

The Ivy Bleeding Time and the Saga of Andrew C. Ivy

Our earliest means for assessing primary hemostasis integrity was the bleeding time (BT). MG Milian provided the first written references in 1901¹²³, and in 1910, WW Duke correlated earlobe BT duration to thrombocytopenia⁴. In 1941, Andrew C Ivy and associates standardized the assay by applying a blood pressure cuff to the upper arm inflated to 40 mm Hg and making a 5 mm long by 1 mm deep longitudinal incision on the ventral surface of the forearm where skin thickness is uniform⁵. From that day the BT was called the Ivy BT. In 1969, Mielke created a template to further standardize the Ivy BT, leading to International Technidyne Corporation's production of the Simplate® and later the Surgicutt® mechanical BT lancets⁶. Subsequent to incision, the blood drop is carefully dabbed onto filter paper every 30 seconds without contacting the wound. Dabbing continues until bleeding stops. In adults, the normal Ivy BT is 2–9 minutes.

From inception, the BT was employed as a presurgical screen to predict the risk of bleeding on the principle that it would accurately identify primary hemostasis deficiencies. Bleeding is prolonged in thrombocytopenia, platelet function disorders, vascular disorders, von Willebrand disease, and during antiplatelet therapy. One 325 mg aspirin doubles the BT within 30 minutes.

Andrew C. Ivy, MD, was the most influential US research physician in the 1940s. He was the Distinguished Professor of Physiology and head of the Department of Clinical Science of the University of Illinois College of Medicine. He was Vice-president of the University, in charge of the Chicago Professional Colleges of Medicine, Dentistry, and Pharmacy. Ivy was the founder and director of the Naval Medical Research Institute during World War II; executive director of the National Advisory Cancer Council; author of the Nuremberg Code of ethics for human experimentation; and president of the Society of Internal Medicine, the American Gastroenterological Association, the American Physiological Society, and the Chicago Institute of Medicine.

On March 27, 1951, Ivy stunned the medical world by proclaiming a cancer cure named Krebiozen to an invited gathering of reporters and politicians at the Drake Hotel in Chicago, “the most publicized unorthodox cancer treatment claim in the whole span of American history⁷.” Stevan Durovic, MD, a physician and native of Yugoslavia, developed Krebiozen, ostensibly an extract of serum from cattle or horses injected with *Actinomyces bovis*, the agent causing “lumpy jaw” in humans. Durovic, who had fled Yugoslavia in 1944 and who managed the Duga Biological Institute in Buenos Aires, in 1949 introduced Krebiozen to faculty at Northwestern University as “Cositerin,” claiming anti-hypertensive properties. Tests failed to confirm this, and he turned to Ivy. Durovic would not disclose his manufacturing process nor allow anyone to analyze the material, fearing his work would fall into the hands of Communists. Krebiozen was thought to stimulate the reticuloendothelial system to enhance natural tumor resistance. Ivy and other physiologists supported this concept of immune surveillance, and after self-administering the substance to confirm its safety, treated 22 cancer patients who were under his care. At the Chicago press conference, Ivy claimed Krebiozin had reduced tumor size; reduced the need for pain medication; restored patients' appetites, their ability to sleep, and their sense of wellbeing. Some bedridden patients were able to return to work. The reporters provided the term “cure.” Ivy reported that 8 of the 22 patients had died, but failed to report two additional deaths that had occurred just days prior to the conference, claiming instead success.

University of Illinois officials, in particular President George Stoddard, College of Medicine Dean Stanley Olson, and the leadership of the American Medical Association were shocked, as Ivy had never shared his Krebiozen data with scientific colleagues. Nevertheless, Ivy's colossal prestige and a widespread and intense public distrust of the AMA forced the officials to move slowly. Ivy and Durovic had the backing of a number of powerful Illinois and Chicago politicians, including the mayor and both Illinois senators, and were made heroes by the popular media. Senator Paul Douglas granted citizenship for Durovic, whose visa was about to expire. Ivy released vials of the drug at the insistence of the AMA to a number of colleagues, who tried it to no effect on over 100 patients in cancer clinics around the country. Further studies showed no response, however none was controlled, and the popular perception was that the AMA's negative report

confirmed that the organization was opposed to all medical advances, a perception Ivy propagated by calling the association a “trade union.”

