1939 (the beginning of World War II [WW2]), the German minority was pleased to be granted German citizenship again. However, the Stoeckel family fled at the end of WW2 (January 1945) for fear of the Soviet Army sending them back to the land of their forefathers, resulting in the loss of their home, identity, and belongings. The experiences of the four Stoeckel generations reflect the centuries-long confounded history of Middle and Eastern Europe. Horst Otto Stoeckel was the fifth generation.

Early Years

On September 26, 1930, Horst Stoeckel was born in Lodz, Poland. Both of Stoeckel's parents worked outside the home during his early formative years. His maternal grandmother, Katharina Reich (born 1879), was a very important influence in his upbringing. She cared for and tutored him on a daily basis while his parents worked in banking. In 1937, Stoeckel began his schooling at home with his grandmother at the age of seven before attending a private German elementary school in Lodz, Poland, from 1937 to 1939. At the age of 14, like many young people his age, he began to think about what career he might pursue once he was grown. A professional career as either an architect or doctor appealed to him. Because of his desire to work for the public good and help people, he chose medicine. Stoeckel described the period of his life up to his 15th birthday as very happy years (Figure 1). During this time, he developed a strong work ethic and was determined to obtain an education with good grades to study toward a profession as a means to help increase his family's economic and social standing.

Education

At the end of WW2, Germany was divided into four occupation zones by the victorious allies. The Stoeckel family lived through the end of WW2 evicted in Meiningen, a small town belonging to the Soviet Occupation Zone that would later form the East German GDR (socialist

Fig. 1. 1936, Stoeckel, age 6 years, with his parents in Lodz.

German Democratic Republic). Now refugees, the members of the Stoeckel family were faced with poverty, eviction, loss of their home, primitive housing, unemployment, and a depleted currency. A new currency was installed after 1948, and in 1949, the Federal Republic of Germany (West Germany) and the Deutsche Democratic Republic (DDR; East Germany) were formed. In October 1949, West Germany experienced a *Wirtschaftswunder*, or economic miracle, in which the West German economy recovered following WW2. The year 1949 was important in Stoeckel's life, as Germany was divided into these Western and Eastern sections with capitalist influence in the West and socialist (Soviet dictatorship) influence in the East. Of the two, Stoeckel stated that he had preferences for the West (capitalism) rather than the East (socialism).

From 1945 to 1949, Stoeckel attended high school (or "gymnasium" in Germany) in Meinigen. Despite having obtained the necessary qualifications for university study, Stoeckel was not admitted to the University of Jena (in DDR) in 1949 because his family did not belong to the working class as defined by the socialistic ideology at that time. Because matriculation based solely on academic qualifications was not possible for these political reasons, he immediately sought application elsewhere. There was a small chance that he might be accepted on a waiting list of another university. A fortunate situation arose with the formation of the Soviet Occupation Zone in the DDR in October of 1949, with transformation festivities held in the new "capital" of Berlin. Having been rejected at Jena, Stoeckel traveled to Berlin to present his documents, and fortunately, the admissions office was open. A friendly female officer looked at the documents and said politely "please give kind greetings and thanks to Herr Geheimrat," having mistaken Stoeckel as a relative of a Professor named Walter Stoeckel (1871-1961) who had chaired the Department of Gynecology and Obstetrics at Humboldt University (*Geheimrat* was the traditional title granted to chair professors as the highest distinction until approximately the end of the 1920s). Stoeckel confirmed that his family was not related to any of the physicians who served in the Hitler regime. Horst was surprised when, without any credentials, he was admitted in November 1949 at the Humboldt University Medical School, which was the former university clinic of Charité Hospital in East Berlin. This name change aimed to demonstrate that the "new German" of the eastern state would identify themselves with the human ideals of the natural scientist.

Stoeckel attended the Humboldt University Medical School of Berlin from 1949 to 1955 where he received clinical training at the University Hospital Charité of Berlin and Hufeland-Teaching Hospital at Berlin-Buch. During his medical education, numerous professors at the University Hospital Charité were very influential in his later professional development and thought process, including Theodor Brugsch (1878-1963, internist, Germany), Karl Lohmann (1898-1978, physiological chemist, Germany), Friedrich Dost (1910-1985, pediatrician and researcher, Germany), Emanuel Papper (1915-2002), and Hans Dengler (1905-1982).

