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The Mutagenesis Moonshot: The Propitious Beginnings of the Environmental Mutagenesis and Genomics Society*

David M. DeMarini**
National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina

Abstract

A mutagenesis moonshot addressing the influence of the environment on our genetic wellbeing was launched just two months before astronauts landed on the moon. Its impetus included the discovery that X-rays (Muller, 1927) and chemicals (Auerbach and Robson, 1947) were germ-cell mutagens, the introduction of a growing number of untested chemicals into the environment after World War II, and an increasing awareness of the role of environmental pollution on human health. Due to mounting concern from influential scientists that germ-cell mutagens might be ubiquitous in the environment, Alexander Hollaender and colleagues founded in 1969 the Environmental Mutagen Society (EMS), now the Environmental Mutagenesis and Genomics Society (EMGS); Frits Sobels founded the European EMS in 1970. As Fred de Serres noted, such societies were necessary because protecting populations from environmental mutagens could not be addressed by existing scientific societies, and new multi-disciplinary alliances were required to spearhead this movement. The nascent EMS gathered policy makers and scientists from government, industry, and academia who became advocates for laws requiring genetic toxicity testing of pesticides and drugs and helped implement those laws. They created an electronic database of the mutagenesis literature; established a peer-reviewed journal; promoted basic and applied research in DNA repair and mutagenesis; and established training programs that expanded the science worldwide. Despite these successes, one objective remains unfulfilled: identification of human germ-cell mutagens. After 50 years, the voyage continues, and a vibrant EMGS is needed to bring the mission to its intended target of protecting populations from genetic hazards.

Keywords

Environmental Mutagen Society; multi-disciplinary research; environmental mutagenesis; genetic toxicology

INTRODUCTION

Approximately two months before Neil Armstrong and Buzz Aldrin stepped onto the lunar surface on July 20, 1969, the Environmental Mutagen Society (EMS), now the Environmental Mutagenesis and Genomics Society (EMGS) [Wilson et al., 2013], was

**Correspondence to: David M. DeMarini, U.S. EPA, B105-03, RTP, NC 27711, USA., demarini.david@epa.gov.
*Dedicated to Dr. Herman E. Brockman, who launched me and many other students into the stratosphere of environmental mutagenesis and genetic toxicology

launched. Its official birthday is May 12, 1969, the date its articles of incorporation were filed with the Recorder of Deeds, Corporation Division, Washington, DC, USA. Scientific achievements, starting nearly 100 years prior to 1969, along with later societal events, were essential for the takeoff of the EMS. These included the classical and molecular characterization of genes and gene action; the development of methods to detect mutations reliably; the discovery of physical (ionizing radiation and UV light) and chemical mutagens; the discovery of DNA repair and its role enabling cells both to make mutations and to avoid them; the development and use of nuclear weapons; the introduction of large numbers of synthetic chemicals after World War II; and social movements focused on concerns for the environment, the integrity of our genome, and the future of our species.

This brief review describes some of these scientific and social developments that fostered the formation of the EMS and recounts some of the early achievements that set the Society on a trajectory that continues 50 years later. I have relied with gratitude on prior accounts of this history by Charlotte Auerbach [1973, 1976], John Wassom [Wassom, 1989; Wassom et al., 2010], Scott Frickel [Frickel, 2001, 2004], as well as historical overviews by more than 70 EMGS members.

THE FIRST MUTAGEN (X-RAYS): EVIDENCE THAT GENES CAN BE MUTATED EXPERIMENTALLY

Although our time-line could be considered to start with the insights of Gregor Mendel [1866] who deduced that particulate units explained hereditary traits in peas, it was the rediscovery of his work in 1900 that sparked thoughts of mutagenesis and mutagens. Within months of each other, Hugo de Vries [1900] in the Netherlands, Carl Correns [1900] in Germany, and Erich von Tschermak [1900] in Austria came to the same conclusions as Mendel, initiating the modern field of genetics.

Soon thereafter, de Vries [1901] suggested that “Knowledge of the principles of mutation in the future will enable a fully planned artificial induction of mutations, i.e., the creation of new properties in plants and animals. Moreover, man will likely be able to produce superior varieties of cultivated plants and animals by commanding the origin of mutations.” (Presaging CRISPR Cas9?) He extended this thought a few years later in 1904 while lecturing in the U.S. when he suggested that X-rays might be used to alter the hereditary particles in the germ cells [Wassom, 1989]. Thus, scientists in the U.S. were among the first to hear the notion that ionizing radiation might be a germ-cell mutagen—even though a germ-cell mutation assay had not yet been invented nor had a mutagen of any sort been discovered. Nonetheless, this idea set the stage for the primary reason for the formation of the EMS.

The spark that ignited the field occurred in 1927 when Hermann Muller reported without data that he had (a) developed a germ-cell mutation assay, i.e., the sex-linked recessive lethal assay in *Drosophila* and (b) discovered that X-rays induced such mutations [Muller, 1927]. The next year, Muller published data supporting his claim [Muller, 1928], and Lewis Stadler also provided data showing that X-rays were mutagenic in maize and barley [Stadler,

1928a,b]. This finally enabled researchers to generate mutations and pursue mutation research without being dependent on the rare occurrence of spontaneous mutations.

