Wegener's granulomatosis: the man behind the eponym

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THE STORY OF Wegener's granulomatosis began in 1931 when Heinz Klinger, of Charity Hospital and the Pathological Institute of Berlin University, reported the first case.[1] Working under Professor Robert Rossle, Klinger described a 70-year-old physician who had severe destructive sinusitis, arthritis, fever, glomerulonephritis, and uremia. At autopsy, splenic granuloma, glomerular lesions, and periarteritis nodosa-like arteritis were found. Serologic and bacteriologic studies and microscopic stains for microorganisms were performed in vain in the search for a causative agent. Klinger felt his case represented a borderline form of periarteritis nodosa (PAN).

Klinger had joined Charity Hospital in 1930, where the great pathologist, Rudolf Virchow, had founded the *Archiv für pathologische Anatomie und pathologische Physiologie und für Klinische Medizine* in 1847. In his autobiography, *Wege und Nebenwege* (Parallel Ways), Klinger noted: "After getting familiar with the Institute Staff, I was asked by Rossle to write a paper on borderline forms of periarteritis nodosa. The works and autopsy records served as a basis for it. My study could be examined as an MD thesis." It appeared in 1931 in *Frankfurter Zeitschrift für Pathologie*.[2]

One year later, Klinger received his medical degree from Berlin University.[3] His name, therefore, is indelibly etched in the history of vasculitides. Unfortunately, Klinger's association with Charity Hospital ended because of his pursuit of the practice of surgery. He joined Dr. Brutt at Hafen Hospital in 1932 and did not write any more articles on this subject.

Klinger's observation was extended by Dr. Klaus Hoffmann in 1932 in his dissertation, "A Case of Granulomatosis with Changes of Arteritis," and by Rossle in 1933 in his paper, "The Rheumatic-Type Inflammation of Vessels."[4] Hoffmann earned his doctorate at the Pathological Institute of Hamburg, but he was not interested in reporting his case.[5] It was during the Congress of the German Pathological Society, held in Breslau in 1936, that Friedrich Wegener became aware of Hoffmann's patient.[5] When Rossle published his case, he was Director of the Pathological Institute of Berlin University and an authority on liver diseases; he had suggested the currently accepted definition of cirrhosis in 1930.[6] However, Rossle wrote no further articles about vasculitis and granulomatosis.

Klinger's 1931 paper remained obscure and buried in the medical literature until the first of Wegener's two reports appeared in 1936.[7] In a short communication, Wegener described three patients with a distinctive disease characterized by a septic course, PAN-like arteritis, glomerulonephritis, and granulomatosis of the nasopharynx and larynx. He freely acknowledged the earlier work of his friend and colleague Heinz Klinger: "In publications available to me, there is a report by Klinger of a case described as a borderline form of PAN in which very severe nasal changes were also found."[7]

Thus, Wegener was very much aware of Klinger's work under Rossle. Wegener and Klinger were con-

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Heinz Klinger, MD, left, and Friedrich Wegener, MD, right, in Lubeck, Germany, April 4, 1982. Both men were 75 years old.
Photograph by Mrs. Ursula Wegener

temporary students at the Kaiser Wilhelm High School in Wilhelmshaven and had both studied and lived in Munich from 1926 to 1929.[4] In 1939, Wegener published a more detailed description of his original three cases.[8] Here he preferred to use the term "rhinogenic granulomatosis" because he believed that the nose was the primary site of the new disease. In a vagary of medical history, it was neither Klinger's nor Rossle's, but Wegener's name that became the eponym of the disease.[9]

PROGRESS SINCE 1940

Typical cases of necrotizing granulomatosis were published in America between 1940 and 1950 under headings of pulmonary cavitation due to polyarteritis, pulmonary lesions of PAN, PAN in granuloma of unknown etiology, chronic granuloma associated with PAN, giant cell granuloma associated with lesions resembling PAN, and necrotizing granulomatosis and angiitis of the lungs.[10–15] These cases were believed to be unusual cases of the "granulomatous" variety of PAN[13] or to be related to, but not identical with, PAN.[15]

In 1952, Dr. Pearl Zeek, whom we lost in 1991,[16,17] published an authoritative article on the classification of necrotizing angiitis. According to Zeek,[18] most vasculitides could be grouped into five distinct types: periarteritis nodosa, hypersensitivity angiitis, rheumatic arteritis, temporal arteritis, and allergic granulomatosis angiitis. Notably absent from this list was Wegener's granulomatosis, which was virtually unknown in America.[19]

In 1954, Godman and Churg[20] described the anatomic features of Wegener's granulomatosis and reviewed the pathologic anatomy and nosologic relationships of this disease; an avalanche of reports in the English-language medical literature followed. As originally defined, the diagnosis relied on recognition of a characteristic histologic triad: granulomatosis, angiitis, and glomerulonephritis. It became known subsequently that all three classic criteria need not be present concurrently in all patients with Wegener's granulomatosis.[21]

At first, however, it was impossible to classify Wegener's granulomatosis in Zeek's system. Although Wegener's granulomatosis possesses the histologic attributes found in Churg-Strauss syndrome, no history of allergic disorders such as asthma or allergic rhinitis is usually present. Over the ensuing years, a number of authors attempted to include Wegener's granulomatosis into the group of vasculitides.[9] The American College of Rheumatology also attempted to establish rigid criteria for the

diagnosis of Wegener's granulomatosis.[22] More recently,[23] Wegener's granulomatosis, PAN (especially microscopic polyarteritis), Churg-Strauss syndrome, and pauci-immune necrotizing and crescentic glomerulonephritis have all been encompassed into the group of antineutrophil cytoplasmic antibody-associated vasculitis.[23] With the possible exception of Churg-Strauss syndrome, all of these syndromes require immunosuppressive treatment that includes the use of cyclophosphamide.[23]

Much has changed in the diagnosis and treatment of Wegener's granulomatosis since 1931. The discovery of antineutrophil cytoplasmic antibody, which appears to be related to the pathogenesis and the natural history of Wegener's granulomatosis, was a step forward.[24] Dr. Klinger was aware of the eponym of the disease but he did not contest the priority of his description. He simply lamented: "My thesis had the effect of a stone when thrown into the water. It created ripples without my knowledge."[2]

Klinger continued to practice surgery in Hamburg and later became a medical adviser to the Ministry of Justice. He maintained a lifelong friendship with Dr. Wegener up to the time of his death in 1983.

Pearl M. Zeek, MD, in Williamsburg, Ohio at age 90.
Courtesy of Dr. Zeek

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