

Living History—Autobiography

Hans-Rudolf Wiedemann in a Half Century of German Pediatric Genetics

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BEGINNINGS

I was born on 16 February 1915 in Bremen. When the First World War broke out, my father—a physician—had been ordered to the Western Front, attached to an infantry regiment. It was not until 1918 that he was discharged from military service. I grew up in Bremen, where I received a classical education at a high school steeped in tradition. Indeed, while I was a pupil there, the school celebrated its 400th anniversary.

My father was not the only physician in the family. One of his father's brothers and one of his father's cousins had chosen the same profession, the latter being the Director of the Medical Policlinic of the University of Kiel for many years. On my mother's side of the family there were six physicians (two female, four male), four of whom were university lecturers (one female, three male). Undoubtedly the most prominent and distinguished of the four was my uncle, Karl Wilmanns (1873–1945). He was a student of Kraepelin and Director of the Psychiatry Clinic at the University of Heidelberg from 1918 until 1933, when he was dismissed from the position by the Nazis for publicly (and quite accurately) proclaiming Adolf Hitler to be a psychopath [39].

MY FATHER

From youth onward my father was socially minded and showed a great interest in the well-being of others; consequently, he chose to become a medical practitioner. Before going into private practice, he worked as a ship doctor for the "Norddeutscher Lloyd" (Lloyd of Northern Germany); during this time he travelled to East Asia, South America, and six times to the United States, gaining experience that doubtlessly widened his outlook. In Bremen, he was highly respected for his extraordinary dedication to the needs of his patients.

Perhaps largely due to the fact that my mother died so early, a close relationship based on mutual trust developed between my father and myself—his only son. I always followed my father's example closely, and this

proved to be very important for me as the Hitler regime approached.

Having a most active interest in politics, my father had scrutinized Adolf Hitler's pamphlets long before 1933. He was quite horrified by what he read, and his clearheadedness and strong feelings of apprehension made a tremendous impression on me and caused me to reject the Nazi Party at a very early stage. After the Nazis had come to power, my father demonstrated extraordinary courage throughout the regime by helping those in danger, particularly his Jewish colleagues and Jewish patients, as I mentioned in a book published a few years ago [154].

I wanted to stress this point before going into the details of my life history to date, as a German with my date of birth is always asked the same question: What was *your* attitude toward the Hitler regime?

MILITARY SERVICE, UNIVERSITY, AND MEDICAL SCHOOL

Immediately after graduating from high school in the spring of 1934, I was drafted into the army to perform 18 months' military service: at that time, military personnel were protected from political indoctrination by the Nazis. In 1935, I then became a medical student, going on to study at the universities of Freiburg/Br., Munich, Hamburg, Lausanne (Switzerland), again in Hamburg, and finally in Jena. In Freiburg (1935–1937), I was fortunate enough to make the acquaintance of the great Hans Spemann (1869–1941), the famous zoologist who later worked on the mechanisms of embryonic development and who had received the Nobel Prize in 1935 for discovering the organizer effect. Spemann, who supervised my course on dissection, left a lasting impression on me. Being allowed to study in Switzerland provided me with the perfect opportunity to observe Nazi Germany "from without"; only a few months before the outbreak of the Second World War I set out from Lausanne to travel through my beloved France. In Hamburg I was particularly impressed by the pediatrician Rudolf Degkwitz and in Jena by the pediatrician Jussuf Ibrahim.

Human genetics, in the pure sense, was hardly touched upon during my studies, and it was only in Jena that I was exposed to the racist ideology of the Nazis

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(*Rassenhygiene* or “racial hygiene”) by an obviously second-rate docent.

In mid-1940 I successfully completed my medical studies in Jena. Owing to a refractory intestinal disorder that I had first acquired in 1937 (and because of which I had been allowed to leave Germany to study for a semester in Lausanne, 1938/1939), I was exempted from a further period of military service.

JENA

Up to the end of the Second World War I worked as a resident under Jussuf Ibrahim at the Department of Pediatrics of the University of Jena. Jussuf Ibrahim's father was an Egyptian pasha and lecturer in medicine at the University of Cairo; his mother was from Berlin. Ibrahim was a physician of high standing, a famous neuropaediatrician, and an outstanding personality. His department in Jena was one of the few “unpolluted islands” in Nazi Germany. In the fall of 1941 I received my medical doctorate from the University of Jena. I went on to specialize in pediatrics and qualified as a lecturer following work that included studies on what is known today as “hereditary spherocytosis” [93, 94]. However, Berlin did not grant me permission to lecture.