As noted by Charlotte Auerbach [1976], the discoveries of Muller and Stadler caused X-ray mutagenesis to dominate the field of genetics for the next 20 years, providing insight into genetic recombination, types of mutations, and the nature of the gene. The data during those years confirming the genetic effects of ionizing radiation also prompted other concerns. In his initial paper, Muller [1927] suggested that mutations might cause cancer. He reiterated this possibility a few years later when he stated “there is a similar danger of producing mutations in somatic cells by radiation, which, in the case of tissues in which mitosis occurs, may result in cancer, leukemia, etc.” [Muller, 1934]. Although not the initial concern of most scientists exploring the ability of ionizing radiation to cause mutation, this idea would become a central concern, overshadowing germ-cell mutation as the raison d’etre of the EMS.

THE SECOND MUTAGEN (UV LIGHT): THE FIRST ENVIRONMENTAL MUTAGEN PROVIDES HINTS AT THE GENETIC MATERIAL AND OF GENETIC REPAIR

By the 1930s, scientists began exploring the mutagenicity of another physical agent, ultraviolet light (UV), whose mutagenicity was first shown in the pioneering work of Edgar Altenburg [1933] in *Drosophila* and Lewis Stadler [1936] in maize. Given that we are all exposed to UV via the sun, UV light was the first environmental mutagen to be discovered. Although others followed by demonstrating the mutagenicity of UV in *Drosophila* and plants, the limited ability of UV to penetrate these organisms prevented a clear demonstration that the maximum action spectrum of UV was the same as the absorption spectrum of nucleic acid [Auerbach, 1976]. It was the use of microorganisms (fungal spores, bacteria, and bacterial viruses) to evaluate the effects of UV that propelled the fields of genetics, mutagenesis, and what would eventually be called DNA repair, by providing the initial evidence that nucleic acid, not protein, was the likely genetic material and that damage to it could be repaired [Auerbach, 1976; Hanawalt, 2001; Hockberger, 2002].

Frederick Gates [1929] at the Rockefeller Institute was the first to show that the maximum bactericidal effect of UV corresponded to the absorption spectrum of nucleic acids (265 nm), leading him to propose that UV-induced damage to nucleic acids caused the bactericidal effect. Consistent with this, he also noted that cell division was more sensitive than cell growth to UV light. In the same year, a central figure in our story, i.e., the founder and first president of the EMS, Alexander Hollaender, entered this field, producing a series of papers throughout the 1930s and 1940s confirming the observations of Gates and others and extending the endpoint to mutagenesis.

Within a decade, Emmons and Hollaender [1939] and Knapp et al. [1939] showed that the maximum mutagenesis induced by UV light in fungal spores occurred at the absorption spectrum of nucleic acids, implicating nucleic acids as the genetic material and the macromolecule upon which UV acted to produce mutations [Hollaender, 1941, 1943]. This

was at a time when the genetic material was generally considered to be protein, or an entity called a plasmagene [Darlington, 1948]. Universal acceptance that nucleic acid was the genetic material did not occur for another decade until the pioneering work of Rosalind Franklin and others [Judson, 1996] provided the necessary information for Watson and Crick [1953] to discern the structure of DNA. The reader is encouraged to read the remarkable account of this period of science and the origins of molecular biology by Horace F. Judson [1979].

The use of UV to study biological phenomena in bacteria also played a critical role in elucidating the phenomenon now called DNA repair, well before it was clear that DNA was the molecule being repaired. Again, the pioneering work of Alex Hollaender led to one of the earliest suggestions that the cell could repair UV damage. Hollaender and Curtis [1935] explained the eventual resumption of growth by UV-irradiated *E. coli* by opining that “the possibility of recovery of the irradiated bacteria is not entirely excluded.” Hollaender and Claus [1936] provided additional evidence for repair (of what, they did not know) when they demonstrated higher survival of UV-exposed fungal spores when the spores were held in liquid medium prior to plating on nutrient medium versus plating immediately after exposure.

Studies throughout the 1940s and 1950s identified photoreactivation and eventually led to the isolation of the first UV-sensitive mutants (which were also sensitive to X-rays) by Evelyn Witkin [1946, 1947] and later by Ruth Hill [Hill, 1958; Hill and Simson, 1961] and Paul Howard-Flanders [1962]. The discovery that UV caused dimerization of adjacent pyrimidines by Beukers and Berends [1960] then made possible the discovery that photoreactivation reversed these lesions [Rupert, 1962]. Then, as chronicled by others [Auerbach, 1976; Ganesan and Hanawalt, 2016; Hanawalt, 1989, 2010; Hockberger, 2002], a remarkable series of studies led eventually to the first clear evidence for a postulated key step in nucleotide excision repair, i.e., repair replication in the gap generated by excision of the UV-induced DNA damage [Pettijohn and Hanawalt, 1964; Setlow and Carrier, 1964].

