BIOGRAPHICAL MEMOIRS

Bruce N. Ames

December 16, 1928–October 5, 2024
Elected to the NAS, 1972

A Biographical Memoir by Gisela Storz

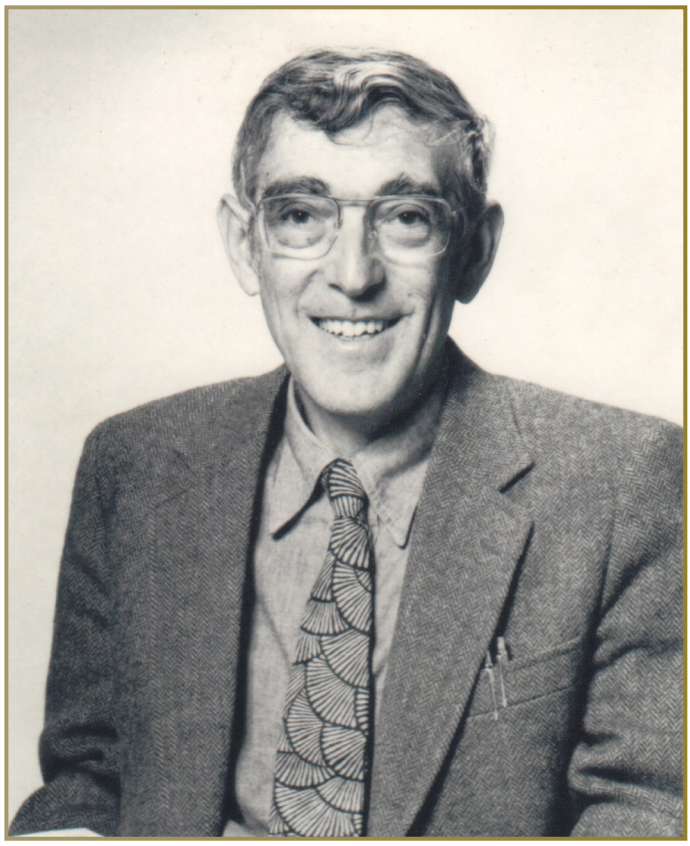

Figure 1 Bruce N. Ames. *Photo courtesy of the Ames family.*

Bruce Nathan Ames was an extraordinarily creative scientist who was not bound by convention. His development of the "Ames test" to rapidly and inexpensively identify mutagens and his comprehensive compendium of assays of potentially mutagenic and carcinogenic natural and human-made compounds changed how we think about mutagenesis and carcinogenesis. Bruce also contributed to many other fields. For his impact, Bruce was elected to National Academy of Sciences in 1972 and received, among other awards, the Gairdner Foundation Award in 1983, the Japan Prize in 1997, the National Medal of Science in 1998, and the Thomas Hunt Morgan Medal in 2004.

Early Life, Education, and Early Career

Bruce Ames was born on December 16, 1928, in New York City. His father, Maurice Ames, was a descendant of German-speaking Jews who immigrated to the United States from what is now Ukraine. Maurice had a law degree but worked as a high school chemistry teacher and principal, later becoming assistant superintendent of New York City Schools. His mother, Dorothy Andres, immigrated from Poland with Russian-speaking Jewish parents and was a secretary at the same high school. Like other eminent scientists of his generation, Bruce's interest in biology was stimulated by summers in the Adirondack Mountains and enrollment at the Bronx High School of Science.

