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Louis J. Acierno
University of Central Florida

L. Timothy Worrel
University of Central Florida

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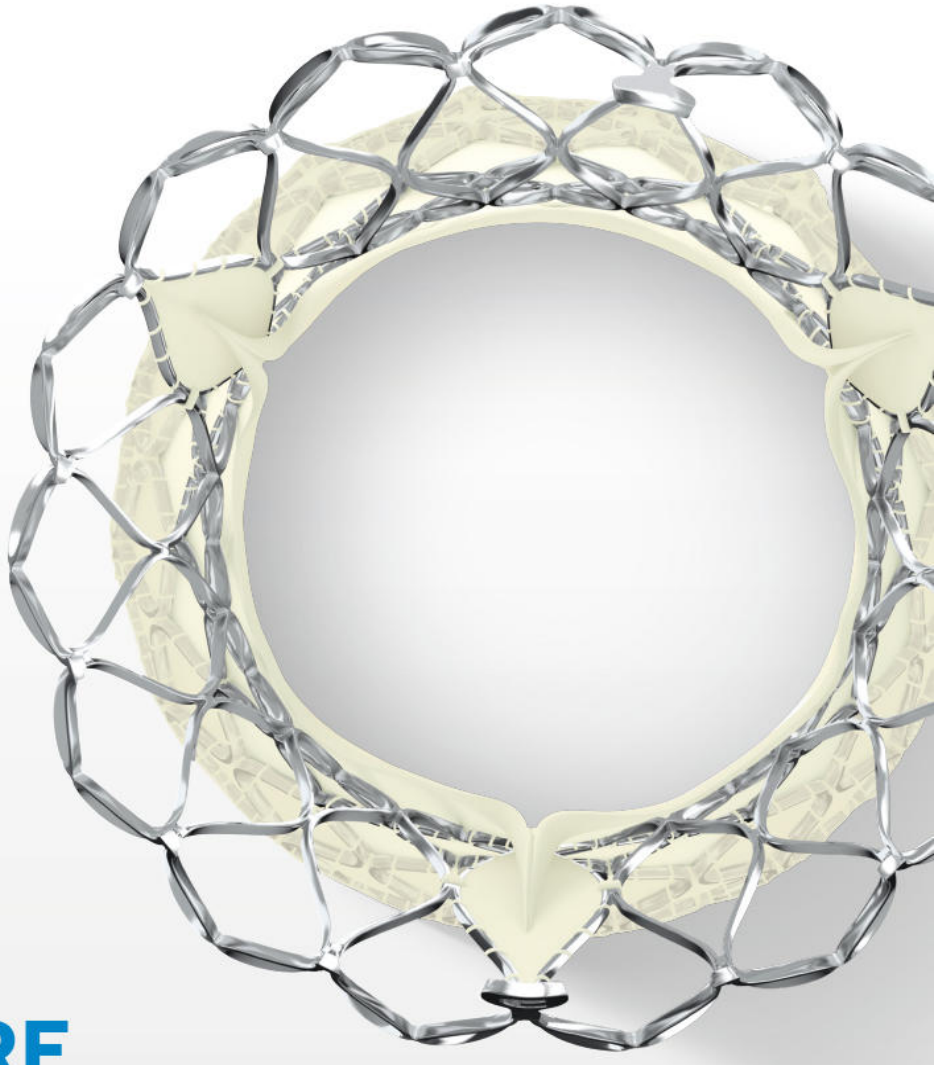

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Profiles in Cardiology

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Albrecht Fleckenstein: Father of Calcium Antagonism

LOUIS J. ACIERNO, M.D., F.A.C.C., L. TIMOTHY WORRELL, M.P.H., R.R.T.

University of Central Florida, College of Health and Public Affairs, Orlando, Florida, USA

Verapamil, the original calcium-channel-blocking agent, along with its congeners, has become a markedly important component in the current management of hypertension, ischemic heart disease, and certain cardiac arrhythmias—and we owe it all to Albrecht Fleckenstein (Fig. 1), described by his peers in the International Society for Heart Research as "an imaginative scientist, a remarkable human being and a colorful personality."[1]

Albrecht Fleckenstein was born in Aschaffenburg, Germany, in 1917 and died in Freiburg in 1992. He received his medical training in Würzburg and Vienna. His scientific career began in the Pharmacology Department of Würzburg University. World War II interrupted his career; during this time he was a prisoner of war of the American army for 2 years. With the cessation of hostilities, Fleckenstein was able to resume his scientific interests under Professor Eichholtz at the Department of Pharmacology at the University of Heidelberg.[2] During this time he completed his "Habilitation" in pharmacology and toxicology. This was in 1947 and he was only 30 years old.