However, what truly catapulted DNA repair into a major research area was the report by James Cleaver [1968] showing that cells from people with xeroderma pigmentosum (XP), which is a hereditary disease featuring extreme sun sensitivity and a high frequency of cancer, were deficient in repair replication after being irradiated with UV. This demonstration that DNA repair deficiency could underpin a devastating hereditary disease illustrated the importance of DNA to human health. In the end, DNA repair research led to our modern understanding of how cells make and avoid mutations [Chatterjee and Walker, 2017; Friedberg, 1997; Thompson, 2012]. As soon became clear, mutagens make DNA damage (e.g., a DNA adduct or a strand break), but it is the cell that makes mutation (i.e., a change in DNA sequence or DNA number) through misrepair or DNA replication past unrepaired DNA damage. Thus, mutagenesis is a cellular process, and mutagens might more appropriately be called DNA damaging agents.

Although outside the scope of this short history of the EMS, one of the key discoveries that marks a beginning of the field of DNA repair was the independent suggestion by Evelyn Witkin [1961] at Rutgers University and Margaret Lieb [1961] at the University of Southern

California, that the observed decline in mutation frequency in bacteria after exposure to UV light might be due to an enzymatic repair process that did not require visible light, i.e., dark repair of UV damage. As related by Witkin [1989, 1994], this first hint at enzymatic dark repair was later shown to function within the soon-to-be discovered nucleotide excision repair pathway and the much-later discovered transcription-coupled repair pathway [Mellon et al., 1987].

THE THIRD MUTAGEN: THE DISCOVERY OF THE FIRST CHEMICAL MUTAGEN

Although efforts to find chemical mutagens began as early as 1914 by Thomas H. Morgan, who failed to show any mutagenic effect of alcohol or ether in *Drosophila* [Auerbach, 1976], clear demonstrations of the mutagenicity of chemicals emerged during and immediately after World War II. Prior to the war, Hermann Muller was at the University of Edinburgh in Scotland in 1938 and was quite interested in seeing if carcinogenic chemicals might also be mutagens. By various accounts, Muller simultaneously encouraged Charlotte Auerbach to pursue such an effort [Beale, 1993] and also discouraged her because he thought it would just be another of the many failed efforts to find chemical mutagens [Crow, 1989]. Auerbach's first experiments with three hydrocarbons confirmed Muller's pessimism; none were mutagenic in *Drosophila* [Auerbach, 1940]. (More than 30 years later, these negative results were understood to likely have been due to the inability of *Drosophila* to metabolize these compounds to mutagenic electrophiles.) What transpired next has been discussed in detail [Auerbach, 1976; Beale, 1993, Sobels, 1975] and is recounted here only in broad outlines.

During the war Auerbach began evaluating dichlorodiethyl sulfide (mustard gas) because its some of its biological effects were similar to those of X-rays [Auerbach, 1976]. As observed during World War I, both mustard gas and X-rays produced similar lesions on the skin that healed slowly and tended to break open again, sometimes years later. By the time of World War II, the X-ray burns were recognized to be due in large part to the effects of X-rays on chromosomes. A pharmacologist at Edinburgh, J.M. Robson, had the idea that the radiomimetic effect of mustard gas might be because mustard gas could break chromosomes as did X-rays [Auerbach, 1973; Beale, 1993]; however, conflicting accounts assign this idea to A.J. Clark, another pharmacologist at Edinburgh [Sobels, 1975]. The person who did many of the experiments, J.M. Robson [Auerbach, 1973] indicated that he had suggested the experiment to Muller [Beale, 1993].

Using the sex-linked recessive lethal assay for germ-cell mutations in *Drosophila*, Auerbach and Robson proceeded to address the question and discovered the first chemical mutagen, mustard gas, which Auerbach described in a report she sent to the U.K. Ministry of Supply on March 14, 1942 [Auerbach and Robson, 1946]. Auerbach let Muller know that the experiment he thought would be a failure had worked, but he did not reveal the result until after Auerbach herself was able to do so [Crow, 1989]. Because mustard gas had been used as a blister agent in World War I, Auerbach and Robson had to wait for security reasons until after the war to name the chemical and publish initially a small portion of the data

[Auerbach and Robson, 1946]; the next year they published the complete set of data [Auerbach and Robson, 1947; Auerbach et al., 1947].

Soon thereafter, Iosif Rapoport in the Soviet Union (now the Russian Federation) showed that carbonyl compounds, ethylene oxide, and glycidol were germ-cell mutagens in *Drosophila* [Rapoport, 1946, 1948]. Rapoport also introduced the term “super mutagen” to describe the highly potent alkylating agents that were discovered in the 1950s and 1960s [Rapoport et al., 1966]. Milislav Demerec at Cold Spring Harbor, NY confirmed Auerbach’s finding and was the first to show that a rodent chemical carcinogen, 1,2,5,6-dibenzanthracene, was also a germ-cell mutagen in *Drosophila* [Demerec, 1947].

