Clin. Cardiol. 28, 158–159 (2005)

Profiles in Cardiology

This section edited by J. Willis Hurst, M.D., and W. Bruce Fye, M.D., M.A.

Albert von Bezold and Nervous Control of the Heart

HEINZ-GERD ZIMMER, M.D.

Carl-Ludwig-Institute of Physiology, University of Leipzig, Leipzig, Germany

Ludwig Friedrich Albert von Bezold (1836–1868) (Fig. 1) was born on January 7, 1836, in Ansbach, located in the southern part of Germany, as the eighth child of a physician. He started his study of medicine in 1853 in Munich. It was there in 1854 that he acquired rheumatic arthritis that also affected his heart, resulting in stenosis of the mitral valve.[1,2] He continued his studies in Würzburg and attended the lectures of Rudolf Albert von Kölliker (1817–1905).[3] In 1857, he moved to Berlin and worked in the laboratory of Emil Du Bois-Reymond (1818–1896). In 1859 he was appointed professor of Physiology at the University of Jena. In 1865, he moved to Würzburg where he became professor and chairman of physiology and successor to Albert von Kölliker who concentrated on anatomy. von Bezold was an extremely productive and energetic physiologist, his writing was straightforward, clear, and crisp. He died at the age of 32 from the consequences of mitral stenosis. His successor became Adolf Fick (1829–1901).

In his research, von Bezold was influenced by the electrophysiologic works of von Kölliker and Du Bois-Reymond. In 1856, von Kölliker and H. Müller had shown that an electrical current accompanies muscle contraction. Furthermore, they had placed the nerve of a nerve-muscle preparation on the ventricular surface of a beating frog heart and showed that the frog leg contracted with each cardiac cycle.[4] Emil Du Bois-Reymond had previously discovered the "action potential."[3] As a student in Würzburg von Bezold had already won a prize for his comparative experimental study on the problem of which nerve fibers crossed in the spinal chord.[2] He published his results on vagus stimulation of the isolated frog heart[5] and confirmed the results of the Weber brothers.[6] He postulated that the heart is under constant vagus influence; he also investigated the effects of Stannius ligatures in the frog heart,[5] and then turned to studies on electrical excitation of nerves and muscles.[2]

In his cardiovascular research, von Bezold became interested in nervous control of the heart. He used veratrine obtained from the poisonous roots of *Veratrum album* or from the seeds of *Veratrum Sabadilla*. When he injected veratrine into the jugular vein of a rabbit, he noted a marked reduction in blood pressure and a negative chronotropic effect; when both vagus nerves were cut, however, heart rate and blood pressure increased immediately.[7] His interpretation of the acute effect was that afferent impulses originated in the heart and were transmitted to the vasomotor center via the vagus. Shortly before, Cyon and Ludwig had found the depressor nerve;[8] von Bezold named his finding the "veratrine reflex."

About 70 years later, Adolph Jarisch (1891–1965), an Austrian pharmacologist, rediscovered and confirmed the "Bezold effect." He showed that veratrine induced a dramatic blood pressure depression in cats (Fig. 2). He could reverse this by blocking the vagus nerve. Instead of cutting, as von Bezold did, he applied cooling to both vagus nerves: blood pressure increased again. After warming the vagus nerves, blood pressure decreased again. These changes could be repeated in a reproducible manner (Fig. 2).[9] The veratrine reflex is now known as "Bezold-Jarisch reflex."

Albert von Bezold also conducted studies on experimental myocardial infarction with regard to nervous control of the heart.[10] In the pulsating heart of ventilated rabbits, he clamped the descending branch of the left coronary artery, thus inducing ischemia of the left ventricular wall, which turned pale. To investigate the relation of ischemia and the intracardiac nervous system, he cut the vagus, the sympathetic nerve fibers, and the spinal chord, and eliminated both brain hemispheres. In addition, he clamped the aorta to vary left ventricular filling. He recorded heart rate and arterial pressure. von Bezold observed no change in heart rate immediately after coronary artery occlusion and thereafter a decrease. After 45 up to 145

Address for reprints:

Heinz-Gerd Zimmer, M.D.
Professor of Physiology, Chair
Carl-Ludwig-Institute of Physiology
University of Leipzig
Liebigstrasse 27
D-04103 Leipzig, Germany
e-mail: zimmer @medizin.uni-leipzig.de

Received: November 13, 2003
Accepted: November 13, 2003

FIG. 1 Albert von Bezold (1836–1868). Reproduced from Ref. No. 2.

seconds, ventricular fibrillation occurred with arrest of the left and then the right ventricle. He was able to resuscitate the heart by electrical stimulation or by rhythmical mechanical compression of the ventricle. He could also increase heart rate by stimulation of sympathetic fibers.

