Franz Volhard in Historical Perspective

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Franz Volhard was the dominant German clinician in the first half of this century. His work placed the classification of renal disease on a firm, pathologically oriented footing and gave the syndrome of uremia meaning in terms of not only renal dysfunction but also with respect to the participation of other organ systems. Furthermore, Volhard elucidated the pathogenesis of hypertension and stimulated important research. George Pickering and Irvine Page, both critical and discerning individuals who did not dispense praise lightly, recognized the contributions and qualities of Franz Volhard. "If I had to pick one person as having been the most influential in developing the field (ie, hypertension), I would without hesitation select Franz Volhard," Page wrote.1 "He had an engaging 'Falstaffian' sense of humor, perceptiveness, and ample common sense," Pickering noted.2

Volhard the Man

Volhard was born in 1872 in Munich and attended school in Erlangen and Halle, where his father was professor of chemistry. He had a rich and varied education that included a solid background in literature and music. Before graduating from high school, he creditably performed the Mendelssohn violin concerto and continued to participate in amateur performances all his life. Music was a passion for Volhard's entire family, and his wife and 10 children commanded a variety of instruments.

Volhard studied medicine in Bonn, Strasbourg, and Halle. His teachers included Pfliiger, Naunyn, Schmieden-berg, and von Mering. He completed his dissertation on the pathology of eclampsia and subsequently worked in the pathology department of Hansemann in Berlin. This experience was to influence him for the rest of his life. He took up a career in internal medicine by chance, in that the department chairman, Rieger in Giessen, was the only chairman who would allow him to marry. In Giessen he identified and characterized gastric lipase and published a series of investigations qualifying him for faculty rank (Habilitation).

Volhard developed an even keener interest in cardiology. He performed a series of studies to characterize the arterial and venous pulses. He noted greatly increased parasystolic venous pressure in patients with pericarditis. These observations, coupled with experience in the autopsy rooms with Hansemann in Berlin, led to his recognition of constrictive pericarditis as a treatable entity. His subsequent paper with the surgeon Schmieden showed how the disease could be recognized during life as well as the excellent results that followed the surgical removal of the constricting pericardium.3 Volhard and Schmieden recognized that the left ventricle had to be freed of constriction before the right ventricle could be addressed.

Volhard developed a method of preserving cardiac specimens by dehydrating them and fixing them in extended position with hot paraffin. The paraffin was poured inside the hearts, so that it filled and dilated the chambers and impregnated the cardiac tissue itself. Later, the excess paraffin inside and outside the chambers was removed and the heart allowed to cool. What remained was a perfect paraffin cast of the whole heart, which with the aid of cut windows allowed an excellent display of the size of the cavities, the thickness of their walls, and the condition of the valves or congenital defects. Volhard showed these specimens during his only visit to the United States. To convince the customs official in New York of the scientific merit of the exhibition, Volhard assured the man that the heart of Otto von Bismarck was among the specimens.4

Pulmonary disease also occupied Volhard's attention, and he developed a positive pressure respirator with clinical utility. He also described a bedside method of assessing peak flow in patients with bronchospastic and emphysematous lung disease, which preceded the current bedside tool by 70 years.4

Volhard led departments of internal medicine at the Luisenhospital in Dortmund (1905-1910) and in Mannheim (1910-1918). He was able to attract a young pathologist, Fahr, to Mannheim to join him, which resulted in a partnership that revolutionized glomerulonephritis (Bright's disease). In 1918, he was called to the University of Halle, his alma mater, where he chaired the department of internal medicine until 1928. In 1928, he was called to become chairman of internal medicine at the University of Frankfurt until 1938, when he was unceremoniously dismissed. Volhard had vociferously declared himself against Nazi candidates for department chairmanships,5 which led to his losing his own. But in 1945, the Nazi rule was finished; Volhard returned to pick up the pieces of his literally shattered department and to rebuild it. This task occupied him until 1950, when he died from injuries obtained in an automobile accident. When he died, he was mourned by his pupils, colleagues, and patients alike.

Volhard's Contributions

Volhard's major contributions were the classification of Bright's disease, the interpretation of its clinical...
manifestations, and the mechanisms of essential hypertension. As Pickering emphasized, scientific advances are simplifications that introduce order into chaos. These simplifications are subsequently testable by the scientific method. Volhard's views were by no means all correct; however, they were clear, concise, and testable by observation and experiment.