Auerbach had been evaluating a variety of chemicals for mutagenic activity, and because of her inability to publish on mustard gas during the war, her first published report in the open literature of a chemical mutagen was of the environmental mutagen allyl isothiocyanate (mustard oil), which is present in cruciferous vegetables, such as cabbage, brussels sprouts, cauliflower, and broccoli [Auerbach and Robson, 1944]. As she noted, “…the search for naturally occurring substances with the capacity to produce the same effect [as X-rays] appears, from the point of view of evolutionary theory, even more important [than the search for synthetic substances].” Although isothiocyanates have since been shown to be mutagenic in a variety of assays [Kassie and Knasműller, 2000], they also account for much of the antimutagenic properties of the cruciferous vegetables in humans [Shaughnessy et al., 2011]. Consequently, because of the vicissitudes of war, the environmental mutagen allyl isothiocyanate was the first chemical mutagen reported in the open literature, setting the stage for the establishment of the EMS precisely 25 years later.

THE FALLOUT FROM FALLOUT: MUTAGENESIS COMES TO OAK RIDGE

For many years Hermann Muller and others had raised the specter of the potential genetic effects of ionizing radiation [Carlson, 1981; Russell, 1989b]. However, the available mutagenicity data were derived largely from studies on an insect, *Drosophila*, which did not provide a compelling basis on which to make public policy decisions [Russell, 1989b]. Thus, when the U.S. government secretly began the Manhattan Project to develop the atomic bomb in the early 1940s, Stafford L. Warren, who was planning the medical investigations associated with the project, started funding Donald R. Charles at the University of Rochester to investigate the genetic effects of radiation in mice [Russell, 1989a]. Although some genetic damage (e.g., morphological changes in the F1 generation of irradiated males) was observed [Charles et al., 1960], the results were inconclusive [Russell, 1989a], despite the breeding of >400,000 mice over a 7-year period.

The detonation of the atomic bombs at the end of the war renewed concerns regarding the genetic effects of ionizing radiation, prompting the U.S. government to establish a Biology Division for this purpose at the Oak Ridge National Laboratory (ORNL) in 1947, with Alexander Hollaender as its Director [Russell, 1989b]. This concern was accelerated during the 1950s and 1960s with the fallout from atmospheric testing of nuclear weapons [Russell, 2013]. As reviewed by Russell [1954], studies in the 1930s had shown that ionizing radiation induced chromosome mutations in mice, and researchers in the U.S. [Snell, 1937] and

Germany [Hertwig and Brenneke, 1937] had provided the scientific foundation for the establishment of the rodent dominant-lethal and heritable-translocation tests to detect the heritable effects of ionizing radiation [Russell, 1989a]. However, there were no methods to detect heritable gene (as opposed to chromosomal) mutations in mammals.

To address this problem, Hollaender hired William (Bill) L. Russell from the Jackson Laboratory in 1947 to initiate such studies. The details of what transpired next have been recounted by both Bill and Liane Russell [Russell, 1989a,b; Russell, 2013]. Bill Russell's development of the mouse (7-locus) specific-locus assay enabled him to show that X-rays induced gene mutations in mice [Russell, 1951], and the results using fractionated doses and different dose rates provided the first evidence of DNA repair in mammals [Russell et al., 1958]. The mouse specific-locus assay was also established in Edinburgh, and new mouse stocks were developed by Mary Lyon [Lyon and Morris, 1966] to score 5 mutations in Harwell, England. Additional critical work was done throughout Europe and Japan during this period; however, further discussion of this is outside the scope of this review, which is focused on the proximal events resulting in the establishment of the EMS.

The impact of the work of Bill and Liane Russell and their colleagues at ORNL, as well as scientists at Harwell and Edinburgh, cannot be underestimated. By the 1950s, these research groups had shown that various forms of ionizing radiation produced germ-cell mutations in mice, just as first shown in fruit flies, suggesting that ionizing radiation most likely also did so in humans. Thus, these results were extrapolated to humans as reviewed by Neel and Lewis [1990] and used to establish genetic risk assessment methods; set safety standards for exposure to ionizing radiation; used to support the concept of the linear non-threshold (LNT) dose-response for genetic effects, first for ionizing radiation and later for chemicals. This was later extended to cancer risk assessment in terms of assuming that the LNT also applied to carcinogenesis [Calabrese, 2019]. This work set the stage for concern about germ-cell mutations being induced by ionizing radiation, with evidence from *Drosophila* and mice suggesting that the same may be true for mutagenic chemicals.

