

# In Memoriam

## Justin A. Zivin, MD, PhD August 17, 1946–February 17, 2018

Patrick Lyden, MD

Justin Zivin was one of the most imaginative investigators in our field. Although his work was synonymous with r-tPA (recombinant tissue-type plasminogen activator) for acute stroke, few working in nonendovascular therapy today know his true contributions. In 1985, Justin published in *Science* the first unequivocal demonstration that thrombolysis with r-tPA improved neurological outcomes.<sup>1</sup> Before that, and for many years afterward, stroke model efficacy equaled recanalization—artery blocked, artery open. By quantifying meaningful functional recovery, Justin challenged contemporary dogma, proving that subjects benefited from thrombolysis after stroke. In other words, successful arteriographic response (recanalization) did not substitute for the documented behavioral benefit.

His work unarguably provided the key foundation for the later successful human trials in thrombolysis.

Further, and far more importantly, Justin's *Science* article influenced subsequent work profoundly. He was aware that to obtain regulatory approval for drug development required demonstration of efficacy, usually measured with a clinically meaningful end point, such as mortality. As a student in a stroke laboratory in 1985, I was thinking that stroke therapy could be assessed with easy-to-measure end points, such as stroke size or recanalization rates. I was struggling to perfect an intra-arterial embolus model when Justin and I first met—he was moving to the University of California, San Diego and I was to be his Fellow. Our interaction in those first few months set the modus operandi for the ensuing 30+ years. First, he patiently and courteously explained why my model was misguided, even though it reflected the state of the art in stroke modeling at the time. Then, he gave me his article to read, saying very little other than that if I understood it, I



Justin A. Zivin

would be welcome in his group. Thankfully, when I read his *Science* article, it made perfect sense.

Justin identified the critical problem with existing stroke models: stroke size varies (considerably) from one subject to the next. Rather than control that variation, Justin and a mathematician colleague Doug Waud, embraced variation.<sup>2</sup> Rather than trying to lodge a single embolic clot precisely in a middle cerebral artery, Justin injected hundreds of tiny microclots into the internal carotid arteries, allowing them to distribute widely and cause neurological impairment. He then created a meaningful functional outcome scale, and with Waud, fit a nonlinear model to the data. The result, the quantal bioassay, elegantly and simply solved 2 key problems with stroke models:

he utilized the inherent variability in stroke to create a more powerful bioassay method, and then he created a functionally meaningful outcome. The result was the first demonstration that r-tPA worked in stroke, and furthermore, taught all of us to think about neurological function (behavior) in animal stroke models as the key, critical outcome variable. This insight, like all brilliant advances, seems simple and obvious in retrospect, and today the notion that stroke therapies must benefit behavioral outcome forms the sine qua non for regulatory approval of stroke therapies. Before Justin's article, however, we fumbled about, scoring open arteries and quantifying lesion volumes.

Justin was born in Chicago, attended the University of Wisconsin, Madison for undergraduate training, and completed a Bachelor's in Medicine at Northwestern University in Chicago, IL. He then attained a master's degree in science in 1970, a doctorate in physiology in 1971, and his medical degree in 1972 as part of the first cohort of Northwestern's prestigious Physician-Scientist Training Program. He

Received March 22, 2018; final revision received March 22, 2018; accepted March 23, 2018.

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(*Stroke*. 2018;49:1051-1052. DOI: 10.1161/STROKEAHA.118.021264.)

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*Stroke* is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.118.021264

subsequently completed his internship year at the University of Michigan in Ann Arbor, MI, and conducted intramural research at the National Institutes of Health in Bethesda MD. He did Neurology residency at the University of California, San Francisco, CA, where his coresidents included several future neurology Department Chairs, who valued his sense of humor and work ethic. Justin's first faculty position was at the University of Massachusetts Medical School in Worcester, MA. He served on key panels for the US Food and Drug Administration, the National Institutes of Health, and the Department of Veterans Affairs throughout his career.