Volhard and Fahr published one of the most important nephrology textbooks of all time, Die Brightsche Nierenkrankheit. Klinik, Pathologic und Atlas, in 1914. In the text, they divided Bright's disease into three entities: (1) degenerative diseases, such as nephrosis (nephrotic syndrome), with an acute, chronic, or end-stage course; (2) inflammatory renal disease, such as either focal (acute, chronic, postinfectious-interstitial) or focal embolic, or diffuse glomerulonephritis with obligatory increased blood pressure in three stages: acute, subacute, or chronic, ie, end-stage; the latter two could occur with or without nephrotic features; and (3) arteriosclerotic renal diseases, either simple benign ("red") hypertension or the combined ("pale") form of malignant, genuine contracted kidney (sclerosis with or without nephritis). Volhard's nephritis with and without nephrotic components correspond to Ellis' types I and II and Longcope's types A and B. Volhard and Fahr's contributions were dependent on their constant, combined collaboration at the microscope, an ideal example of "clinical" research.

Volhard defined the clinical aspects of uremia. He recognized the work of Koranyi regarding dilution and concentration of the urine and applied these principles clinically with appropriate tests of his design. He realized that isosthenuria is a feature of chronic renal failure. More importantly, he emphasized the "body as a box" phenomenon as applied to renal insufficiency. Whatever goes in, must come out, Volhard concluded. In this regard, he formulated sensible dietary approaches to uremia, initially to deal with an epidemic of infectious (probably poststreptococcal) glomerulonephritis during World War I. His approach of curtailing salt, water, and protein intake by means of dietary restriction reduced the mortality of this condition from 20% to almost 0%. Volhard extended this treatment with success to patients with severe hypertension and noted improvements, a fact that was not lost on subsequent observers such as Walter Kempner. Pickering visited Volhard in Frankfurt and observed that Volhard also had his difficulties with compliance to a reduced salt regimen. This amused Pickering, and German patients developed their own cliché, Lügen wie ein Salzlöser, ie, lying as one who is "salt free." Volhard also realized the importance of volume depletion, as it accompanies the relief of lower urinary tract obstruction for example, and advocated appropriate administration of saline for this condition.

Volhard divided the symptoms of uremia into true uremia, a consequence of reduced renal function, and pseudo uremia, symptoms that have an independent origin, such as those related to elevated arterial blood pressure or eclampsia. He was a student of the eye, and saw within it a clinical key. He recognized vasospasm, hemorrhages, exudates, and papilledema. He coined the term retinitis vasospastica, ie, vasospasm in the face of severe hypertension with proteinuria. Volhard recognized that papilledema represented increased intracranial pressure.

Volhard was able to show that uremic conditions, such as psychosis, cardiac asthma, Cheyne-Stokes respiration, claudication, Raynaud's disease, and transient blindness, were not related to decreased renal function per se but rather were accompanying phenomena, which he believed were due to ischemia from resulting vasospasm. He may have been in part correct, although embolism from various sources including mural thrombi, platelet emboli, and detritus from atheromatous plaques also provides an explanation.

Finally, Volhard was fascinated by hypertension. He recognized that high blood pressure distinguished nephritis from nephrotic syndrome and also felt that it separated acute diffuse from focal glomerulonephritis. In 1923 (Vienna), he first separated the condition into "pale" hypertension, in which patients tended to show pallor of the skin, extremely narrowed retinal vessels, and eventually papilledema, and "red" hypertension, which followed a more benign course. He believed that intense vasospasm and increased vascular resistance were etiologically responsible for tissue ischemia in patients with pale hypertension, which included patients with eclampsia, chronic glomerulonephritis, accelerated or malignant hypertension, and nephrosclerosis. In red hypertension, he could see no signs of intense vasoconstriction. These patients included most of what is termed essential hypertension. They had no evidence of pronounced peripheral vascular constriction and may have had an increase in cardiac action or decrease in large vessel compliance responsible for their
condition. Volhard believed that the red hypertension could proceed to pale under appropriate conditions.

Volhard believed that age and inheritance were primarily responsible for changes in the condition of the blood vessels and concluded that these were incisive factors indeed in the development of red essential hypertension. Volhard ascribed a major role to genetic variance and was aware of the studies of Waiz from Tübingen, who first gave the genetic idea a firm scientific footing. It remained for Pickering to convincingly demonstrate the polygenetic nature of the condition.

Eventually, Volhard considered the idea that alterations in baroreceptor reflexes played a role as well. He developed this notion in Frankfurt after World War II and based it on the findings of his resident physician, Lampen, who succeeded in anesthetizing the carotid sinus with procaine and thereby observed a significant increase in blood pressure in normal volunteers. Lampen's experiment may have been the first example of experimentally induced neurogenic hypertension in humans. The significance that these observations had in terms of suggesting a role for altered baroreceptor reflex sensitivity, increased sympathetic nervous system tone, and possibly a central nervous system participation in the pathogenesis of essential hypertension cannot be overemphasized. Volhard concluded that red essential hypertension most likely begins as a genetically influenced phenomenon of increased cardiac action (ie, output), perhaps directed by altered regulation from centers in the brain via the autonomic nervous system. Secondary vascular changes, including thickening in small arteries and decreased compliance in large ones, would then account for the eventual increase in peripheral vascular resistance. Volhard's speculations prompted a whole line of research in this direction.