The Biology Division at ORNL was perhaps the primary locus of mutagenesis research in the 1950s and 1960s, and it is no accident that Hollaender took the lead to establish the EMS, running it initially from the Biology Division. Although a history of the Division is not reviewed here, it is worth noting some key scientists that Hollaender hired who played a role in developing critical tools of genetic toxicology and who were founding members of the EMS. One of these was Frederick de Serres, who developed a forward-mutation assay at the *ad-3* locus in the fungus *Neurospora crassa* that he designed to simulate Russell's mouse specific-locus assay, becoming the first microbial assay able to detect quantitatively both gene and multi-locus (chromosomal) mutations [de Serres and Kølmark, 1958]. Applying complementation analysis and reversion analysis, he and Heinrich Malling, also hired by Hollaender, were able to make presumptive determinations of the molecular changes (types of base substitutions and sizes of deletions) in the mutants, long before molecular analysis was available [de Serres and Malling, 1968; de Serres et al., 1971]. In a collaboration with the National Aeronautics and Space Administration (NASA), they and others were able to evaluate the biological effects of cosmic radiation in anticipation of extended human space flights [de Serres et al., 1969]. (I had the privilege of doing my Ph.D. work with de Serres'

system in the 1970s in the laboratory of Herman Brockman at Illinois State University in Normal, IL; Herman had been a postdoc in de Serres' laboratory at Oak Ridge.)

Another Hollaender hire was Ernest H.Y. Chu who, with Heinrich Malling, developed one of the first gene-mutation assays in mammalian cells, the V79/BrdU assay [Chu and Malling, 1968]. At the same time Kao and Puck [1968] working in Denver, Colorado, showed the induction of BrdU-resistant mutants by methylnitronitrosoguanidine (MNNG) and ethyl methanesulfonate (EMS) in CHO cells. Hollaender then hired Abraham Hsie from Puck's lab, who proceeded to develop the quantitative CHO/*Hprt* assay [Hsie et al., 1975], which became a standard mammalian cell mutagenesis assay. (I had the good fortune to join Hsie's laboratory at Oak Ridge in 1980 as a postdoc.)

Perhaps no one had a greater impact on genetic toxicology in terms of developing the basic tools of the field than Heinrich Malling [2004]. In addition to working with de Serres to extend the development of the *Neurospora ad-3* assay and co-inventing the V79/*Hprt* assay with Chu, Malling also developed the first reverse-mutation tester set; it was in *Neurospora* and consisted of four mutant strains that reverted by specific molecular mechanisms, permitting one to infer the type of mutation induced by a mutagenic agent [Malling and de Serres, 1968]. This tester set to identify mutagenic specificity formed the basis for the set of tester strains Bruce Ames assembled for his mutagenicity assay in *Salmonella* [Ames, 1971]. Malling also developed the first in vitro metabolic activation system (a 30,000 x *g* rat liver homogenate)—showing for the first time that a rodent carcinogen (dimethylnitrosamine) could be metabolized in vitro by a fortified rodent liver homogenate [Malling, 1971]. This proof-of-concept led to the use of liver S9, developed by Garner et al. [1972], and incorporated into his eponymous assay by Bruce Ames [Ames et al., 1973] with his *Salmonella* mutagenicity assay [Ames, 1971].

Although beyond the scope of this review, which covers primarily the antecedents of the EMS, Malling's contributions continued apace after he moved to the National Institute of Environmental Health Sciences (NIEHS) in the 1970s. There he and Larry Valcovic developed the mouse biochemical specific-locus test for mammalian germ cells [Malling and Valcovic, 1977]; and later he and James Burkhart developed one of the first transgenic mouse assays for gene mutation [Malling and Burkhart, 1989]. Another transgenic mouse assay was developed at the same time in the Netherlands at the TNO [Gossen et al., 1989]. Many other EMS members developed some of the most important assays in the field of mutagenesis, of which the development of most have been reviewed [Brusick, 1980; Choy, 2001; Claxton et al., 2010; Li and Heflich, 1991; Zeiger, 2010].

POLLUTION, POLITICS, AND PERSUASION: CAN THE ENVIRONMENT DAMAGE OUR GENOME?

Auerbach's work stimulated the search for chemical mutagens—both in *Drosophila* and in newly developed microbial (bacteria, fungi, bacterial viruses) assays. Horowitz et al. [1946] extended Auerbach's finding of the mutagenicity of mustard gas by showing that it was also mutagenic in *Neurospora*, and Tatum [1947] found a related compound, the nitrogen mustard β,β-dichlorodiethylmethylamine, was mutagenic in *E. coli*. Demerec et al. [1951]

reported that 19 out of 31 chemicals tested were mutagenic in *E. coli*, including hydrogen peroxide, copper sulfate, acetic acid, and formaldehyde. These and other developments prompted Alfred Barthelmess [1956] in Munich to review the emerging literature, noting "Formerly, therapeutic and toxicological considerations were the main point of interest in studies of the action of drugs, stimulants, food and mixtures, cosmetic agents, etc. The results of research in genetics within the last two decades call for increased consideration of possible cytogenetic side effects and all their consequences."

Iyer and Szybalski [1958] at Rutgers in New Brunswick, NJ, introduced the paper disk method for rapid screening of mutagens in the streptomycin-dependent strain of *E. coli* developed earlier by Bertani (1951). Using this system, Syzbalski [1958] used a spot test to evaluate 431 chemicals for mutagenicity in *E. coli* (in the absence of mammalian metabolic activation) as a screen for antineoplastic agents, which were assumed might be mutagenic. Although only 5.1% of the 431 compounds were strong mutagens, 86.4 % of those were antineoplastic agents, whereas antineoplastic agents accounted for only 6.8% of the non-mutagens. His study was the first to identify many of the now classic mutagens, such as mitomycin C, 4-nitroquinoline-1-oxide, 6-mercaptopurine, and ethylenimine. Throughout the 1940s to 1960s, studies mostly in *Drosophila* and microbes (*Neurospora, E. coli* and bacteriophage) identified many other chemical mutagens spanning a range of chemical classes: alkylating agents, nitrosoamides, alkaloids, peroxides, nitrous acid, dyes, and base analogues [Auerbach, 1973, 1976; Drake 1970].