As an undergraduate at Cornell University, Bruce majored in chemistry and minored in biology but was distracted by folk dancing, history, and classical music. After receiving a bachelor of arts in 1950, Bruce moved to the West Coast to carry out graduate work with Herschel K. Mitchell at the California Institute of Technology. Three years later, he received his Ph.D. in biochemistry at the age of twenty-four. Bruce's thesis work focused on histidine biosynthesis, mapping out the pathway using histidine-requiring mutants of the *Neurospora* mold.[1]

After his PhD work, Bruce returned to the East Coast to work at the National Institutes of Health (NIH) as a postdoctoral fellow with Bernard L. Horecker for two years before transitioning to an independent Biochemist position at the

NIH.[2] During this time, influenced by Philip Hartman at Johns Hopkins University, Bruce started to use the bacterium *Salmonella* as a model for studying histidine biosynthesis and thereby gained more insights into the enzymology and regulation of histidine biosynthesis. At the NIH, Bruce also met an accomplished and enchanting postdoctoral fellow, Giovanna Ferro-Luzzi, whom he married in 1960. In 1961, Bruce spent a sabbatical year, which he described a "honeymoon year, both personally and intellectually,"[3] with Francis Crick at the University of Cambridge and François Jacob at the Pasteur Institute in Paris, before returning to the NIH to become Chief of the Section of Microbial Genetics. Bruce made his final transition back to the West Coast in 1968, when he joined the faculty of the Division of Biochemistry and Molecular Biology at the University of California, Berkeley.

Throughout his time as an independent investigator both at the NIH and in Berkeley, Bruce mentored an amazing cohort of accomplished students and fellows who went on to a variety of stellar careers. Here, I summarize Bruce's major scientific contributions and mention students and fellows who participated in the work, but this summary is by no means comprehensive. The great breadth of the discoveries illustrates Bruce's fearlessness of following your nose until you find something interesting and then you follow up.[4]

Discovering the Histidine Operon and Transcription Attenuation Control

During his time as a Section Chief at NIH, stimulated by his sabbatical time in Cambridge and Paris, Bruce and his first postdocs, Gerry Fink, John Roth, and Bob Martin, focused on characterizing the genes required for histidine biosynthesis in *Salmonella* together with the regulation of these genes.[5] This work showed that many of the genes encoding the enzymes required for histidine biosynthesis are encoded adjacent to each other and are regulated together, reinforcing the concept of a gene operon proposed by François Jacob and Jacques Monod. The group also found that expression of the histidine operon was regulated by the level of histidine via a mechanism, later termed transcription attenuation, whereby cellular histidine levels are reflected in charged histidine tRNA levels, which in turn affect the translation of a small histidine-rich open reading frame encoded upstream of the histidine operon. Low levels of histidine cause translational pausing at this site, which leads to changes in the mRNA structure such that transcription is no longer terminated and the operon is expressed. In addition to obtaining these important biological insights, Bruce and his colleagues developed new methodologies such as sucrose gradient centrifugation as a means to determine protein molecular weight.[6]

Based on multiple accounts from Bruce and former lab members, Bruce's time at NIH was extremely stimulating both intellectually and socially. Although the lab space occupied by Bruce's group was very small, as was common at the NIH, there were frequent exciting discussions with the fellows and other colleagues in nearby labs, including those of David Davies, Gary Felsenfeld, Marty Gellert, Harvey Itano, Todd Miles, and Gordon Tomkins. The spirit in the Ames group at the NIH, and later at Berkeley, is illustrated by reflections by Gerry Fink.[7] Upon joining the Ames lab, Gerry wondered "Do they do anything but gab here?" Gerry remembers:

> Bruce would initiate the gabfest after he arrived in the morning with whomever he first encountered.… His sermon on his latest obsession in gene regulation inevitably began: "Have I told you my latest idea about...?" This scenario was repeated several times a day, and since Bruce never waited for an answer to his question, he often lost track of his audience and in the afternoon preached the same soliloquy to the identical person he had addressed in the morning. These confrontations with Bruce's fertile mind provided fodder for chatter among the postdocs, who then debated both the implications and feasible experimental approaches that might prove or disprove Bruce's latest proposals. These debates provided a constant source of entertainment in the lab, and the wrangling and banter often extended to cocktail talk at evening parties Bruce and Giovanna graciously hosted at their home.

