In 1957, my wife, Agnes (also a pathologist), two young sons, and I immigrated to Canada from Budapest, Hungary, where, inspired by Joseph Balazs, 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 cate-cholamine 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.1

On publication, our studies aroused great interest. The close correlation of dose to degree of severity offered a standardized technique for observing various interactions2 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++ antagonistic drugs.3 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 factors4 in the evolution of catecholamine-induced and reperfusion injury.5 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.

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 SCP indicates that this paper has been cited over 270 times since 1961.]

G. Rona
Department of Pathology
Pathology Institute
McGill University
Montreal, Quebec H3A 2B4
Canada
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