Meanwhile, many synthetic chemicals were being introduced into the marketplace and the environment, with minimal or no toxicological testing, let alone genotoxicity testing. These parallel developments caused concern among leading scientists in the field that perhaps many of these newly developed synthetic chemicals were carcinogens and/or germ-cell mutagens, posing a threat to the integrity of the human genome and survival of the species.

Although Muller had been making this argument for years regarding ionizing radiation, he and others began to make this case for chemicals [Carlson, 1981]. Perhaps one of the earliest and strongest voices joining Muller was Joshua Lederberg at the University of Wisconsin, who was another founding member of the EMS. In 1951, Lederberg inferred that a variety of compounds with effects similar to ionizing radiation, such as nitrogen mustards, formaldehyde, hydrogen peroxide, dimethyl sulfate, and ethylene oxide, were mutagens [Lederberg, 1951]. He wrote to Muller in 1950 to express his concern that environmental chemicals might be causing heritable mutations in the population. The letters between the two [Lederberg, 1997] reveal how strongly Lederberg thought about this issue and how he and Muller strategized to bring the issue to the attention of the National Research Council (NRC), the National Academies of Science (NAS), and the World Health Organization (WHO).

In 1955, Lederberg wrote to Detlev Bronk, who was president of the Rockefeller Institute and chair of the NAS Committee on Genetic Hazards of Atomic Energy. Lederberg asked him for "…consideration of genetic hazards of atomic energy from a perspective which includes similar hazards from many other sources, in the light of evidence of mutagenic activity of many chemical substances which may be found in the environment." [Lederberg,

1997]. He expressed this concern at the same time in print [Lederberg, 1955]. Lederberg [1997] has noted that a conference in 1960 [Schull, 1962] on human genetics devoted to mutagenesis and attended by himself, Auerbach, Demerec, and others, likely helped to form a consensus around the issue of environmental chemicals and germ-cell mutation, leading to national action.

James Crow [1989], another founding member of the EMS, noted that Auerbach's work with mustard gas did not cause great environmental concern at the time because mustard gas was highly toxic, and the public was unlikely to be exposed to it. The discovery later of the less toxic but highly mutagenic ethyl methanesulfonate, EMS, which better represented the variety of environmental chemicals to which humans could be exposed, caused more interest in the potential of environmental chemicals to cause mutations in the population. At the urging of Matthew Meselson, another EMS founder, the National Institutes of Health (NIH) Genetics Study Section (Chaired by James Crow) held a conference at the Jackson Laboratory in 1966 to discuss the issue of environmental chemicals and the risk for germ-cell mutation; a highly influential summary of the conference was published later by Crow [1968].

Crow [1968] noted "There is reason to fear that some chemicals may constitute as important a risk as irradiation, and possibly a more serious one. Although knowledge of chemical mutagenesis in man is much less certain than that of radiation, a number of chemicals—some with widespread use—are known to induce genetic damage in some organisms. To consider only radiation hazards is to ignore what may be the submerged part of the iceberg." The agents he suggested that should be evaluated for mutagenicity included industrial and agricultural chemicals, especially herbicides, food additives, insecticides, and chemosterilants; pharmaceuticals such as antibiotics, vaccines, contraceptives, and cosmetics; processed food; and air pollutants.

Coincident with this were studies addressing precisely some of these issues. Lűning [1966] in Sweden published a study in *Drosophila* designed as a screening test to evaluate drugs in which he evaluated 6 derivatives of phenobarbital. Another cofounder of the EMS, Sam Epstein at Harvard, screened 39 chemical agents for germ-cell mutation using the mouse dominant-lethal assay [Epstein and Shafner, 1968], which Bateman [1966] had argued was more relevant for drug testing than tests in an insect, *Drosophila*.

The ground-breaking study by Epstein and Shafner was the first such evaluation of an extensive array of environmental agents in mammals; it included naturally occurring carcinogens (aflatoxin), organic extracts of air pollution and chlorinated drinking water (the first time these complex mixtures were ever evaluated for mutagenicity), food additives, pesticides, and pharmaceuticals. Soon thereafter, as reviewed by Zeiger [2010], a committee of the U.S. Department of Health Education and Welfare (DHEW), now the Department of Health and Human Services, which included some EMS founders such as Legator and Epstein, proposed in the so-called Mrak Commission Report that mutagenicity testing should be required for pesticides prior to approval for use [DHEW, 1969].