Exploiting the Histidine Operon to Develop the Ames Test

Having spent considerable time thinking about mutagenesis in the context of the histidine operon and taking note of all the chemicals listed on a box of potato chips, Bruce began to "wonder whether preservatives and other chemicals could cause genetic damage to humans."[8] Thus, he set out to develop a simple test for mutagenesis, taking advantage of the many available *Salmonella* mutants that required histidine for growth. Bruce's curiosity, together with his continuous passion for developing new assays, led to the development of the transformative Ames test in which the histidine mutants, "tester strains," are plated, in the presence of a compound of interest, on culture media with very limited histidine.[9] If an increased number of cells grew within a day or so after acquiring revertant mutations that allowed histidine biosynthesis, the compound tested was likely to be a mutagen. Given how easy and inexpensive this Ames test was to conduct, it was rapidly adopted by thousands of labs and drug and chemical companies, allowing them to "weed out mutagenic

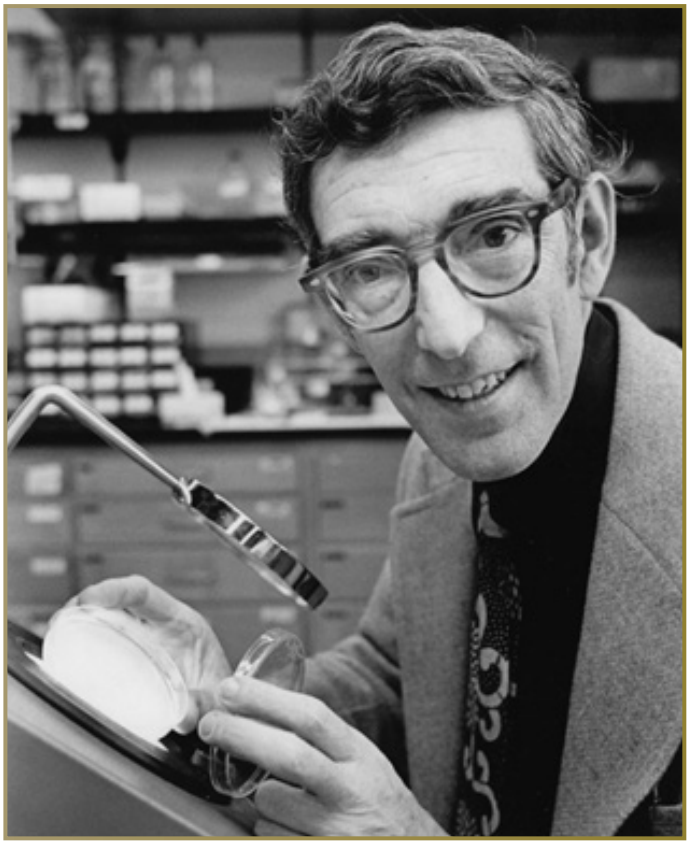

Figure 2 Bruce Ames demonstrating the Ames test. *Photo courtesy of the Ames family.*

chemicals inexpensively early in their development."[10] It is interesting to note that Bruce's application to get initial funding for this project was turned down by the National Cancer Institute (NCI) because of the assessment that bacteria could not "teach us much about cancer," but he was able to obtain funding from the Atomic Energy Commission and later did receive an NCI Outstanding Investigator Grant that supported his group for many years.

The Ames test was conducted by Berkeley undergraduate students in lab classes and in Bruce's lab for many years. Through the efforts of these students and multiple technicians, including Edie Yamasaki and Dorothy Maron, graduate students such as David Levin, and postdoctoral fellows such as Graham Walker, Joyce McCann, and Pauline Gee, the Ames test was improved in several ways. These improvements included the addition of rodent liver lysate to metabolize compounds,[11] introduction of the plasmid pKM101, which increased mutability,[12] and tester strains with specific mutations that allowed scientists conducting the Ames test to determine the type of mutation induced by the tested compound.[13,14] The societal impact the Ames test had on changing the landscape of chemicals in commonly used products, ranging from hair dyes to flame retardants in children's sleepwear, cannot be overstated.

