Mutation Research - Genetic Toxicology and Environmental Mutagenesis 900 (2024) 503832

Contents lists available at ScienceDirect

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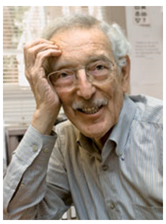
journal homepage: www.elsevier.com/locate/gentox

Bruce Nathan Ames: A scientist to remember (December 16, 1928—October 5, 2024)



The idea was sparked by a package of potato chips in 1964. Bruce Ames wondered if the preservatives and other chemicals listed on the package could cause genetic damage, so he decided to develop a test to detect mutagens. Little did he know that more than half a century later, his test would be a pillar and primary referent of genetic toxicology, environmental mutagenesis, drug development, evaluations of agents as possible human carcinogens, and legal regulations for the approval of drugs, pesticides, and other synthetic chemicals. Bruce Ames, who has died, age 95, saw all this and more develop from his simple curiosity about a list of ingredients. He is survived by his wife of 64 years, Giovanna Ferro-Luzzi Ames, their children Matteo and Sophia, and two grandchildren.

Ames recalled, in an autobiographical reminiscence in 2003, that he enjoyed a happy childhood, with summers spent in the Adirondack Mountains, upstate New York, where his forays into the woods to collect various creatures were punctuated by weekly visits to the local library. He would return home with his parents and two younger sisters to the Washington Heights area of Manhattan in New York City, where there was less nature but a lot more books.

In a 2019–2020 interview for the Berkeley Oral History Center, Ames noted that, like many Jewish families at that time, his was only one or two generations removed from Europe. His mother, Dorothy Andre Ames, immigrated to New York City as a young child from a Russian-speaking area of eastern Europe; she worked as a secretary at a high school. His father, Maurice, was born in New York City; his father had come from a German-speaking family in Lviv (now Ukraine). Maurice earned a law degree and a master's degree in chemistry, eventually becoming the Assistant Superintendent of Schools in New York City. Fortunately for the field of genetic toxicology, Maurice and his brothers changed their last name to Ames, making possible the alliteration for the eponymous "Ames assay," which would have been impossible with the surname Uschweif.

Ames passed a competitive exam granting him entrance into the Bronx High School of Science. In his oral history at Berkeley, Ames recalled several defining events in his early education. He said that his interest in science really started when he did a project where he applied a plant hormone to tomato roots, causing them to grow in the absence of the remainder of the plant. Another competitive exam led to a scholarship to attend Cornell University, where he majored in chemistry/biochemistry and discovered the first thing he thought he did really well in life — folk dancing. He would soon become famous for far more than dancing the polka. Ames recalled that he was only a B+ student, both in high school and at Cornell, because he was too undisciplined and too easily distracted by a new enthusiasm. Although the University of Wisconsin turned him down for graduate school, he was accepted at the California Institute of Technology (Cal Tech) in 1950, something he thought might have been facilitated by references from his Cornell biochemical genetics professor, Adrian Srb, who must have recognized his potential.

Ames arrived at Cal Tech concerned that his memory and focus were too poor to succeed in graduate school. Such concerns were clearly unfounded. He began his PhD work in Herschel K. Mitchell's laboratory where he quickly established most of his research plan in the first year and spent just two more years completing the work, graduating at the age of 24. He determined the pathway of histidine biosynthesis in the fungus *Neurospora crassa*, using a combination of genetics, to isolate histidine-requiring mutants, and biochemistry, using paper chromatography to identify precursor imidazole compounds from *Neurospora* extracts. All this occurred in a remarkable biochemistry department chaired by George Beadle, with faculty including Max Delbrück and Seymour Benzer, the first two of whom won Nobel Prizes.

Ames spent the next 15 years at the National Institutes of Health (NIH) in Bethesda, MD, first as a postdoc in Bernard Horecker's lab, where he completed the histidine pathway in *N. crassa*. He became an independent investigator at NIH, working on gene regulation in the histidine biosynthetic pathway in *Salmonella typhimurium* in collaboration with Phil Hartman at Johns Hopkins University. In 1960 he had his honeymoon year both personally, marrying a postdoc, Giovanna Ferro-Luzzi, who also became an NIH scientist and later a professor of biochemistry at UC-Berkeley, and professionally, taking a sabbatical in Francis Crick's lab in Cambridge, England, and Francois Jacob's lab at the Pasteur Institute in Paris. He was in the midst of some of the key people who would form the field of molecular biology.