Initially Fleckenstein's research was concentrated on the physiologic changes associated with pain and muscle contraction. As time went on, his attention shifted increasingly to metabolic and electrophysiologic changes of the heart.[2] In 1951, he became one of the first post-war German scientists to be offered an exchange appointment. His was at the Department of Pharmacology at Oxford University under Professor Burn. While working with Professor Burn at Oxford, he analyzed the mechanism of the potentiation and inhibition of the sympathomimetics by cocaine, and it was at this time that he introduced the term "neurosympathomimetics." Several years later, he introduced another term, "cathelectrotonic," which emphasized the importance of cation movements through the cell membrane for many physiologic processes. This term appeared in a monograph entitled "the potassium-sodium exchange as energy principle in muscle and nerve."[3] In 1956, he was appointed Chair of Physiology at Albert-Ludwigs-Universität in Freiburg im Breisgau. This was to become his intellectual home for the rest of his life despite invitations to move to both Basel and Graz. During his first year at Freiburg, his research concentrated on the relationship between energy-rich phosphates, contractility of cardiac muscle, and metabolic aspects of the excitation-contraction coupling. While he was engaged in this work he became interested in the interaction of cations with the contractile processes of cardiac muscle. This led him to report, in 1964, that prenylamine and verapamil have the same inhibitory action on the excitation-contraction coupling as calcium withdrawal from the Ringer's solution. He continued to use verapamil, originally known as iproveratril,[5] as a tool in the initial pharmacologic studies that led him toward the discovery of the "calcium antagonists" in 1968–1969. It was at this time that Dr. H. G. Kroneberg gave Fleckenstein a sample of nifedipine with the suggestion that it could also be a calcium antagonist.[3] Fleckenstein confirmed that nifedipine was indeed not only a calcium antagonist, but also one of the most active ones he "ever had in his hands."[3] Twenty more years of intensive pharmacologic work stimulated extensive theoretical and clinical research and development with important therapeutic consequences regarding calcium antagonists. In time, with verapamil leading the group, these antagonists were to become a new group of drugs for the treatment of angina pectoris, hypertension, and certain types of atrial arrhythmias.[3]

Fleckenstein also discovered the relationship of calcium to necrotization of cardiac muscle by isoproterenol. He discovered that blocking high-energy phosphates, resulting from excessive activation of calcium-dependent ATPase, prevented subsequent necrosis of the heart muscle. All this was attributable to the action of calcium antagonists.[1]

Address for reprints:

Louis J. Acierno, M.D., F.A.C.C.
University of Central Florida
College of Health and Public Affairs
P.O. Box 1622000
Orlando, FL 32816-2200, USA

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FIG. 1 Albrecht Fleckenstein. Reprinted from *Cardiovascular Drugs and Therapy*, 1992;7:182, Kluwer Academic Publishers, Boston, Mass., with permission.

Fleckenstein presented himself as a formidable figure with his booming voice and large physical presence. Despite this, he revealed himself as a generous, kind, and committed individual interested in the contributions of others and always willing to debate other points of view.[6] Fleckenstein was described by Bing[1] as an individual who disliked pretense and whose approach to science was original and refreshing because he went directly to the point. Bing goes on to describe an incident at the international meeting of the International Society for Heart Research in Freiburg, Germany, in 1973, wherein Fleckenstein, with apparent equanimity, silenced a group of rebel students who were about to disrupt the meeting for a banal reason. The students wanted to complain about the visiting Americans who, during a visit to the local museum, had deposited cigarette ashes into containers which the medieval sculptor had intended for a different purpose.[1] At another time, Nayler[4] describes an argument he had with Fleckenstein over the appropriate terminology for the drugs that Fleckenstein had labeled calcium antagonists. Some pharmacologists including Nayler believed a more appropriate term would be calcium-channel blocker. Again Fleckenstein "won the day" by saying with his usual honesty and simplicity that the term calcium antagonist was more appropriate because he thought of that designation.[4]

Fleckenstein was a prolific author, with more than 800 references documenting his intensive scientific activity. He received numerous international and national honors, which included honorary doctoral degrees from the universities of Munich, Heidelberg, Basel, Limburg (the Netherlands), and the National University of La Plata (Argentina). He also received the Albert Einstein World Award of Sciences, the Distinguished Investigator Award of the American Society of Clinical Pharmacology, the Award for Outstanding Cardiological Research of the International Society for Heart Research, and the American Society for Pharmacology and Experimental Therapeutics (ASPET) Award for Outstanding Basic Pharmacological Investigations. He was also an honorary member of national and international physiologic and cardiological societies too numerous to mention.[3]

Albrecht Fleckenstein was fortunate in sharing his professional and private life with his wife, Dr. Gisa Fleckenstein-Grün, who was also Professor of Physiology at the same university. Survived by his wife and three daughters, he was buried in St. Ulrich, a village in one of the valleys of the Black Forest.[3]

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