More Contributions to Understanding Bacterial Stress Responses

The work on the histidine operon and the tester strains influenced other ongoing projects in the lab. This included further investigation of the mechanisms by which expression of the histidine operon is regulated in *Salmonella,* carried out by postdoctoral fellow Chuck Turnbough and others.[15]

Bruce also had the idea that bacteria could signal stress through small molecules such as ZTP and AppppA, which he termed "alarmones." The model proposed that specific nucleotide derivatives would be synthesized in response to a specific stress as a consequence of whichever metabolic pathway was disrupted. The importance of the alarmone hypothesis and the work, conducted by postdoctoral fellows Stan Artz, Jim Broach, Martin Buck, and Barry Bochner among others,[16] was not fully appreciated until several decades later after multiple proteins and RNA elements termed riboswitches were found to specifically bind and respond to these nucleotide signals.

At the same time Bruce was proposing that reactive oxygen species were an important contributor to DNA damage, graduate students Michael Christman, Gisela Storz, and Louis Tartaglia and postdoctoral fellows Fred Jacobson and Robin Morgan identified *Salmonella* mutants that were resistant to hydrogen peroxide and other oxidants. These mutations led to the identification of genes encoding a new enzyme, an alkylhydroperoxide reductase capable of protecting cells by reducing peroxides[17] and encoding the key transcriptional regulator, OxyR, of the transcriptional response to hydrogen peroxide.[18] Additional biochemical characterization of OxyR showed that the transcription factor was uniquely sensitive to oxidation and thus was the direct sensor of cellular oxidative stress.[19]

Establishing the Carcinogenic Potency and Human Exposure Dose/Rodent Potency Databases

While work to improve the Ames test was ongoing and thousands of labs were using the test to identify mutagens, Bruce decided to collaborate with Lois Swirsky Gold to assemble the Carcinogenic Potency Database, a publicly accessible database of all studies of the mutagenic and carcinogenic potential of different compounds.[20] The analysis of this compendium led to, among others, two important conclusions. First, the compendium provided extensive documentation that many carcinogens were mutagens. The second provocative conclusion was that "99.9% of all chemical exposure is from ingesting natural chemicals in food."[21] As part of this analysis, Bruce and colleagues developed an index to compare the usual high doses received by mice and rats in the carcinogenicity tests with the tiny levels of exposure received by

humans resulting in the Human Exposure Dose/Rodent Potency Database.[22] Through these comparisons, Bruce reached the conclusion that "we must concentrate on major risks if we are to make any progress and that concern with hundreds of minor, hypothetical risks is a distraction from major risks, such as imbalanced diets and cigarette smoking."[23]

This work was yet one more illustration of Bruce's fearless pursuit of unpopular ideas. As reflected in the correspondence in top journals between Bruce and scientists challenging his ideas, many people disagreed with the conclusions he and Lois reported. Bruce stated that he became "inured to ad hominem attacks on Gold and myself that allege we are a tool of industry, despite the fact Gold and I have always had a policy not to accept money from industry, or to testify in lawsuits, or to consult."[24] The analysis of all the mutagenesis and carcinogenesis studies set the stage for much of the focus in the later stages of Bruce's career, projects on endogenous sources of cellular damage that could lead to cancer and ways to counteract this damage.

Describing the Detrimental Impacts of Oxygen Free Radicals

Bruce hypothesized that oxidants from normal metabolism were an important source of mutagenesis. To test this idea and gain more insights into the DNA damage induced by reactive oxygen species, multiple Ames lab members, including postdoctoral fellows Rick Cathcart, Robert Saul, and Mark Shigenaga, measured the presence of DNA oxidation in different human samples. A major goal was the detection of oxidized DNA bases in rat and human urine.[25,26] One -80°C freezer in the Ames lab was nicknamed the "bladder" given the large collection of urine samples it contained. Extrapolations from these measurements suggested that there are a high number of instances of oxidative damage to DNA of approximately 100,000 hits per cell per day in rats.[27] Additionally, the work suggested that although DNA repair is very effective, some oxidative lesions escape repair, such that there is an increase in the steady-state levels of oxidative lesions with age.

