

# This Week's Citation Classic

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**Rona G, Chappel C I, Balazs T & Gaudry R.** An infarct-like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat. *Arch. Pathol.* 67:443-55, 1959. [Research Labs., Ayerst, McKenna, and Harrison, Ltd., Montreal, Canada]

This paper reported that the synthetic catecholamine isoproterenol produced massive myocardial necrosis in rats which resembled human myocardial infarction. The fact that coronary arteries were patent suggested that a relative ischemia, elicited by exaggerated  $\beta$  adrenergic stimulation and reduced coronary blood flow, is responsible for the infarct-like character of the myocardial necrosis. [The **SC<sup>®</sup>** indicates that this paper has been cited over 270 times since 1961.]

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"In 1957, my wife, Agnes (also a pathologist), two young sons, and I immigrated to Canada from Budapest, Hungary, where, inspired by Joseph Bal6, I had been involved in research on diabetic glomerulosclerosis. Good fortune brought me a position as head of pathology and toxicology at Ayerst Research Laboratories, Montreal, where R. Gaudry and C.I. Chappel initiated comparative studies on bronchodilators including a synthetic catecholamine in the developmental stage, CC-25. T. Balazs, who performed the subacute toxicity study, notified me of unexpected high mortality. I made the stunning discovery that the deaths appeared to be due to myocardial infarct. Previous toxicity studies in Germany made no mention of this lesion; furthermore, CC-25 was related to isoproterenol (ISO), a synthetic  $\beta$  adrenergic depressor catecholamine not known to have such an effect. On my recommendation, we investigated ISO under similar conditions, and

to our amazement, use of a wide dose range resulted in massive infarct-like myocardial necrosis. While the pharmaceutical companies concerned were very upset, I was elated as the door opened on 20 years of rewarding research.

"Appreciation- of the scientific value of our results was far from immediate; the paper cited as a classic was refused by several reputable journals including *Science* and *Lancet*. The finding that infarct-like myocardial necrosis could be produced without cutting off the blood supply to the myocardium was irreconcilable with the current medical knowledge. The only solid support came from the studies at the Büchner Institute at Freiburg im Breisgau during the 1930s which demonstrated the role of hypoxia in experimental disseminated myocardial necrosis.<sup>1</sup>

"On publication, our studies aroused great interest. The close correlation of dose to degree of severity offered a standardized technique for observing various interactions<sup>2</sup> and also the effects of drugs used to manage human myocardial disease. Among the scientists who applied our findings to basic research on cardiac metabolism and ultrastructure as well as in clinical cardiology was A. Fleckenstein, who developed a series of widely used Ca<sup>++</sup> antagonistic drugs.<sup>3</sup>

"Our research, based at Ayerst until 1965, moved to McGill University where, assisted by a succession of brilliant research fellows, we investigated the pathogenesis of ISO-induced myocardial necrosis, particularly the role of coronary microcirculatory factors<sup>4</sup> in the evolution of catecholamine-induced and reperfusion injury.<sup>5</sup> International recognition came in 1976 when I was awarded the prestigious Arthur Weber prize. In the same year, I was elected president of the American Division of the International Society for Heart Research."

1. **Büchner F, Weber A & Haager B.** *Koronarinfarkt und Koronarinsuffizienz.* Leipzig: Georg Thieme Verlag, 1935.
2. **Rona G, Chappel C I & Kahn D S.** The significance of factors modifying the development of isoproterenol-induced myocardial necrosis. *Amer. Heart J.* 66:389-95, 1963.
3. **Fleckenstein A.** Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle and their role in the prevention of production of myocardial lesions. (Harris P & Opie L, eds.) *Calcium and the heart.* London: Academic Press, 1971. p. 135-88.
4. **Rona G, Huüttner I & Boutet M.** Microcirculatory changes in myocardium with particular reference to catecholamine-induced cardiac muscle cell injury. (Meesen H, ed.) *Handbuch der allgemeinen Pathologie: Mikrozirkulation.* Berlin: Springer-Verlag, 1977. Vol. III, part 7. p. 791-888.
5. **Rona G, Badonnel M C, Huüttner I & Boutet M.** Reperfusion effect upon ischemic myocardial injury. *Exp. Mot. Pathol.* 31:211-18, 1979.