Prof Theodor Brugsch (Figure 2) belonged to a family of scientists and artists with extensive social contacts. Brugsch lectured on the history of medicine, frequently ending his lectures on his favorite subject of Egyptology, as his father (Heinrich Brugsch-Pascha) was a world famous Egyptologist. Stoeckel regularly attended these lectures as one of a small group of students. Stoeckel remembers Brugsch as a fascinating teacher, a Grandseigneur, and a polyglot who spoke six

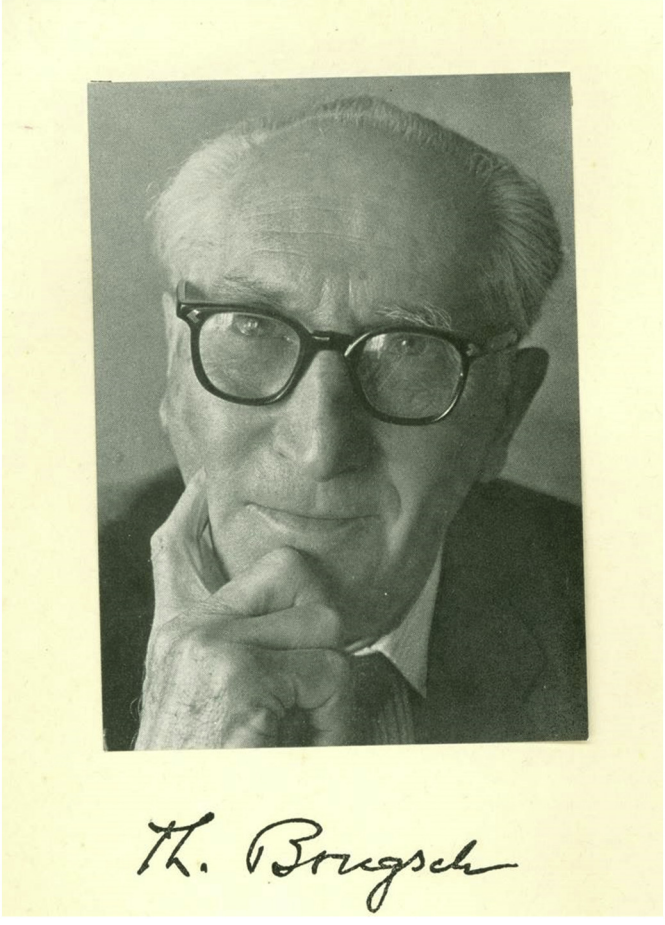

Fig. 2. Professor Theodor Brugsch.

Fig. 3. Professor Karl Lohmann.

languages, including Arabic. Brugsch was highly respected by the political authorities for his international reputation. Brugsch had obligations at the University Hospital Charité as vice-chair of the Internal Medicine Department after his official retirement as chair at 75 years of age. Although Stoeckel had never planned to become an internist, he wanted to learn more about medicine and asked Professor Brugsch to be his *Doktorvater*, which is a German term meaning *doctor-father* or mentor. "Doctor-father," in the German context, is a very close relationship between a mentor and mentee, and it was an honor to be a mentee of someone as internationally known as Brugsch. As Professor Brugsch was 79 years old and retired, Stoeckel became Brugsch's last mentee ("doctor-son").

Prof Karl Lohmann (Figure 3) was another of Stoeckel's teachers who had the ability to explain complex biochemical formulas and mathematical equations in an understandable manner. As one of the international founders of the area of "Dynamic Biochemistry," in the 1920s and 1930s, he isolated and later discovered the chemical structure of adenine triphosphate—the energy-providing process for the contraction of muscles.[1,2] Because of this work, he received three nominations for the Nobel Prize in Physiology or Medicine in 1952.[3] Stoeckel first learned the process of analytical and quantitative thought from Lohmann.

Prof Friedrich Dost (Figure 4) is best known as the author of the equation to calculate the area under the curve[4] and the 1953 book *The Blood Level*.[5] In 1962, Dost introduced a name for the new science of "pharmacokinetics." Stoeckel attended Dost's lectures and considered him to be his most important "professional influence," with introductory talks between Dost and Stoeckel occurring on an individual level numerous times from 1953 to 1954. This influence is apparent in Stoeckel's later research on quantitative clinical pharmacology. Profs Dost, Papper, and Dengler were especially influential in both teaching Stoeckel about and solidifying his personal development in the clinical science of pharmacokinetics and pharmacodynamics.