At this time there was no U.S. Environmental Protection Agency; instead, the U.S. Department of Agriculture (USDA) was responsible for approving pesticides. There was no genotoxicity testing required for drugs, pesticides, or anything else; however, that was about to change. The development of genetic toxicity assays and research funding on radiation and chemical mutagenesis throughout the 1950s and 1960s in Europe, Japan, and the U.S. resulted in the recognition that beyond X-rays and UV, whole categories of chemicals were also mutagenic, such as alkylating agents, base analogues, acridines, nitrous acid, hydroxylamine, and others [Drake, 1970]. Thus, by the late 1960s, the ability to detect both gene and chromosomal mutation in microorganisms and mammals was established, and the results were revealing that radiation was not the only source of mutagenic activity. It was mutagenesis, first by X-rays, then by UV, and later by various chemicals, that gave insight into the nature of the genetic material and the role of mutation in evolution and in the genetic integrity of the species.

THE EMERGENCE OF THE ENVIRONMENTAL MOVEMENT

The scientific developments described above occurred in parallel with some of the most important social movements of the 20th century. Some of the key events catalyzing the environmental movement occurred after the war, especially in the 1960s (Table I). These provided the additional impetus needed to get the EMS off the ground. Several environmental disasters and some acclaimed books and articles helped to create the zeitgeist in the 1960s that formed the backdrop for the establishment of the EMS. Scott Frickel [2001, 2004] has written extensively about this, but some highlights are reviewed here.

After the war, *A Sand County Almanac* by Aldo Leopold [1949] was published a year after Leopold's death. Leopold argued for a "land ethic," which held that people had a responsibility to care for the air, water, soil, plants, and animals of the earth in a responsible way so that the land should be sustained for future generations. His book was a cautionary tale to the development and rebuilding that occurred *en masse* around the world after the war, frequently with little regard to the effects such development had on the land. His book became foundational in the wildlife conservation, ecology, and general environmental movements of the 1950s and 1960s.

Rachel Carson's *Silent Spring* [Carson, 1962] has been credited by Brulle [2000] as one of the key texts underlying the environmental movement at the time. Carson's book focused on a variety of issues, but especially on the indiscriminate use of pesticides. In addition, based on the studies published through the 1940s and 1950s on chemical mutagens (including pesticides) and the writings of some of the key geneticists noted above, Carson [1962] incorporated concern for environmental mutagens into her book. "For mankind as a whole, possession infinitely more valuable than our individual life is our genetic heritage, our link with past and future. Shaped through long eons of evolution, our genes not only make us what we are, but hold in their minute beings the future—be it one of promise or threat. Yet genetic deterioration through man-made agents is the menace of our time, 'the last and greatest danger to our civilization.'"

The publication of *The Population Bomb* by Paul Ehrlich [1968] generated widespread discussion in the scientific and popular press about population control, food availability, and the ability to have sufficient resources to support a growing population in light of population growth, environmental pollution, and limited land and water for food production. Several articles in *Science* [Hardin, 1968; White, 1967] received wide attention and contributed to the public conversation regarding the sustainability of the environment.

A number of environmental tragedies occurred in the 1960s had profound impacts locally or regionally in terms of death or ill health to people, environmental damage, and economic disruption (Table I). Most critically, many of these events brought public attention to key environmental issues and ignited public and governmental action. As listed in Table I, some of these included (a) the teratogenic effect of the drug thalidomide starting in 1961, which initiated discussions about reproductive and developmental toxicity testing of drugs for adverse side effects; (b) the London smog in 1962 that was estimated to have killed 750 people and a weather inversion in New York in 1964 that was estimated to have killed 80 people, which focused attention on air pollution, resulting in the formation of regulatory authorities and efforts to reduce such pollution; (c) large oil spills off the coasts of England and France in 1967 and Santa Barbara, CA, in 1968, leading to the stricter regulation of oil drilling and transport; and (d) the Cuyahoga River near Cleveland, Ohio, catching on fire in 1969 due to oil and chemical pollution, initiating discussions that led to legislation to clean up and protect waterways.

Television brought these events into the homes of most people, raising the concern about environmental pollution and its potential adverse effects on public health and the environment. The iconic photograph of earthrise (Figure 1) taken by Apollo 8 astronaut Bill Anders in December 1968 galvanized, if only temporarily, the citizens of earth by showing our collective dependence on each other and our fragile “blue marble” planet. By the time astronauts set foot on the moon six months later, the attention of the world was focused briefly on that singular event, creating a new sense of our connectedness and of the precious nature of our planet earth.