Justin's father was an Internist in private practice. According to Justin, his father devoted himself to his patients, making daily rounds into his 80s. Although Justin valued clinical medicine, he did not approve of any particular clinician seeking to substitute personal experience or anecdote for rigorous, quality data. His patient care model included evidence-based medicine long before the term existed, and this commitment to data influenced his students, residents, and Fellows.

Over our 30 years working together, I came to appreciate how deeply and profoundly he loved science and investigation. In addition to his grant-funded research, Justin cofounded a contract research organization, CerebroVascular Advances. Justin and his collaborators ran a pivotal trial of enlimomab for acute stroke, and finished recruitment ahead of schedule, a remarkable accomplishment, even today. Their approach was fresh, effective, and CerebroVascular Advances was ultimately purchased by Quintiles. Later, he served as co-principal investigator of a stroke prevention trial using statins SPARCL (Stroke Prevention with Aggressive Reductions in Cholesterol Levels), and as principal investigator of a large trial of laser light therapy for acute stroke NEST-3 (Efficacy and Safety Trial of Transcranial Laser Therapy Within 24 Hours From Stroke Onset).

The most important opportunity in our time together came in the form of a National Institutes of Health contract solicitation. We applied to participate in the National Institute of Neurological Disorders and Stroke r-tPA for Acute Stroke Trial, and thanks to Justin's reputation, writing skills, and his pioneering preclinical work, our University of California, San Diego team was selected as one of the sites. The trial ultimately proved to be a landmark event in the history of neurology because not only were there no existing treatments for acute stroke, neurology, in general, was a diagnostic, not a therapeutic specialty. Justin wrote a memoir about it that is well worth reading.<sup>3</sup> After the National Institute of Neurological Disorders and Stroke r-tPA for Acute Stroke trial was published,<sup>4</sup> it began to attract skepticism and derision from the established medical thought leaders who simply could not imagine a therapy as powerful and effective as thrombolysis proved to be. Nevertheless, Justin remained steadfast in his confidence about the findings. Justin was the smartest person

I ever met, so he was used to being alone sometimes for an opinion or position. He saw what the rest of us could not see, well before anyone else saw it, and he was patient. Eventually, he taught, the truth emerges. And so it did.

Besides work, his life centered on his family, including his wife of nearly 50 years, Reni-Zoe and their 2 daughters, Kara and Leslie. One of my most vivid memories of him: near sunset one afternoon I looked out the clinic window and saw him leaving work for the day, walking into the parking lot with one of his young daughters. He reached down and she reached up and they walked hand-in-hand beyond my view. He bragged incessantly when he published an article with Kara in the *Archives of Neurology*<sup>5</sup>—he mentioned it far more often than his 1985 *Science* article. He maintained other deep interests and hobbies, including a lifelong love of classical music, and reading about history, science, and politics. Over the last decade, he was pleased to become a grandfather. After I left San Diego, we spoke less often, yet when we did reconnect, we talked about family, including his children and grandchildren (Lewis, Aylah, Reed, and Aitan), and of course, his dog Thor.

This past January, I spoke with him for the last time, at the International Stroke Conference, standing on the Mezzanine level at the Los Angeles Convention Center, surrounded by the streaming crowd, including a younger generation of scientist strangers. They may not have recognized him, but all of them had benefitted from his work. We caught up on the many Fellows he trained, of whom he remained quite proud. As we spoke, he focused eagerly on some new opportunities, this time in business. As always, he could not tell me much, but it was going to be big, another opportunity not to be missed.

In the weeks since he died, I have spoken with dozens of colleagues and former trainees—we are all profoundly saddened by the loss of a great scientist, clinician, and friend. Justin built a legacy of trainees committed to rigor and the primacy of data. Justin Zivin taught dozens of trainees, cared for his family, influenced the course of medical history, and left the world a better place than when he entered it. He will be deeply missed.

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# Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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*Stroke*. 2018;49:1051-1052; originally published online April 18, 2018;  
doi: 10.1161/STROKEAHA.118.021264  
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://stroke.ahajournals.org/content/49/5/1051>

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