As the measurements of oxidized DNA bases proceeded, Bruce became interested in compounds that protect the body from oxidative damage and thus was fascinated by the work of postdoctoral fellows Roland Stocker, Balz Frei, and others, who showed that multiple compounds including bilirubin[28] and ascorbate[29] had antioxidant activity in human plasma. As before, given Bruce's continuous interest in developing new approaches, the postdocs measuring the oxidized bases and determining antioxidant activities developed many new assays, such as a new method for the detection of 8-oxo-deoxyguanosine and 8-oxo-guanine.[30] Bruce stated, "I have always felt that developing new analytical methods helps to open up a field and is well worth the effort."[31] In the course of the work on oxidants and antioxidants, Ames and his team realized that "mitochondria are the main source of endogenous oxidants and mitochondria are the main targets of oxidants," and thus their focus shifted to "delaying the mitochondrial decay of aging."[32]

Describing Contributions of Micronutrients in Genetic and Age-Related Diseases

Developing and testing hypotheses about how to delay genetic and age-related diseases was extremely exciting for Bruce for the last few decades of his career,[33] first at the University of California, Berkeley, and later at the Children's Hospital Oakland Research Institute (CHORI), where the Ames group moved in 2000 after the Berkeley lab space had to be vacated for renovations. During this period, Bruce proposed that inadequate intake of various micronutrients (vitamins such as B12, B6, C, E, folate, and niacin and minerals such as zinc) can cause DNA breaks, genome instability, and accelerate mitochondrial decay, which collectively result in increased susceptibility to cancer and age-related diseases.[34,35] Consistent with this hypothesis, postdoctoral fellow Emily Ho and several other lab members showed that deficiencies in various vitamins and minerals was indeed associated with increased oxidative DNA damage and other

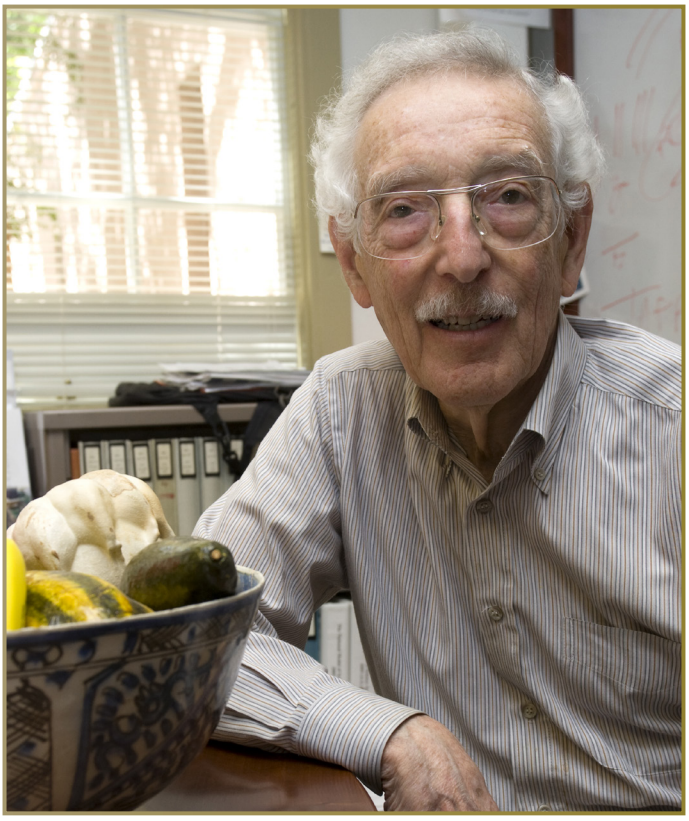

Figure 3 Bruce Ames with fruits and vegetables with beneficial micronutrients. *Photo by Jim Block, courtesy of the Ames family.*