Based on and inspired by these results, Julius Friedrich Cohnheim (1839–1884)[11] ligated branches of the coronary arteries in curarized and ventilated dogs and measured blood pressure in the carotid, pulmonary, and femoral artery as well as in the right and left ventricle. The chest was opened after removal of four ribs. The pericardium was cut, and one of the coronary arteries was ligated. This had no immediate effect on heart function and blood pressure. At the end of the first minute, however, arrhythmias developed while blood pressure remained normal. After approximately 105 seconds, there was a precipitous fall in arterial pressure, and cardiac arrest occurred in diastole in both heart chambers at the same time. After 10 to 20 seconds, fibrillations developed for 40 to 50 seconds while atrial contractions remained regular. When the ventricles were finally and completely arrested, they were dilated and could not be resuscitated,[12] in contrast to von Bezold's findings in the rabbit.

Cohnheim hypothesized that

> a positive substance which is directly poisonous for the heart had been generated during ligation of the coronary artery. On the one hand, nobody can deny a certain similarity of our typical curve with that obtained for instance with potassium poisoning; on the other hand, it is a long-known fact that products originate in the metabolism of muscles during contraction which are definitely dangerous for muscle and nerve activity. These substances are washed out continuously during normal contraction; when circulation is arrested, however, as after ligation of the nourishing arteries, these substances accumulate and are available in such amounts that they can execute their poisonous effect.[12]

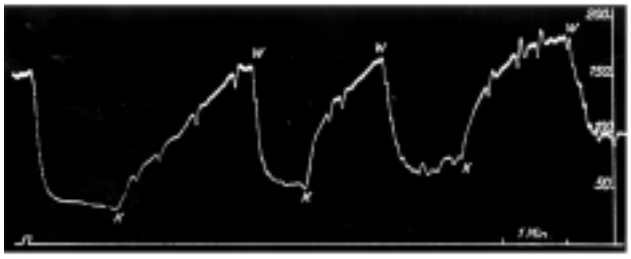

FIG. 2 Changes in blood pressure (mmHg) in an anesthetized cat in which 50 µg of veratrine were injected at the mark (bottom line). At K cooling, at W warming of both vagus nerves. Original Figure 2 in Ref. No. 9.

Cohnheim did additional experiments on rabbits and basically confirmed the results obtained by von Bezold.[12] He noted that weak rabbit hearts were more resistant to coronary artery ligation than strong healthy ones. The same was true for previously damaged dog hearts. It was concluded that a strongly contracting and healthy heart produces more of the poisonous substance after coronary artery ligation and thus is more sensitive to the occurrence of cardiac arrest. Also, von Bezold had observed that the occurrence of arrhythmias was delayed when the hearts had undergone previous maneuvers or when the coronary artery had been clamped repeatedly, which he attributed to the drop in temperature. On the other hand, elevation of aortic pressure accelerated the occurrence of arrhythmias in the ischemic heart.[10]

References

1. Rothschuh KE: *Geschichte der Physiologie*, p.133. Berlin, Göttingen, Heidelberg: Springer Verlag, 1953
2. Herrlinger H, Krupp J: Albert von Bezold, 1836–1868. Ein Pionier der Kardiologie. Stuttgart: Gustav Fischer, 1964
3. Fye WB: Rudolf Albert von Koelliker. *Clin Cardiol* 1999;22:376–377
4. von Kölliker A, Müller H: Nachweis der negativen Schwankung des Muskelstroms am natürlich sich kontrahierenden Herzen. Verhandlungen der Physikalisch-Medizinischen Gesellschaft in Würzburg. 1856;6:528–533
5. von Bezold A: Zur Physiologie der Herzbewegungen. *Virchows Arch* 1858; 14:282–309
6. Weber EH: Ueber Eduard Weber's Entdeckungen in der Lehre von der Muskelcontraction. *Arch Anat Physiol* 1846;483–527
7. von Bezold A, Hirt L: Über die physiologischen Wirkungen des essigsauren Veratrins. II: Von der Wirkung des Veratrins auf den Kreislauf. *Untersuchungen aus den physiologischen Laboratorien zu Würzburg* 1867; 95–115
8. Cyon E, Ludwig C: Die Reflexe eines der sensiblen Nerven des Herzens auf die motorischen der Blutgefässe. *Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft der Wissenschaften zu Leipzig. Mathematisch-Physische Classe* 1866;18:307–328
9. Jarisch A: Der Einfluss der Vagusausschaltung auf den Blutdruck. (Nachweis des Bezold-Effektes.). *Arch Kreislaufforsch* 1941;9:1–10
10. von Bezold A. Von den Veränderungen des Herzschlages nach Verschliessung der Coronararterien. *Untersuchungen aus den physiologischen Laboratorien zu Würzburg* 1867;I:256–287
11. Fye WB: Julius Friedrich Cohnheim. *Clin Cardiol* 2002;25:474–577
12. Cohnheim J, von Schulthess-Rechberg A: Ueber die Folgen der Kranzarterienverschliessung für das Herz. *Virch Arch Path Anat* 1881;85: 503–537