In 1942 I married Gisela von Sybel in Jena. Gisela was employed at “my” clinic as a pediatric nurse. We wanted to have six children, and our wish duly came true: between 1943 and 1953, my wife gave birth to three boys and three girls (boy, girl, boy, girl, boy, girl!). They are all alive and healthy; we now have 14 grandchildren.

BREMEN AND BONN: THE FIRST PAPERS ON SKELETAL DYSPLASIAS

Immediately after the end of the Second World War I accepted an appointment as senior consultant at a large children's hospital in my hometown of Bremen. It was here, where I worked for just over a year, that I first became fascinated by a hereditary skeletal disorder. It was on the basis of two new cases and the case reported by Engelmann back in 1929 that I was able to establish what is nowadays called “progressive diaphyseal dysplasia” to be a separate entity. Initially, I termed this entity “systemic sclerotic hyperostosis of childhood with myopathy,” and for the first time made special reference to the simultaneous involvement of the musculature ([95, 96]; see also [49, 50]).

I was not aware of the case described by Camurati in 1922. At that time it was almost impossible for Germans to gain access to foreign literature. By the same token, for many years little notice was taken in other countries of the work being performed in Germany.

In the fall of 1946, Otto Ullrich (1894–1957) offered me the opportunity to become his chief consultant at the Department of Pediatrics at the University of Bonn. Ullrich was an outstanding clinical geneticist and an inspiring mentor, and a close friendship developed between us. I continued to devote most of my attention to hereditary skeletal dysplasias, particularly to the different types of mucopolysaccharidoses [99–101, 104, 105], later recognized as such. Of course, I maintained an interest in other subjects, for example exogenous birth defects [102, 103, 108, 109, 165, 185].

I still remember quite vividly my first journey to a foreign country after the Second World War. In 1948 I returned to Switzerland to visit the pediatric departments at the universities of Zürich (G. Fanconi), Berne (E. Glanzmann), and Basle (E. Freudenberg, A. Hottinger). Being able to participate actively (together with O. Ullrich) in the Sixth International Congress of Pediatrics in Zurich in 1950 was an equally satisfying and gratifying experience. Germany and the Germans were at last regaining contact with freedom and the “outside world.”

Following a temporary appointment as Head of the Department of Pediatrics at the University of Münster in Westphalia in 1949, I was appointed as professor in 1950. I left Bonn at the end of 1952 to become Head of the Krefeld Children's Hospital. I turned down the opportunity to succeed Ibrahim as Director of the Children's Hospital at the University of Jena. My first mentor had died; however, with six children of school age and in consideration of the difficult conditions that prevailed in the Soviet-controlled eastern zone of Germany, my wife and I agreed that I should not accept the offer.

KREFELD: GENETIC SKELETAL DISORDERS, NUCLEAR SEXING, AND AN EPIDEMIC OF EMBRYOPATHIES

In Krefeld (from the end of 1952 to 1961) I continued to pursue my interest in genetic skeletal disorders, but my work also involved other hereditary diseases and traits [20, 34, 92, 106, 111]. In 1953 I gave the first lecture on hereditary skeletal disorders ever to be delivered before the full assembly of the German Society for Pediatrics [107]. A short monograph on the same topic appeared afterward [116]. In a sibship in which *fenestrae parietales symmetricae* (*foramina parietalia permagna*) had occurred in five consecutive generations, I was able to provide clear evidence in 1957 that a large, accidental, parietal fontanel that presented as a congenital trait was actually a preliminary stage of the *fenestrae* ([110]; see also [40]). We studied the nuclear anomaly of Pelger and established that its incidence in healthy individuals in West Germany was around 0.02% [11, 53, 177]. Moreover, we introduced into the literature the concept of the “cloverleaf skull” (*Kleeblattschädel*) ([29]; see also [171]).

It was during the time I spent in Krefeld that Barr and Bertram's discovery of sexual dimorphism in resting nuclei of mammalian tissues [4] grew in importance and the possibilities for its practical application increased. In 1954 Davidson and Smith [9] described an analog of “Barr bodies” in polymorphonuclear neutrophil leukocytes of females, and we became the first European researchers to confirm their findings [56]. Subsequently, my colleagues and I devoted much time and effort to the question of the so-called “true sex” (*das wahre Geschlecht*) in human intersexes and related states. In extensive studies we tested the hematomorphologic method for the identification of what is now referred to as the X chromatin. We found the method to be quite useful [57, 58, 86, 87, 113–115, 173–176, 183, 184] and subsequently received material from many European countries for evaluation; eventually we were able to provide

almost the whole of Europe with the possibility for hematomorphologic "nuclear sexing" in cases with errors of sexual development. In 1957 I was invited to London, England to give a lecture on this subject [112]. In 1956 I had reported on corresponding investigations on psycho-intersexes, together with the Zürich psychiatrist, M. Bleuler [6]. Anomalies of sexual development were repeatedly to be the focus of my interest in the years to follow [62, 123, 124, 127, 164].