Pursuing his interest in mutagenesis, Ames and his postdocs Harvey Whitfield and Robert Martin at NIH started research in this field. In 1966 they published their initial determination of the classes of mutations (frameshift, nonsense, or missense) in some of Hartman's *Salmonella* mutants, based on the revertability of each mutant by different mutagens. The next year, he began a 33-year career at the University of California at Berkeley, where he continued his work on the histidine operon in *Salmonella*. Ames initially failed to get support from the National Cancer Institute (NCI) because NCI did not think that studies with

https://doi.org/10.1016/j.mrgentox.2024.503832

Available online 6 November 2024
1383-5718/Published by Elsevier B.V.

bacteria could provide much insight into cancer, but support from the Atomic Energy Commission (AEC), which was clearly interested in mutations, funded his initial paradigm-shifting papers in the 1970s.

His mutagenesis work was not considered sufficiently "basic" research with which to train graduate students and postdocs. So, with his usual enthusiasm, he attracted large numbers of undergraduates to conduct much of the work. Ames introduced his initial version of his mutagen test system in 1971. Although other microbial mutagenicity test systems had been developed previously, including one in *E. coli* that was used to survey >400 chemicals for mutagenicity in the 1950s, Ames developed new tester strains over the years, introduced the novel procedure of adding the metabolic activation to the top agar, and conducted a survey of 300 compounds (many of them rodent carcinogens) for mutagenic activity. All of this demonstrated the utility, general simplicity, and value of the assay. He said that he received > 3000 requests for his strains from labs worldwide, especially industrial labs. He saw that industry had an incentive not to release mutagens into the marketplace, enhanced, no doubt, by the passage of the Toxic Substances Control Act (TSCA) in the U.S. in 1976 and the incorporation of his mutagenicity assay into the regulatory process by the U.S. EPA in 1978.

As he described in his oral interview at Berkeley, the idea of incentives coincided with his libertarian leanings, which he indicated were unique in a generally leftist family. He said that he became a friend of the economist Milton Friedman and that he read books by Friedrich Hayek. In the interview, Ames said that he thought like an economist, weighing the risks and benefits of things, a mode of thinking that influenced his approach to much of his work.

After many refinements to the assay, the ensuing decades saw > 10,000 papers published using his assay, and they showed what no one had imagined: that much of the environment (essentially all ambient air, chlorinated drinking water, and soil) and many foods and chemicals were mutagenic. Much of the mutagenic burden came from natural sources, largely plants in our diet, rather than synthetic chemicals. This discovery was, perhaps, not so surprising given that the very first report of a mutagenic chemical, which was by Charlotte Auerbach and John M. Robson in 1944, was of allyl isothiocyanate (mustard oil), a natural component of cruciferous vegetables. They noted that "…the search for naturally occurring substances with the capacity to produce the same effects [as X-rays] appears, from the point of view of evolutionary theory, even more important [than the search for synthetic substances]." Ames and his colleagues would provide considerable evidence for this early observation 46 years later in a paper on "nature's pesticides" in 1990.

Although several scientists had speculated that mutagens/mutations might cause cancer, Ames presented a convincing set of data in his 1973 *PNAS* paper showing that metabolic activation converted 18 previously non-mutagenic rodent carcinogens into mutagens. In addition, he coupled this with the compelling statement "carcinogens are mutagens" in the title of the paper, which convincingly began to draw the connection between mutagens and carcinogens.

Prior to 1973, cancer was mostly thought to be caused either by viruses or by the interactions of chemicals with proteins, and few carcinogens had been shown to be mutagenic, largely due to the absence of metabolic activation in the available test systems. He and his collaborator, Lois Gold, developed a carcinogenic potency index for > 1000 agents that had been tested for cancer in rodents, and in 1987 they developed an exposure/potency index, which provided evidence that the world was full of rodent carcinogens as well as mutagens, and that many were natural, not synthetic, chemicals.

Always following the data, Ames considered this revelation and wondered how we can survive if much of the natural and modified environment was mutagenic and potentially carcinogenic. Thus, he embarked on a decades-long investigation into the other side of the coin: the protective mechanisms by which the body deals with such an onslaught of toxic substances. He explored the role of oxidants, anti-oxidants, micronutrients, and diet on cancer and aging.

As with environmental mutagens, Ames and his colleagues found that normal metabolism produced oxidative DNA damage, resulting in 100,000 hits/cell/day in the rat. He went on to research mitochondrial decay as a basis for aging; the role of oxidants, anti-oxidants, and free radicals on disease and aging; and the importance of micronutrients (perhaps as many as 40) in diet and general health.