Clinical Medicine and Anesthesiology

At the end of his final oral state examinations in September 1955, Horst was offered a position as a research associate at the Pharmacological Institute of Humboldt University in East Berlin. This additional training helped solidify his interest in quantitative pharmacokinetics research. However, Stoeckel had to leave this position after only 5 months due to a political order for the exclusion of students from all universities in East Germany who did not have an adequate standing to teach young students to become "socialistic doctors" according to the government. This ended Stoeckel's plans of an academic career at any university in the country in which he lived. Stoeckel's situation was precarious in that he had no income and his doctorate dissertation in medicine was not yet completed. In this context, he remembered family hardships post-WW2 in which his family found themselves in poverty with no steady income or plan of future business. In 1956, the economy was still difficult following currency reform, and for Stoeckel, being a newly certified physician, finding a job was urgent. Stoeckel found his future career in anesthesiology as he was searching for a medical profession that combined clinical practice, experimental research, and manual

Fig. 4. Professor Friedrich Hartmut Dost and his 1953 published book *Der Blutspiegel* (*The Blood Level*).

dexterity. However, a residency position in anesthesiology was not available to him in East Germany in an era of Soviet control and influence. These setbacks stressed and disappointed Stoeckel profoundly.

The 5-year period from 1956 to 1960 was an interruption in Stoeckel's plan for an academic career, and he referred to this period as his "academic exile." This interval began with Stoeckel accepting a position as a physician in general primary care medicine at a community hospital in Marienberg, Saxonia, East Germany, located about 200 km from Berlin. Here, he gained clinical experience in primary care, basic surgery, internal medicine, obstetrics, and pediatrics. An internship in surgery was required to obtain the anesthesia specialist qualification in East Germany, and this experience allowed him to fulfill this requirement. This experience also allowed him to gain clinical experience and insight to establish contacts for a future job referral, preferably to Berlin. This period helped Stoeckel form his political views as he gained insight into the restrictive living conditions of East Germany and "life behind the iron curtain."

In 1959, after nearly 3 years in Marienberg, Stoeckel returned to Berlin-Buch, where the teaching hospital Hufelandkrankenhaus was attached to the Research Institute for Lung Diseases. There, he stayed for the obligatory 2-year (1959-1960) clinical training period in anesthesia under Prof Ferdinand Poppelbaum (1920-2007, head of the division of Anesthesiology and Bronchology and responsible for the translation of numerous textbooks from English to German) to obtain certification as an anesthesia specialist.

Here, two events occurred which indicated to his superiors that Stoeckel was a good diagnostician. The first event in March 1959 involved a diagnostically difficult clinical case where a diagnosis could not be confirmed. The patient was a young man employed as a gardener. On physical examination and radiography, a cavity was identified in the patient's chest. The patient was thought to have contracted tuberculosis; however, this diagnosis was not verified by laboratory tests or cultures. Stoeckel correctly made the diagnosis, having read about mycetomas several weeks prior. He published this case report in 1960 as his first scientific publication.[6]

The second event occurred in April 1959, involving a patient who had undergone a total thoracoplasty for lung tuberculosis. In the early postoperative period, the patient developed respiratory insufficiency secondary to a flail chest. This event occurred during the weekend when senior members of the department of surgery were attending a meeting 200 km from Berlin. When a mechanical ventilator was not available, Stoeckel and an operating room technician manually ventilated the patient for the entire weekend (2½ days and 3 nights) using a Draeger Romulus Anaesthesia machine. Manual ventilation continued until the following Monday morning, when a Swedish Lundia Ventilator became available from another hospital. The patient recovered after another 10 days of artificial ventilation and a brief weaning period. This event had a lasting impression on Stoeckel and intensified his interest in critical care medicine, an interest that also was encouraged by his chairman, Professor Poppelbaum. Stoeckel obtained useful operating room and critical care clinical experience during this early part of his training career (Figure 5).

In January 1961, he accepted a position from Prof Josef Pichotka (1911-1991), who was the chair of the Department of Physiology. Stoeckel needed to complete the East German requirements for Board Certification in Anesthesiology, which included a research thesis. In this position, Stoeckel obtained permission from Professor Pichotka to organize an animal research program investigating oxidative metabolism at different body temperatures by perfusing an isolated limb with a pump oxygenator.

Fleeing Through the Brandenburg Gate (1961) and the Long Academic Way to Appointment of Chair (1973)

After the Soviet Union's President Khrushchev's Berlin Ultimatum in 1958 and his appearance at the United Nations General Assembly in 1960 in New York City, the Cold War escalated. This led to the total separation of East from West Berlin and the erection of the Berlin Wall by Soviet and East German authorities in 1961.

