



Matters @ Heart

Franklin Delano Roosevelt and the treatment of hypertension

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Franklin Delano Roosevelt, President of the United States, died on April 12, 1945 in Warm Springs, Georgia, of a cerebral hemorrhage resulting from hypertension. As related by his attending cardiologist, Howard G. Bruenn, his blood pressure on the day of his death was 300/190 mm Hg. The President had suffered from hypertension since 1935. Bruenn ends his article written in 1970, "I have often wondered what a turn



◀ Irvine Heinly Page (1901-1991) was active in the field of hypertension for almost 60 years with major discoveries relating to serotonin, the renin-angiotensin system (coining the word "angiotensin"), and the mosaic theory of hypertension. © National Library of Medicine, History of Medicine Division.



◀ Harry Goldblatt (1891-1977) showed, in his celebrated landmark experiments, that clamping the kidney arteries of dogs resulted in production of a "pressor substance," causing constrictions of the arterioles throughout the body. In its April 15, 1940 edition, Time Magazine ventured the pessimistic opinion that, "although fellow physicians hail Dr Goldblatt's work as one of the great medical contributions of the last 20 years, they admit that, so far, nothing much can be done with it...." © National Library of Medicine, History of Medicine Division.

the subsequent causes of history may have taken if the modern methods of the control of hypertension had been available." Since Roosevelt's death, treatment of hypertension has been spectacular. This is astonishing when one considers that there were questions in 1940 as to the rationale of treating high blood pressure; it was



Eduardo Braun-Menéndez (1903-1959), hailed by fellow Argentinean Nobel prize winner (Physiology or Medicine) Bernardo Houssay as "an extraordinarily gifted master, devoted to science and culture... who was like an powerful beacon guiding us with certainty through the dark night of ignorance and confusion..." Braun-Menéndez' "hypertensin" and Page's "angiotensin" were ultimately re-minted to become "angiotensin."

Photo courtesy of: Centro de Divulgación Científica (CDC), Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires.

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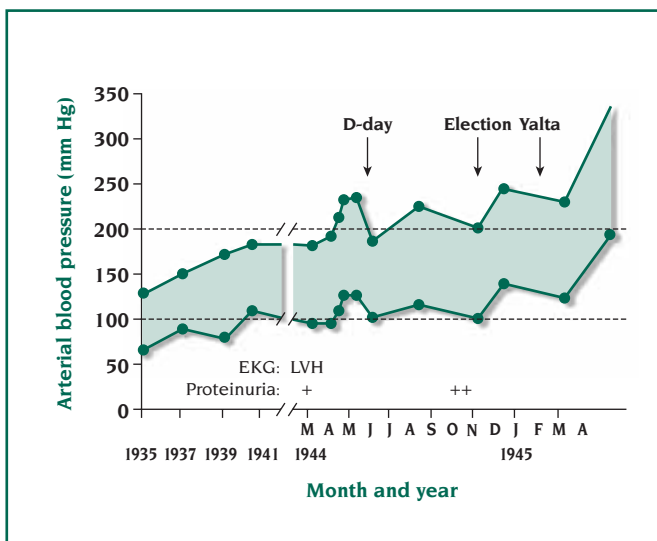
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Newspaper headline announcing Franklin Delano Roosevelt's death in Warm Springs. © CORBIS.



Diastolic and systolic arterial pressure of Franklin Delano Roosevelt from 1935 until his death on April 12, 1945, with major highlights of his presidency.

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Molecular model of angiotensin I-converting enzyme. © Wellcome Images.

thought that one could not treat a disease without knowing its exact cause. We know now that even an elevation of 5-6 mm Hg in the diastolic pressure is sufficient to result in complications.

Amongst the pioneers, Harry Golblatt, Irvine Page and Eduardo Braun-Menéndez stand out. Goldblatt's studies focused on the kidneys, Braun-Menéndez and Page pioneered the work on which much of the modern treatment of hypertension is based. The work of Braun-Menendez and Page goes back

to the discovery of renin by Tigerstedt and Bergman who showed that extracts of rabbit's kidneys and renal vein blood raised the blood pressure when injected into nephrectomized animals. Braun-Menéndez, an Argentinean born in Chile, belonged to the circle around Houssay, a Nobel prize winner; his group showed that the renal vein blood from kidneys grafted into the neck was pressor in nephrectomized dogs and

that renin activated a substrate in the plasma to produce a substance which they called hypertensin. Almost simultaneously, thousands of miles to the north in Indiana, Irvine Page and O. M. Helmer published an article in 1940, which also described that renin acts with a renin activator to form a strong pressor substance which is heat stable and which they called angiotonin.



Bothrops jararaca, or South American pit viper, the venom of which was recognized to lower the blood pressure through potentiation of bradykinin achieved by inhibiting the kininase enzyme responsible for bradykinin clearance and later found to be identical to angiotensin-converting enzyme. Would a brush with this snake have saved FDR? © 2005, Daniel Loebmann.



What sort of men were Page and Braun-Menéndez? Eduardo Braun-Menéndez was born into a family of great wealth. He had nine children. Braun-Menéndez died in a plane accident together with one of his daughters. When I met Braun-Menéndez in the early 1950s, Houssay and his group had left the University in Buenos Aires because of the severe restrictions of academic freedom by Perón, the dictator of Argentina. They worked in a private villa which had been converted into laboratories away from the University and its political intrigues and restrictions. Braun-Menéndez was a quiet, polite, cultured man, who was totally unpretentious. Irvine Page was mercurial, a man who did not shy from arguments. He was one of those individuals who are propelled to success and into political difficulties by a personality which does not shy away from political fights. As a result, Page was not elected to the Society of Clinical Investigation and the Association of American Physicians, although amazingly he was elected to the National Academy. In 1955, the American College of Cardiology asked Page to resign because he had criticized the way scientific meetings were conducted. Page became a chemist, working at the Rockefeller Institute and the Kaiser Wilhelm Institute (later the Max-Planck Institute), in Munich.

Two individuals had come to the same conclusion which influenced the treatment of thousands of patients. Braun-Menéndez and Page compromised by naming the pressor substance “angiotensin.”

The consequences of this discovery were stunning. The group at Western Reserve University in Cleveland demonstrated the existence of two forms of angiotensin, and confirmed the existence of the angiotensin-converting enzyme. It was now only one step from the discovery of the angiotensin-converting enzyme to the discovery of

blocking agents which inhibit the conversion of angiotensin I to II. This was accomplished by a group from the University of Colorado, the University of Ribeirao Preto in Brazil, and the Biology Department, Brookhaven National Laboratory. A peptide from a poisonous snake inhibits the enzyme that normally inactivates bradykinin and is identical to the enzyme responsible for the conversion of angiotensin I to angiotensin II. Angiotensin-converting enzyme inhibitors are now one of the most important treatment modalities for progressive heart failure, acute myocardial infarction, and hypertension.

After Roosevelt’s death, hypertension had become a treatable disease.