Ames became especially interested in vitamins and micronutrients in 1990 when a postdoc in his lab, Jim MacGregor, showed that folic acid deficiency caused chromosome breaks. In 1985 Ames and his colleagues discovered the OxyR regulatory protein, which they showed is used by cells to detect and respond to oxidative stress. Work on these topics continued until 2020 and involved a move from the Berkeley campus to the Children's Hospital of Oakland Research Institute (CHORI) in 1999.

The impact of Bruce Ames, as a mentor of the hundreds of students, postdocs, and visiting scientists that passed through his lab, and for his work on our lives, is immeasurable. His lab's discovery that hair dyes were mutagenic caused the industry to change their formulations, and his discovery that a flame retardant in children's pajamas (Tris) was mutagenic and present in the urine of children wearing such pajamas, supported by the rodent carcinogenicity of this compound, caused it to be banned in the U.S.

His lab's finding that cigarette smoke condensate was mutagenic in 1974 and that smokers had mutagenic urine in 1977, followed by dozens of confirmatory studies from labs worldwide provided key mechanistic evidence for the World Health Organization's International Agency for Research on Cancer (IARC) to evaluate tobacco smoking as a human carcinogen in 1986. Likewise, hundreds of scientists used his assay to show that essentially all of ~ 2400 air samples collected over 30 years from five continents were mutagenic. This massive data set provided key mechanistic evidence to support the evaluation of outdoor air pollution by IARC as a human lung carcinogen in 2016.

A review by Ronald D. Snyder in 2009 showed that only ~ 7 % of 525 U.S. FDA-approved drugs were mutagenic in the Ames assay. Along with drugs, numerous pesticides and other industrial chemicals likely never reached the market because they were mutagenic in the Ames assay and, thus, were never submitted for approval by the regulatory agencies. The application of the Ames assay, in combination with the law and agency regulations, has restricted the number of mutagens into our environment for half a century and is a testament to the impact that Bruce Ames has had on public health. He never took money from industry nor patented his mutagenicity assay.

Bruce Ames received many accolades, including the National Medal of Science, the Japan Prize, the Thomas Hunt Morgan Medical (Genetics Society of America), the Gairdner Foundation Award (Canada), and the Society of Toxicology Lifetime Achievement Award. He was inducted into the U.S. National Academy of Sciences in 1972 for his histidine operon work, and he was a charter member of the Environmental Mutagen Society (now the Environmental Mutagenesis and Genomics Society). He is among the most cited scientists, with 187,990 citations of his > 560 papers. However, despite the impact of his mutagenicity assay, only three of his ten most-cited papers involve this assay; five are from his work on oxidants, and the other two are from the 1960s: an assay to determine the molecular weight of enzymes by sedimentation, and another assay to detect isophosphate, total phosphate, and phosphatases.

After his mutagenesis assay had been in use worldwide for more than a quarter of a century, he gave an invited lecture in the 1990s at the main laboratory of the U.S. Environmental Protection Agency in Research Triangle Park, North Carolina, where he presented a wide-ranging overview of environmental mutagens and carcinogens and stressed the importance of risk/benefit analyses, thinking like an economist. He suggested that living was mutagenic, and that poverty was an important carcinogen. At a luncheon reception afterwards, he was observed to be eating lots of potato chips. It seems that after so many years, those chips had finally passed the Ames test.

Acknowledgements

Photo by Jim Block, courtesy of Chemical & Engineering News, 89 (7):38, 2011.

Material from which some of this obituary was drawn is listed here.

B.N. Ames, An enthusiasm for metabolism, J. Biol. Chem. 278 (2003) 4369–4380.

L.D. Claxton, Gde. A. Umbuzeiro, D.M. DeMarini, The *Salmonella* mutagenicity assay: The stethoscope of genetic toxicology for the 21st century, Environ. Health Perspect. 118 (2010) 1515–1522.

Bruce N. Ames, "Bruce N. Ames: The Marriage of Biochemistry and Genetics at Caltech, the NIH, UC Berkeley, and CHORI, 1954–2018" conducted by Paul Burnett in 2019 and 2020, Oral History Center, The Bancroft Library, University of California, Berkeley, 2021. https://digitalassets.lib.berkeley.edu/roho/ucb/text/ames_bruce_2021.pdf.

Other obituaries of Bruce Ames have been published recently by Errol Zeiger in Environmental and Molecular Mutagenesis, by Teddy Rosenbluth in the New York Times, and by Comfort Dorn in ASBMB Today.

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