On August 13, 1961, the border between East and West Berlin was closed, and traffic came to a complete halt, as the East German government feared many people would flee East Germany and the economy would collapse. Stoeckel coincidentally met two colleagues who informed him of a transitory situation where for 36 hours it would

Fig. 5. 1959. Stoeckel in an operating room using a Draeger Narkosespiromat 5000 anesthesia machine.

still be possible (with a special-purpose ID card) to pass through the Brandenburg Gate. As a member of a research institution in East Berlin with travel privileges, Stoeckel was permitted to visit scientific libraries and attend meetings in West Berlin. Stoeckel immediately changed plans and fled to West Berlin, as it was apparent that he would not be able to achieve his goal of becoming a university professor in East Germany. The wall was built in the coming weeks. The story of Stoeckel escaping East Berlin by driving his own car through the Brandenburg Gate, which was guarded by armed military police, is a story in itself involving an empty suitcase in the car's trunk, a forgotten red ID card, and a love story to be with his future wife, Karin, who had just finished her studies in dental sciences at the Free University of West Berlin (Freie Universitat Berlin).

During the days following his escape, Stoeckel contacted surgery and anesthesiology professors at the Free University of West Berlin, which was founded with American support in 1948 as a free, Western alternative to East Berlin's Humboldt University (formerly named *Frederick William University*) that faced communist political influence. These included Profs Fritz Linder (1912-1994) and Otto Heinrich Just (1922-2012) who, while still working in West Berlin, had accepted positions as chairs of surgery and anesthesiology, respectively, at the University of Heidelberg. They promised Stoeckel a full-time position as an Associate Anesthetist at the University of Heidelberg beginning March 1, 1962. In May 1962, Stoeckel received approval to be a Specialist in Anesthesiology in West Germany, which was a certification by established documents of Teaching Hospitals or University Departments to the Medical Association (*Arztekammer*) responsible for the district of the local state in which the applicant lives or works. In Stoeckel's case, Karlsruhe was responsible for the Heidelberg area. After the defeat of Nazi Germany in 1945, the fascist central government in Germany was replaced by the *Bundeslander* (federal states). The law for medical doctors (*Reichsarzteordnung*) that had been decreed by Nazi Germany's chamber of medical doctors (*Reichsarztekammer*) had been dissolved by the allied forces council (*Kontrollrat*) in 1945 and was successfully replaced by the federal German medical council (*Bundesarztekammer*) in all West German federal states. The *Bundesarztekammer*, as a part of the federal state government, was directly responsible for certifying that medical doctors had achieved the qualifications to practice or be designated a specialist. The British zone, which included Heidelberg, was the first to establish this new political system. The only exception to this was Berlin, which was governed by the three allied forces and to which the new German medical council was not installed until 1962. However, this did not affect Stoeckel, as he became certified at the University of Heidelberg. In 1969, Stoeckel then completed the long approval process of University lectureship (called *habilitation* in Germany), which he felt was the actual beginning of his "dream of achieving an academic top position." The long habilitation process required that an individual qualify as a specialist before submitting scientific publications focusing on research achievements, culminating in a thesis. Whereas certification as a Specialist in Anesthesia was given by state authority, the recognition of habilitation is given by an academic body.

As a senior staff member in anesthesiology from 1963 to 1973 at the University of Heidelberg, Stoeckel supervised the divisions of newborn and infant surgery, cardiovascular surgery, and neurosurgery, including performing surface hypothermia in patients undergoing procedures in these surgical specialties. Stoeckel earned special merit for his efforts in developing the intensive care unit (ICU) to a higher standard. In 1963, he earned the respect of the Chair of Surgery, Prof Fritz Linder, for the successful treatment of a tetanus patient who had severe convulsions. For patients with respiratory insufficiency, Stoeckel performed long-term artificial mechanical ventilation using diazepam sedation and muscle relaxation. The ICU treatment of many cases of respiratory failure followed, and an ICU with 10 beds was opened in 1969 under the direction of the Anesthesiology Department. In 1973, he passed a lectureship qualification called *habilitation*, which is a German academic qualification beyond an anesthesia specialist that entailed an additional examination. Following this qualification, several scientific publications and a comprehensive research thesis are required to achieve Professorship. A comparison to the American system is difficult.