Since 1960 I had been confronted in my work by an increasing incidence of congenital malformations of a most unusual type. I had observed 13 such cases, 9 of them children with phocomelia or amelia, and following a simultaneous inquiry that led to knowledge of nearly 100 cases born since 1959, I wrote a paper that was to set alarm bells ringing, providing evidence of a convincing nature for an exogenous cause ("a newly introduced toxic substance") of these malformations. The publication appeared on September 16, 1961 [117]; it was the first to draw attention to what was later to be called the thalidomide catastrophe.

W. Lenz and W.G. McBride were credited with the successful identification of the noxious substance in question, just a few months later. I had been called to the chair of Pediatrics at the University of Kiel in the spring of 1961. The multitude of tasks and problems involved in moving to Kiel as a family of eight while at the same time planning new premises for the university's department of pediatrics, proved so time-consuming that I was not able to continue to devote the necessary energy to researching further the causes of the "epidemic of malformations."

However, since that time I have repeatedly addressed problems related to exogenous and, in particular, pharmacogenic teratogenesis [118–120, 144]. The thalidomide disaster inspired researchers from all over the world to perform more detailed and intensive research not only in the field of human teratology but the whole area of prenatal nosology and pathology. As a member of the committee founded by the German Research Association (*Deutsche Forschungsgemeinschaft*, DFG) soon after the "epidemic of embryopathies," I was involved in the DFG-sponsored study on "The course of pregnancy and child development." In this study, which can be compared with the U.S. "Collaborative Perinatal Project" (1959–1966), a total of 14,774 women were enrolled between 1964 and 1972. In all, 7,870 pregnancies were followed and the children examined regularly up to the age of 3 years [12–14, 33, 169]. Although, thankfully, we did not find any exogenous causes of malformations comparable to thalidomide, we cannot be sure that such a teratological catastrophe will not happen again—whatever the cause might be.

KIEL: SKELETAL DYSPLASIAS, INBORN ERRORS OF METABOLISM, MALFORMATION SYNDROMES

Most of my scientific work during the years I spent as Head of the Department of Pediatrics at the University of Kiel (1961–1980) was again related to hereditary skeletal dysplasias [2, 8, 25, 26, 38, 42, 44–46, 54, 55, 68, 72–74, 82, 83, 125, 126, 134, 163, 166, 172, 178], the

mucopolysaccharidoses and mucolipidoses [1, 69–71, 75–81], as well as other dysmetabolic and congenital disorders [10, 18, 19, 27, 28, 31, 60, 64–66, 84, 85, 143, 157, 159, 160]. My interest occasionally also turned to chromosome aberrations ([35, 88–91, 121, 180–182]; see also [32]), malformations, and malformation syndromes [17, 21, 22, 36, 37, 61, 135, 139, 140, 161].

I had at my disposal a thesaurus of unusual cases of skeletal dysplasia, which I had compiled—in part together with the human geneticist Hans Grebe (see [20])—during my years in Bonn and Krefeld. When Jürgen Spranger, a highly talented and resolute pediatrician, joined my staff in Kiel in 1963, I assigned him to my "old" field of interest, and we made contact with Maurice Lamy and Pierre Maroteaux in Paris. Maroteaux possessed a similar thesaurus of considerable size and significance, and we began to work together closely. The results of our collaboration included the identification of "metatropic" dysplasia [45]. In the same year we described dysplasia spondyloepiphysearia congenita ([68]; see also [42, 46]) and also reported, soon afterward, on the first observations in Europe of the cartilage hair hypoplasia described by Victor McKusick [166]. Further, we presented a new type of "metaphyseal" dysplasia as well as a special type of "campomelic" dysplasia [178; 83]. At the Thirteenth International Congress of Pediatrics, held in Vienna in 1971, I gave a lecture on skeletal dysplasias [134]. Three years later, our atlas of "Bone Dysplasias" was published [82].

Jürgen Spranger deserves the major part of the credit for this atlas, which was soon recognized as a standard reference work. His contributions to the studies on mucopolysaccharidoses and mucolipidoses were even more significant.