indicators of aging.[36] In parallel work, postdoctoral fellows Tory Hagen, Kenny Beckman, Jiankang Liu, and others found that they could decrease signatures of oxidative aging by feeding rats with metabolites such as acetyl-L-carnitine and lipoic acid.[37,38] The group proposed that the activity (K_m) of mitochondrial enzymes was decreasing with age and that increases in the concentrations of appropriate "micronutrient" compounds would lead to increased enzymatic activity.

In 2002, Bruce again wrote a summary, this time compiling what was known about human genetic diseases resulting from defective enzymes[39] and proposing that high doses of micronutrients, such as vitamin B (that would bypass the defect or restore enzyme activity), could remedy or ameliorate some of the diseases. Thinking about micronutrient deficiencies led Bruce to propose his "Triage Theory" of micronutrient allocation mechanisms, whereby adjustments in protein affinity for required micronutrients to compensate for episodic micronutrient shortages favor short-term survival but accelerate cancer, aging, and neural decay.[40] He suggested that the vitamin and mineral inadequacy experienced by more than half the population increases many health risks associated with old age.

Toward the end of his life, Bruce was most passionate about work aimed at remedying micronutrient inadequacies through the optimization of micronutrient intake (via diet and dietary supplements) to reduce the risks of age-related chronic diseases and promote healthy aging.[41] With this in mind, Bruce and his colleagues at CHORI developed a high-fiber, low-calorie, nutrient-rich fruit-based supplement bar and conducted several clinical trials. One of these studies showed that the CHORI-bar led to decreases in indicators of future disease in overweight adults.[42] The value of appropriate micronutrient intake perhaps is best exemplified by the fact that Bruce's abundant enthusiasm for research never diminished with age.

Concluding Remarks

I want to end this biography by reiterating Bruce's boundless creativity and optimism coupled with a fearlessness to explore whatever problems he found interesting. This approach led to a surprising number of discoveries that had a great impact on society. Bruce inculcated his trainees and fellows with his perspectives on science, even though each of us at some time rolled our eyes at some suggestion on how to improve the lab or an assay. Bruce was exceptionally generous about allowing lab members to develop and take projects to start their own groups, frequently encouraging lab members to publish research conducted in his lab without including himself as co-author. He believed so strongly in the visions of his former trainees and fellows that he also personally invested money, on multiple occasions, into companies started by his mentees (such as Biolog and Operon).

Figure 4 Dr. Giovanna Ferro-Luzzi and Dr. Bruce Ames. *Photo courtesy of Ames family.*

Finally, beyond science and the lab, Bruce's devotion to his family, his wife Giovanna Ferro-Luzzi Ames, also a professor at the University of California, and son Matteo and daughter Sofia, must be mentioned. Giovanna was an unwavering source of support to Bruce throughout their (just about) 65 years of marriage.

Acknowledgments

I am grateful to Ames lab alumni Gerry Fink, Graham Walker, Robin Morgan, and Emily Ho and Giovanna Ferro-Luzzi Ames for their comments on this memoir.

References

1 Haas, F., Mitchell, M. B., Ames, B. N., and Mitchell, H. K. 1952. A series of histidineless mutants of *Neurospora crassa*. *Genetics* 37(3):217-226.

2 Ames, B. N., and Horecker, B. L. 1956. The biosynthesis of histidine: imidazoleacetol phosphate transaminase. *J. Biol. Chem.* 220(1):113-128.

3 Ames, B. N. 2003. An enthusiasm for metabolism. *J. Biol. Chem.* 278(7):4369-4380.

4 Walker, G. C. 2020. A special issue dedicated to Dr. Bruce N. Ames: Introduction. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* 849:503115.