Administrator, Chairman, and Dean

Stoeckel and his wife, Karin, enjoyed the Rhineland area of Germany, which is where Stoeckel's maternal ancestors had previously lived before immigrating to Lodz, Poland. In 1972, the University of Bonn implemented a West German law specifying that the Division of Anesthesia, which was part of the Department of Surgery, should be separated into its own independent department. To fulfill one of his lifetime ambitions, Stoeckel applied for the chair position at the Faculty

(School) of Medicine of the University of Bonn. After a rigorous interview and selection process in February 1974, at the age of 43, he was selected to be the first chair of anesthesiology at the Rheinische Friedrich-Wilhelms-Universitat, Bonn. Bonn was the provisional capital of West Germany from 1949 to 1990. The position of chair at the university clinic was a prestigious position, and Stoeckel's appointment as chair reflected his scientific reputation. He held this position for 22 years from 1974 to 1995.

Stoeckel felt that his major goals and later achievements as chair were (*a*) developing a modern and efficient clinical department combining all the University Klinik anesthesia staff who worked in different surgical departments (and often different campus buildings) into one department, (*b*) establishing intensive care medicine and subspecialty units, and (*c*) forming and leading research teams. His prior research and critical care medicine experience at the Universities of Berlin and Heidelberg helped immensely in developing programs at the University of Bonn, particularly to (*a*) perform open heart surgery, (*b*) develop and improve postgraduate education, (*c*) improve the existing Emergency Service (which was of importance in the former Capital of the Federal Republic of Germany), and (*d*) introduce pain therapy in a special division of the anesthesia department. A significant achievement during his tenure as anesthesiology chair was his election by a vote of the academic faculty to Dean of the School of Medicine for the years of 1980-1981. In Germany, a Dean of the Medical Faculty in a School of Medicine serves in this position concurrent to their duties as Chair and/or Professor, with the period of duty being 1 year.

A Vision for Research

Stoeckel's vision for a research program aimed to build upon previous research in pharmacokinetics and pharmacodynamics. In particular, Stoeckel's research vision had been influenced by the substantial works of three important researchers and mentors: Friedrich H. Dost (1953 and 1968, Berlin and Giessen), Emanuel Papper (1962, New York City), and Hans Dengler (1964-1969, Heidelberg and Bonn). Other pharmacokinetics research studies had mainly been performed by Hermann Druckrey (1904-1994) (1949, Germany), Ekkehardt Krueger-Thiemer (1918-1969) (1962 and 1968, Germany), and Richard Kitz (born 1929) (1962, New York City). In pharmacodynamics, research studies had been performed by Albert Faulconer (1911-1985) (Mayo Clinic) and Reginald Bickford (1913-1998) (San Diego).

Stoeckel discovered symposium proceedings detailing research by Emanuel Papper and Richard Kitz while in the library of the Department of Anesthesiology at the University of Heidelberg, in particular "uptake and distribution of anaesthetic agents"[7] and the paper "pharmacokinetics of inhalation anaesthetics: clinical applications." Papper and Stoeckel met for the first time in person in the late 1970s and developed a lasting friendship. They would frequently discuss progress in clinical pharmacokinetics and pharmacodynamics research.

Stoeckel met Hans J. Dengler, Associate Professor of internal medicine, when he began working at the University of Heidelberg in 1962. Dengler was a pioneer in the development of clinical pharmacology in Germany and had been a long-standing consultant for the Surgery Department where he regularly accompanied his patients to the operating theater, where Stoeckel administered anesthesia. Dengler had just returned from studying at the US National Institutes of Health (NIH), where Bernhard B. Brodie (1907-1989, Head of the Laboratory for Chemical Pharmacology at NIH) played a decisive role in the development of patient programs such as the well-known malaria program in the 1950s including the introduction of the first chemotherapeutical drugs. From Dengler, Stoeckel learned about pharmacokinetics literature, written mainly in German. In particular, there were four landmark publications on pharmacokinetics following the first symposium held in 1933: (*a*) W Gehlen's 1933 study [transl., "The Efficiency of Intravenous Application of Drugs as a Function of Time. A Contribution to the Mathematical Handling of Pharmacological Problems"][8]; (*b*) H Druckrey and K Kuepfmueller's 1949 book [transl., *Dose and Effect*][9]; (*c*) EM Papper and R Kitz's 1962 publication, "Uptake and Distribution of Anesthetic Drugs"[7]; and (d) E Krueger-Thiemer's 1962 paper [transl., "Dosage Calculation with a Program-Controlled Calculating Machine"].[10] These publications created a growing interest in quantitative clinical pharmacology in anesthesia.[11]