I have devoted a considerable amount of time and energy to studies on sphingolipidoses and other inborn errors of metabolism, including a special type of disorder that comes closest to type C of Niemann–Pick disease ([157]; see also [31, 64, 65, 85]). Other studies have been concerned with questions of heredity and diagnostic problems [10, 18, 19, 27, 28, 66, 84, 143, 159, 160]. The credit for our communications on various chromosomopathies is mainly due to Marlies Tolsdorf, with whom I worked for many years. It was she who organized and chaired the 1970 Annual Meeting of the Federal German Human Cytogeneticists, which was held in Kiel.

I shall mention only a few of the syndromes with which I was involved. In 1973, on the basis of a few brief descriptions in the early literature, as well as of a report by E. Genée of a patient diagnosed as a case of Treacher Collins syndrome and the studies in a case of myself, I described and distinguished a syndrome that is nowadays termed "acrofacial dysostosis of Genée–Wiedemann type" ([135]; see also [47]).

In the spring of 1964, based on the findings in three cases, I published a report on a "new syndrome" [122], the symptoms of which were later combined with the findings reported by Bruce Beckwith in a pathologic-anatomic lecture in November 1963 [5] to form what I later termed the "EMG," i.e., exomphalos–macro-glossia–gigantism syndrome. Today this syndrome is

more commonly known as Beckwith–Wiedemann syndrome or Wiedemann–Beckwith syndrome and has proved to be not only of practical importance but also most problematic for obstetricians, neonatologists, pediatricians, oncologists, and human geneticists. I have repeatedly addressed this topic [128–130, 133, 136–138, 179].

My interest has also been directed repeatedly to progeria and progeroid syndromes [51, 97, 98, 131, 132, 141, 142]. In 1979 I attempted to define a “neonatal pseudo-hydrocephalic progeroid syndrome,” referred to in the literature today also as the Wiedemann–Rautenstrauch syndrome [15]. However, as it was not possible to draw definite nosologic boundaries, I prefer to maintain that the question as to whether or not this syndrome represents a separate entity remains open.

In 1976 the first edition of my atlas “The Characteristic Syndrome” (*Das charakteristische Syndrom*) [161] was published, which I prepared with the help of F.R. Grosse and the photographic skills of Herta Dibbern. This atlas apparently filled a gaping void in the European market and was soon translated into other languages. Further, I authored a chapter entitled “The pathology of heredity” (*Pathologie der Vererbung*) that was included in the 20th to the 24th editions (1962–1980) of the oldest German-language textbook on pediatrics, founded and originally edited by the Swiss pediatrician, Emil Feer. In 1972 I contributed a chapter entitled “Malformations and dysmorphia syndromes” (*Mißbildungen und Dysmorphie-Syndrome*) to the 9th (and last) edition of an international textbook on pediatrics edited by G. Fanconi (Zürich) and A. Wallgren (Stockholm).

PROFESSOR EMERITUS: PEDIATRIC GENETICS AND HUMANITIES

Although I have tended to occupy myself more and more with the humanities since I retired from academic life in 1980, I have still remained faithful to clinical genetics [3, 7, 16, 23, 24, 30, 41, 43, 47, 48, 59, 63, 145, 146, 148–150, 152, 153, 156, 158, 168, 170]. As I have almost always proceeded from clinical observations, I have had (and still have) a good basis for further studies. To mention just a few, these have included my description of a previously unknown type of “mesomelic” dysplasia [41] and a variety of other reports on unusual observations [16, 24, 30, 48, 150, 168, 170]. Perhaps particularly worthy of mention was my description in 1983 of the Proteus syndrome as a separate entity [156; 7, 43, 149] on the basis of four observed cases. This article led to an abundance of other publications on the same subject.

Since 1980 I have published further articles on the EMG syndrome, progeria, and progeroid disorders [67, 147, 155; 52, 151]. The second, considerably more voluminous edition of my “Syndrome Atlas” appeared in 1982. Moreover, an English edition was published in 1985 and a Spanish edition in 1987 [162]. My “pupil” Jürgen Kunze (Berlin) made a significant contribution to the third edition, which was even larger and more extensive than the second and appeared in 1989 [167]; English version appeared in 1992). The atlas includes a number of long-term studies (some lasting over three

decades), which are far easier to perform in “old Europe” than, for example, in the United States.

If our field of clinical genetics can be compared to a mosaic, then I hope that I have succeeded in contributing a few small stones to the overall picture. I would be delighted if I were able to add a few more in the years to come.

Finally, I should like to take this opportunity to express my sincere thanks to my dear wife, Gisela, without whose inexhaustible patience and constant, gladly given support I could hardly have achieved my professional and scientific goals. I am equally grateful to magnanimous friends all over the world—not least to those in Helena, Montana.

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