5 Roth, J. R., Silbert, D. F., Fink, G. R., Voll, M. J., Antón, D., Hartman, P. E., and Ames, B. N. 1966. Transfer RNA and the control of the histidine operon. *Cold Spring Harb. Symp. Quant. Biol.* 31:383-392.

6 Martin, R. G., and Ames, B. N. 1961. A method for determining the sedimentation behavior of enzymes: application to protein mixtures. *J. Biol. Chem.* 236:1372-1379.

7 Ames, B. N. 2021. Bruce N. Ames: The Marriage of Biochemistry and Genetics at Caltech, the NIH, UC Berkeley, and CHORI, 1954–2018. In P. Burnett, ed. University of California, Berkeley.

8 Ames, B. N. 2003.

9 Ames, B. N., and Whitfield Jr, H. J. 1966. Frameshift mutagenesis in *Salmonella*. *Cold Spring Harb. Symp. Quant. Biol.* 31:221-225.

10 Ames, B. N. 2003.

11 Ames, B. N., Durston, W. E., Yamasaki, E., and Lee, F. D. 1973. Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection. *Proc. Natl. Acad. Sci. USA* 70(8):2281-2285.

12 McCann, J., Spingarn, N. E., Kobori, J., and Ames, B. N. 1975. Detection of carcinogens as mutagens: bacterial tester strains with R factor plasmids. *Proc. Natl. Acad. Sci. USA* 72(3):979-983.

13 Gee, P., Maron, D. M., and Ames, B. N. 1994. Detection and classification of mutagens: a set of base-specific *Salmonella* tester strains. *Proc. Natl. Acad. Sci. USA* 91(24):11606-11610.

14 Levin, D. E., and Ames, B. N. 1986. Classifying mutagens as to their specificity in causing the six possible transitions and transversions: a simple analysis using the *Salmonella* mutagenicity assay. *Environ. Mutagen.* 8(1):9-28.

15 Turnbough Jr, C. L., Neill, R. J., Landsberg, R., and Ames, B. N. 1979. Pseudouridylation of tRNAs and its role in regulation in *Salmonella typhimurium*. *J. Biol. Chem.* 254(12):5111-5119.

16 Bochner, B. R., Lee, P. C., Wilson, S. W., Cutler, C. W., and Ames, B. N. 1984. AppppA and related adenylylated nucleotides are synthesized as a consequence of oxidation stress. *Cell* 37(1):225-232.

17 Jacobson, F. S., Morgan, R. W., Christman, M. F., and Ames, B. N. 1989. An alkyl hydroperoxide reductase from *Salmonella typhimurium* involved in the defense of DNA against oxidative damage. Purification and properties. *J. Biol. Chem.* 264(3):1488-1496.

18 Christman, M. F., Morgan, R. W., Jacobson, F. S., and Ames, B. N. 1985. Positive control of a regulon for defenses against oxidative stress and some heat-shock proteins in *Salmonella typhimurium*. *Cell.* 41(3):753-762.

19 Storz, G., Tartaglia, L. A., and Ames, B. N. 1990. Transcriptional regulator of oxidative stress-inducible genes: direct activation by oxidation. *Science* 248(4952):189-194.

20 Ames, B. N., Magaw, R., and Gold, L. S. 1987. Ranking possible carcinogenic hazards. *Science* 236(4799):271-280.

21 Ames, B. N., Profet, M., and Gold, L. S. 1990. Dietary pesticides (99.99% all natural). *Proc. Natl. Acad. Sci. USA* 87(19):7777-7781.

22 Gold, L. S., Slone, T. H., Stern, B. R., Manley, N. B., and Ames, B.N. 1992. Rodent carcinogens: setting priorities. *Science* 258(5080):261-265.