During the years 1950-1960, the area of anesthesia related to pharmacodynamics was dominated by the Mayo Clinic research team led by Albert Faulconer and Reginald Bickford, who authored a synopsis on "Electroencephalography in Anesthesiology."[12] Although their studies included the common volatile and gaseous anesthetics, as well as the barbiturate pentothal injected by intravenous bolus, they had not yet incorporated a processed electroencephalograph (EEG). Incorporating the EEG into a feedback algorithm was one of Stoeckel's research goals.

Between 1968 and 1973, Stoeckel prepared for a comprehensive research project and team of his own. In 1969, he had adequate time to outline his long-term ideas for a research program. Enormous progress had occurred with the development of pharmacokinetics in Germany and the United States, as it was becoming a clinical science. A timeline of milestones in the progress of pharmacokinetics is as follows:

a. 1968: 15 years after Friedrich Dost's pioneering book *The Blood Level*, his classic book *Essentials of Pharmacokinetics* was published.[4]
b. 1969: Schering Workshop on Pharmacokinetics in Berlin.
c. 1969: Hans Dengler Symposium on Pharmacological and Clinical Significance of Pharmacokinetics.
d. 1972: Fogarty International Center at the NIH: Conference on Pharmacology and Pharmacokinetics, Problems, and Perspectives.

In the autumn of 1973, Stoeckel traveled to the United States (New York; Boston; Chicago; Denver, CO; Rochester, MN; San Francisco and Los Angeles, CA) to gain knowledge of current research in the field of pharmacokinetics. After returning to Heidelberg in January of 1974, he completed a written formulation of his research philosophy.

Developing a Research Program

In February 1974, Stoeckel had been appointed Chair of the Medical Faculty at University of Bonn and was not yet in office when he was asked by the university and government authorities to formulate a detailed comprehensive and diversified long-term research program. The program would be called *Quantitative Clinical Pharmacology in Anesthesia*, aimed at investigating the optimization of anesthesia dosing in clinical patients. This had been developed by a logical sequence: from quantitation via modeling and control to automation of dosing for an adequate depth of anesthesia. This new anesthesia research field would allow the simultaneous acquisition of knowledge on the pharmacokinetics and pharmacodynamics of anesthetics resulting in the improvement of clinical anesthesia practice. The implementation of this model-based control algorithm would hopefully lead to automatic dosing in a closed-loop feedback system.

The research program outlined by Stoeckel to conduct research over 10-15 years needed an interdisciplinary research team consisting of the following:

1. One biochemist for developing and measuring pharmacokinetics and modeling.
2. One physicist with expert knowledge in mathematics and the development of pharmacodynamic parameters relevant for clinical anesthetic dosing and the "missing link" for the combined kinetic-dynamic model.

3. One (or more) medical doctoral student candidate(s) having relevant talents and interests in becoming specialists in anesthesiology and continuing their academic career from lecturers to professors. Individuals with PhD backgrounds in physics and biochemistry were what Stoeckel needed to complete his pharmacokinetic research team.
4. Stoeckel, who would serve as the inaugurator and head of the specific research program, academic promotor, and architect of the "Team of Four" concept.

Stoeckel was convinced that his prospective and long-term program would only be successful if the interdisciplinary expert team worked together continuously from a study's beginning to end. Stoeckel was committed to this project, and within 18 months, the "Team of Four" had been assembled with Drs. Peter Lauven (born 1948, biochemistry), Helmut Schwilden (1949-2015, physics), and Jürgen Schuttler (born 1953, analytical methods).

How did Stoeckel come up with the idea to create an interdisciplinary "Team of Four," who, by the 1980s and 1990s, gained international recognition and respect in the areas of pharmacokinetics and pharmacodynamics? The story begins when Stoeckel was a medical student. During his early clinical education with an interest in pharmacology, Stoeckel came to the conclusion that anesthesia was being performed according to judgments made from previous individual experiences, especially in relation to drug dosage, resulting in pharmacologic inadequacies. A step-by-step comprehensive research program based on a rational analytical foundation was developed, beginning with learning quantitative processes from pharmacokinetic modeling and drug control application strategies such as target-controlled infusion. Correlating pharmacokinetics and pharmacodynamics was Helmut Schwilden's model-based closed-loop feedback control algorithm,[13] culminating 18 years of research as the final step in the automation of anesthesia.