Volhard believed that pale hypertension was caused by humoral substances, most likely released by the kidneys. Work from his own collaborators was not entirely successful in corroborating a sustained hypertension after a reduction of renal blood flow, although they were close. In 1930, Volhard's collaborator Hartwich was able to show that ligation of branches from the renal artery of the dog led to at least a transient increase in blood pressure and speculated that a humoral mediator was responsible. Volhard was aware of and excited by the work of Harry Goldblatt, which was in accord with his own notion. In 1938, additional work from Volhard's laboratory showed that Goldblatt hypertension developed even in the absence of the pituitary or the adrenal gland (see Reference 12). It has since been shown that malignant hypertension is invariably accompanied by an excess of renin in the blood or tissues. Volhard realized that malignant pale hypertension was accompanied by vessel wall destruction, vasoconstriction, and eventually irreversible organ (renal) damage. His own work, writings, and teaching in this area of hypertension research greatly enhanced important work by others.

**Volhard the Clinician and Teacher**

Volhard was a bedside clinician, who wrestled with his patients' problems and took these directly to the laboratory or to the autopsy suite if necessary to find their solutions. His keen and compulsive sense of observation, adroit clinical reasoning, and application of the scientific method led to his seminal contributions to cardiovascular and renal disease. As a teacher, mentor, and role model, he was unsurpassed. In that regard, he represented for Germany the embodiment of an international tradition of clinical inquiry founded by individuals such as Rudolf Virchow, William Osler, and Harvey Cushing. (Volhard and Cushing both received honorary doctorates from the University of Paris in 1933.) Volhard was instrumental in promoting clinical research and advanced the notion of the clinician scientist in the framework of basic science. He was focused in his activities but not to the extent of narrow-mindedness.

His house staff and students were expected to perform their own routine laboratory testing on their patients before presenting them at morning report. The laboratories were close to the wards and provided an ideal opportunity for clinical research. Volhard collaborated eagerly and actively recruited pathologists and laboratory scientists to partake in his endeavors. He strayed from the teutonic format of didactic lectures and relied on patient presentation and case solutions, and audience participation. Volhard realized that the latter is seldom voluntary, so he actively involved the listeners with penetrating questions.

Volhard was a spellbinding teacher. His clinical and scientific contributions were contained within his lectures, which he found most successful when spoken freely rather than when read from a prepared text. However, Volhard kept careful lecture notes and published these in a volume that first appeared in 1942. An example of his depth and perception is a lecture titled "The funduscopic examination in the understanding of hypertension and renal disease," which was delivered in Dresden in 1936. In the lecture, Volhard illustrates the systemic nature of hypertension and renal disease by drawing attention to intense retinal vasospasm, which accompanies severe hypertension. The worst cases were accompanied by choked discs, discrete retinal lesions, and decreased vision. Volhard interpreted this finding as indicative of generalized vasospasm in other areas of the body, particularly the brain, heart, and kidneys. He believed that the functional disturbance of ischemia was subsequently followed by vascular structural changes. Volhard illustrated the reversibility of this condition by presenting a patient with a blood pressure of 220/150 mm Hg, who presented with headache and blindness. The heart was enlarged, and the renal function was reduced, as reflected by a blood urea concentration of 116 mg/dL. The patient was treated with dietary salt, protein, and caloric reduction and eventually left the hospital with normal vision and only moderately reduced renal function. The choked discs and intense vasospasm were gone. Volhard also recognized that not all such cases were primarily due to pale hypertension or renal disease. He indicated that eclampsia and tumors of the adrenal medulla could also cause a similar clinical picture. Furthermore, he emphasized that attacks of sudden tachycardia and sweating were useful clues in identifying the latter.

Despite his outspokenness, Volhard expressed an inner humility and was openly able to recognize errors and misinterpretations, including his own. He was familiar with and used the phrase "today's dogma will be tomorrow's blunder" (*die Wahrheit von heute ist der
Irrtum von morgen). The German government has decided to honor the name of Franz Volhard by dedicating a clinic for cardiovascular and renal research in Berlin in his honor. This clinic is to provide not only exemplary patient care but also to conduct research on the topics that preoccupied Volhard. In light of Volhard's own contributions and the above statement, the challenge is considerable.

Acknowledgments
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References

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