23 Ames, B. N. 2003.

24 Ames, B. N. 2003.

25 Cathcart, R., Schwiers, E., Saul, R. L., and Ames, B. N. 1984. Thymine glycol and thymidine glycol in human and rat urine: a possible assay for oxidative DNA damage. *Proc. Natl. Acad. Sci. USA* 81(18):5633-5637.

26 Shigenaga, M. K., Gimeno, C. J., and Ames, B. N. 1989. Urinary 8-hydroxy-2'-deoxyguanosine as a biological marker of in vivo oxidative DNA damage. *Proc. Natl. Acad. Sci. USA* 86(24):9697-9701.

27 Helbock, H. J., Beckman, K. B., Shigenaga, M. K., Walter, P. B., Woodall, A. A., Yeo, H. C., and Ames, B. N. 1998. DNA oxidation matters: the HPLC-electrochemical detection assay of 8-oxo-deoxyguanosine and 8-oxo-guanine. *Proc. Natl. Acad. Sci. USA* 95(1):288-293.

28 Stocker, R., Yamamoto, Y., McDonagh, A. F., Glazer, A. N., and Ames, B. N. 1987. Bilirubin is an antioxidant of possible physiological importance. *Science* 235(4792):1043-1046.

29 Frei, B., England, L., and Ames, B. N. 1989. Ascorbate is an outstanding antioxidant in human blood plasma. *Proc. Natl. Acad. Sci. USA* 86(16):6377-6381.

30 Helbock, H. J., Beckman, K. B., Shigenaga, M. K., Walter, P. B., Woodall, A. A., Yeo, H. C., and Ames, B. N. 1998.

31 Ames, B. N. 2003.

32 Ames, B. N. 2003.

33 Ames, B. N. 2022. Musings in the twilight of my career. *Free Radic. Biol. Med.* 178:219-225.

34 Ames, B. N. 1999. Micronutrient deficiencies. A major cause of DNA damage. *Ann. N. Y. Acad. Sci.* 889:87-106.

35 Ames, B. N. 2001. DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. *Mutat. Res.* 475(1-2):7-20.

36 Ho, E., and Ames, B. N. 2002. Low intracellular zinc induces oxidative DNA damage, disrupts p53, NFkB, and AP1 DNA binding, and affects DNA repair in a rat glioma cell line. *Proc. Natl. Acad. Sci. USA* 99(26):16770-16775.

37 Hagen, T. M., Ingersoll, R. T., Wehr, C. M., Lykkesfeldt, J., Vinarsky, V., Bartholomew, J. C., Song, M. H., and Ames, B. N. 1998. Acetyl-L-carnitine fed to old rats partially restores mitochondrial function and ambulatory activity. *Proc. Natl. Acad. Sci. USA* 95(16):9562-9566.

38 Hagen, T. M., Liu, J., Lykkesfeldt, J., Wehr, C. M., Ingersoll, R. T., Vinarsky, V., Bartholomew, J. C., and Ames, B. N. 2002. Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proc. Natl. Acad. Sci. USA* 99(4):1870-1875.

39 Ames, B. N., Elson-Schwab, I., and Silver, E. A. 2002. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K_m): relevance to genetic disease and polymorphisms. *Am. J. Clin. Nutr.* 75(4):616-658.

40 Ames, B. N. 2006. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. *Proc. Natl. Acad. Sci. USA* 103(47):17589-17594.

41 Ames, B. N. 2018. Prolonging healthy aging: Longevity vitamins and proteins. *Proc. Natl. Acad. Sci. USA* 115(43):10836-10844.

42 McCann, J. C., Shigenaga, M. K., Mietus-Snyder, M. L., Lal, A., Suh, J. H., Krauss, R. M., Gildengorin, G. L., Goldrich, A. M., Block, D. S., Shenvi, S. V., et al. 2015. A multicomponent nutrient bar promotes weight loss and improves dyslipidemia and insulin resistance in the overweight/obese: chronic inflammation blunts these improvements. *FASEB J.* 29(8):3287-3301.