Schwilden would go on to develop the formulas necessary for the correlation of pharmacokinetics and pharmacodynamics in intravenous and inhalation anesthesia. He was also the inventor of the model-based control algorithm. Schwilden's responsibilities and successful research from 1978 to 1995 were investigations in pharmacokinetics and pharmacodynamics within the Quantitation Modeling and Control-Control and Automation research program. This included general calculating methods in linear pharmacokinetics; strategies for infusions for intravenous anesthesia; pharmacodynamic modeling by processed EEG analysis; theoretical considerations correlating pharmacokinetics and pharmacodynamics; quantitative processed EEG versus minimum alveolar concentration; and the construction, development, and adoption of closed-loop feedback systems for intravenous and volatile agents.

Peter Lauven was the expert in blood level analysis using, at that time, innovative new analytic methods such as automated gas chromatography. His responsibilities involved analytical methods and investigations of pharmaceuticals and special applications in anesthesia. Lauven developed automated gas chromatography methods for various drugs such as local anesthetics, benzodiazepines, and volatile agents.

The third member of the research team was Juergen Schuettler who, while still a medical student, was skilled in the development of analytical methods. He designed analytical methods for pharmacokinetic blood level measurements such as high-pressure liquid chromatography and the radioimmunoassay of drugs and hormones.[14]

These three individuals worked hard and efficiently as clinicians and researchers. Stoeckel, as the leader, was the final member of this "Team of Four" (Figures 6 and 7). Thus began a 20-year collaborative research effort which produced numerous data and manuscripts on the pharmacokinetics and pharmacodynamics of anesthetic agents. Two important results were (*a*) the development of formulas for the correlation of pharmacokinetics and pharmacodynamics and (*b*) the first closed-loop feedback control system in a clinical patient on July 7, 1987, using a model-based control algorithm invented by Helmut Schwilden.[13,15] The patient was a 35-year-old woman who received anesthesia for 3 hours during plastic surgery following radical breast surgery (Figure 8).

Stoeckel's "Team of Four" published numerous articles important to research in quantitative clinical pharmacology.[13–17] They demonstrated the development and progression from the beginning of research (based solely on clinical quantitative pharmacokinetics and on pharmacodynamics) proceeding to the correlation of pharmacokinetics and pharmacodynamics.

Microprocessor-controlled infusions serve as a powerful tool for research in clinical pharmacology. The achievement of linearly increasing plasma levels of etomidate allowed further pharmacokinetic and pharmacodynamic modeling concepts to be discovered. Formulas developed by the team helped to assess the action of drugs, degree of unconsciousness and sleep, and changes in the EEG, while correlating all of these with blood levels and depth of anesthesia. As a consequence, the entire research program of this group led to the discovery of basic algorithms forming the foundation of automatic regulation of dosing control by the closed-loop feedback system, a concept now important to the target-controlled infusion of intravenous anesthetics Figure 9). At the time, these concepts were not readily available in clinical anesthesia but were of great value as research instruments, especially for clinical pharmacologic studies during anesthesia.

Fig. 6. 1976, the pharmacokinetics research "Team of Four." From left to right: Peter Lauven, Juergen Schuettler, Horst Stoeckel, and Helmut Schwilden.

Fig. 7. 1984, from left to right: Schuettler, Stoeckel, and Schwilden in the Pharmacodynamic Laboratory after finishing the investigation in a volunteer.

After their time at the University of Bonn, all three researchers became Professors of Anesthesiology. Juergen Schuettler spent a year doing pharmacokinetic research with Dr. Donald Stanski at Stanford University in Palo Alto, CA. Schuettler later became Chair and Head of Anesthesiology at the University of Erlangen in Germany. Lauven left the "Team of Four" to become head of a comprehensive teaching hospital at the University of Hannover in Bielefeld, Germany. Schwilden became Chair and Head of Experimental Anesthesiology at the University of Erlangen-Nuremberg. He earned high respect and gained a reputation as a leading person in the ethics committee of the university. Stoeckel described the selection and collaboration of his research team as "recognizing and developing talent, proper planning and good fortune." Stoeckel's vision had become a reality.