Olson published several stinging criticisms of Ivy’s work and resigned in 1953. The Chicago Medical Society suspended Ivy for three months in 1952, but President Stoddard issued a politically motivated declaration of support, and recommended further research on the drug, which Ivy repeatedly thwarted. In 1953 the University trustees forced Stoddard to resign, soon the University lost several outstanding faculty and department heads. The trustees were unable to find competent people willing to take the vacant positions. Controversies over the drug spread from Illinois to Washington as Krebiozen continued to be distributed. The US Food and Drug Administration attempted to force its withdrawal in 1963; to the protests of the public and patients who were certain they were dependent on the drug for their lives. Withdrawal was recommended on the basis of the lack of efficacy in controlled clinical trials and upon chemical analyses that proved the drug was in some cases creatine and in others, mineral oil, but distribution continued until 1973 when Illinois finally passed a law to prevent its manufacture. In 1964 a Chicago grand jury indicted Ivy on mail fraud, however he was acquitted after a 9-month jury trial. A juror was later convicted of illegally influencing the verdict by presenting outside information and jailed for 18 months. Ivy discontinued his Krebiozen work after the trial, but began investigating Carcalon, another mysterious substance derived from cattle serum, which he believed would stimulate the body’s natural defenses. He continued with this work until his death in 1979.

There is no evidence that Ivy profited from Krebiozen distribution. His motivation appears to be a combination of altruism and his belief that the University, AMA, and FDA were conspiring to protect physicians’ practices by failing to clear new therapies. Although Krebiozen, Carcalon, and another 1951 cancer cure, Laetrile (an apricot pit extract) have been discredited, new remedies continue to arise to take their place in an effort to entice a credible and often desperate public.

Lastly, in the 1990s a series of studies led the College of American Pathologists and the American Society of Clinical Pathologists to conclude that the preoperative BT lacks clinical benefit⁸. They indicate that the BT does not predict nor exclude the possibility of intraoperative bleeding, nor does it reliably identify aspirin, non-steroidal anti-inflammatory drugs, or platelet disorders. Today the BT is discontinued, and has been replaced by recording the bleeding history, by physical examination, and by whole blood lumiaggregometry, light transmittance aggregometry, thromboelastography, the Multiplate analyzer, the Siemens PFA-100®, the Accumetrics VerifyNow aggregometer. There is a considerable effort to provide laboratory means for monitoring antiplatelet therapy, and new assays are likely to appear in the future.

¹ Milian MG. Influence de l'apau sur la coagulabilite du sang. CR Soc Biol (Paris) 1901;53:576–8.

² Milian MG. Contribution a l'etude de la coagulation du sang. CR Soc Biol (Paris) 1901;53:556–7.

³ Milian MG. Technique pour l'etude clinique de la coagulation du sang. Bull Mem Soc Med Hop Paris 1901;18:777–83.

⁴ Duke WW. The relation of blood platelets to hemorrhagic disease. Description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion. JAMA 1910;55:1185–92.

⁵ Ivy AC, Nelson D, Bucher G. The standardization of certain factors in the cutaneous “venostasis” bleeding time technique. J Lab Clin Med 1941;26:1812–22.

⁶ Mielke CH, Kaneshiro MM, Maher IA, et al. The standardized normal Ivy bleeding time and its prolongation by aspirin. Blood 1969;34:204–15.

⁷ Ward PS. “Who will bell the cat?” Andrew C. Ivy and Krebiozin. Bull Hist Med 1984;58:28–52.

⁸ Peterson P, Hayes TE, Arkin CF, et al. The preoperative bleeding time test lacks clinical benefit. Arch Surg 1998;133:134–9.