Research Program on Molecular and Systematic Mechanisms of Anesthesia

It was Stoeckel's intention to eventually extend the program on quantitative clinical pharmacology in anesthesia to the systemic and molecular level. A second Research Professorship, held by Prof Bernd W. Urban (born 1950), was initiated in 1989. The importance and success of this work resulted in the publication of an international conference of the "Proceedings of the Sixth International Conference on the Molecular and Basic Mechanisms of Anesthesia," organized in Bonn by Professor Urban and his colleagues.

Special Meetings in Bonn, Historical Exhibitions

In 1980, a premeeting of the VIII World Congress of Anesthesiology in Hamburg, Germany, convened at the University of Bonn and at the Castles Gutenfels and Schoenburg in the Rhine Valley. The theme of the premeeting was "New Insights in Clinical and Research Progress in Anaesthesiology." Moderators were Profs Emauel (Manny) Papper and Richard "Dick" Kitz. Participants and speakers included Profs Quintin Gomez (1919-2003, President of the WFSA, Manila), Jan Crul (Nijmwegen, the Netherlands), Richard Kitz (Boston), Otto Mayrhofer (Vienna), Kenjito Mori (Kyoto), Carlo Morpurgo (Milan), Olof Norlander (born 1920, Stockholm), Carlos Rivas (Caracas), Guenther Schlag (1924-1998, Vienna), Horst Stoeckel, Tapani Tammisto (1932-2017, Helsinki), and Reinhold J. van de Walle (Louvain, Belgium) (Figure 10).

In 1985, the First International Workshop on "Quantitation Modelling and Control in Anaesthesia" was held in Bonn.[17] Stoeckel organized this meeting on the occasion of the 10-year anniversary of his installation as Chair of Anesthesiology (Proceedings: Thieme Basel-Karger,

Fig. 8. July 7, 1987, the team of the first clinical anesthesia using a closed-loop feedback control system. A 35-year-old female patient received anesthesia lasting 3 hours for plastic surgery following radical breast surgery. Team members from left to right: informatics expert Jean-Louis Griffoul, Helmut Schwilden, Horst Stoeckel, and the surgeon Klaus Jaeger.

Fig. 9. The laboratory configuration of an anesthetic research place for TIVA (total intravenous anesthesia) with two infusion pumps in the open-loop system (CATIA, CACI) for control of depth of anesthesia.

Fig. 10. 1980, premeeting of the Seventh World Federation of Societies of Anesthesiology, Hamburg, Germany. Photo from left to right: Horst Stoeckel; Otto Mayrhofer, Vienna; Emanuel "Manny" Papper, Miami; Carlos Rivas, Caracas; and Richard Kitz, Boston, during a lecture-free afternoon visiting the Moselle Valley.

Switzerland, 1984). The second international workshop on "Control and Automation in Anesthesia," a continuation of the first workshop, occurred 10 years later in 1994 (Proceedings: Springer Heidelberg–New York, 1995)[18] (Figure 17).

Distinguished Awards

Horst Stoeckel has received numerous honors and awards. In 1985, Stoeckel became the second German anesthesiologist to receive certification as a Fellow of the Faculty of Anesthetists of the Royal College of Surgeons of England—the first being Prof Rudolf Frey (1917-1981) of Mainz, Germany, the founder of the Society of Anaesthesiology and its journal in Germany. In 1990, Stoeckel was honored as a full member of the German National Academy of Sciences Leopoldina (founded 1652). In the same year, Stoeckel received distinctions as an honorary member of the Polish Society of Anesthesiology and a dr. med. Honoris causa from the University of Lodz, his birth town. In 1991, he was the first German anesthesiologist to be made an honorary member of the Association of University Anesthesiologists of the United States. In 1993, he became an honorary member of the Japan Society of Anesthesiology. In 1997, he received the degree of dr. med. Honoris causa from the medical school Charité in Berlin where he had been a medical student from 1949 to 1955. In 1997, he was also made an honorary member of the German Society of Anesthesiology.

Conclusion

Commenting on lessons learned and possible mistakes over the course of his career, Stoeckel responds by citing Karl R Popper's phrase of "all life is problem solving," and adopts the view that "fortune is rare but real." Stoeckel regards the solutions of the major problems in his career as fortunate and the minor problems caused by either a lack of talent or adverse conditions in life. If he could repeat his life story, he would have placed a greater emphasis on work-life balance to spend more time with his family. He also would have spent more efforts on building skills in the rapidly developing computer sciences. In his retirement, Stoeckel opted for a second career as a collector and museum founder. He holds the position of museum director and curator today.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.janh.2018.08.003.

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