EMS TAKES OFF

Scientific and social developments had set the stage for the launch of the EMS, which was a combination of both a scientific society and a social movement [Frickel, 2004]. As noted by Frickel [2004], after Hollaender stepped down in 1967 as Director for 20 years of the Biology Division at ORNL, he toured many laboratories in Europe that summer to convince people of the importance of chemical mutagenesis. He thought that chemical mutagenesis, like radiation research, could “...become a kind of focal point for further development of cooperation with different government agencies in building up new approaches to basic biology…”

Following his European tour, Hollaender and his Oak Ridge colleagues sponsored an “informal discussion” on mutagenesis at the Biology Division of ORNL in April 1968. In the June/July issue of *Scientist and Citizen*, Crow [1968] published his summary of the 1966 NIH conference on the risk of chemicals to future generations and disseminated the main

conclusions in a variety of talk and conferences. This NIH conference had four recommendations, which Hollaender and his colleagues were aware of as they proceeded to explore the possibility of establishing a scientific society. The recommendations from the NIH conference, most of which were adopted by the soon-to-be established EMS, were (1) establish a registry of mutagens, (2) make mutagenicity testing routine for drugs and other chemicals to which humans would be exposed, (3) develop better mutagenicity assays, and (4) explore the feasibility of monitoring of the population for increased chromosome breakage and genetic disease [Crow, 1968].

In September 1968 Hollaender organized a “Roundtable on Mutagenesis” in Gaithersburg, MD for 40 mostly U.S. biologists to discuss mutagenicity tests, population monitoring for mutational load, and needs for future research. Critically, consensus was obtained at this meeting to establish a scientific society to address these issues, initiating the formal efforts to establish the EMS [Frickel, 2004]. The group mailed a questionnaire to ~100 scientists mostly in the U.S. to determine their sense of a need for a scientific society to deal with and encourage interest in “environmental factors that could have a genetic effect” [Wassom, 1989].

On January 8, 1969, an *ad hoc* committee composed of Hollaender, de Serres, Malling, Marvin Legator, Ernst Freese, and Samuel Epstein met in the offices of Union Carbide Corp. in New York City (Union Carbide was the contractor that operated ORNL for the Department of Defense) where the secretary of the committee, Samuel Epstein, reported that the respondents to the survey endorsed the formation of a society. They agreed unanimously that a society should be established and selected the name Environmental Mutagen Society (EMS) partly because EMS was the abbreviation of the well-known mutagen at that time, ethyl methanesulfonate. The Society was founded to encourage the study of chemicals in the human environment for mutagenic effects and to promote scientific investigation and dissemination of information related to the field of genetic toxicology.

The group elected Hollaender as president, Matthew Meselson as vice-president, Samuel Epstein as secretary, and Marvin Legator as treasurer; the council consisted of Fred de Serres, Ernst Freese, Heinrich Malling, James Crow, and Bruce Ames. By the time of the first council meeting at the National Academy of Sciences in Washington, DC, on August 4, 1969 [Wassom, 1989], the following charges, which Hollaender had given to the committee and some of which were derived from the 1966 NIH conference [Crow, 1968], had been implemented: (a) the Environmental Mutagen Information Center (EMIC) had been established, which was the first curated and computerized literature database, presaging PubMed by nearly 30 years; (b) the first issue of the *EMS Newsletter* had been published (June, 1969); (c) Plenum Press had agreed to publish a set of 10 monographs, which were edited initially by Hollaender and later by him and de Serres [Hollaender, 1971–1980]; (d) a proposal was ready for submission for funding a conference on cyclamates as a potential germ-cell mutagen; and (e) the organizing of the first annual meeting had begun.

Preceding the first EMS meeting in March 1970, scientists in Germany organized a symposium on chemical mutagenesis within their meeting of the Gesellschaft fűr Anthropologie und Humangenetik on October 7, 1969, and this was associated with the

opening of the Central Laboratory for Mutagenicity Testing in Freiburg, Germany on October 10th [EMS Newsletter, 1969]. Scientists from Germany included A. Barthelmess (Munich), G. Rohrborn (Heidelberg), T.M. Schrodeder (Heidelberg), F. Vogel (Heidelberg), and I-D Adler (Munich); some organizers of EMS also made presentations, such as M. Legator, H. Malling, F. de Serres, E. Chu, and S. Epstein.

Much of the early history of the Society has been recounted by Wassom [1989], Wassom et al. [2010], and Frickel [2004] and is not repeated here. However, several aspects of the first meeting of the Society, which was held at the Sheraton Park Hotel in Washington, DC, on March 22–25, 1970, are worth noting. One is that the conference had 268 attendees, 169 of whom were members, and after only one year, the EMS had an overall membership of 452, 64 of whom were European scientists; within just 10 years, the Society had a membership of 1,050, 182 of whom were from outside of the U.S [Wassom, 1989].

Second, the program of that first meeting [EMS Newsletter, 1969] contained all the elements one might see in a current EMS program in that there were talks on (a) mutagenicity testing (by F. de Serres, M. Legator, G. Rȍhrborn, S. Epstein, and P. Neurath); (b) mutational mechanisms and DNA repair (by J. Drake, R. Kimball, M. Meselson, and W. Nichols); (c) agents of concern at the moment, in this case nitroso compounds (by W. Lijinsky and P. Stout), as well as cyclamates (by L. Goldberg, S. Green, P. Nees, and Jacqueline Verrett; and (d) population monitoring (by J. Miller, H. Kalter, J.E. Cleaver, and J. Crow). The registration form also reflected the times: $10 for members, $15 for non-members, and $2 for wife (not spouse, but wife). However, the form for reserving a hotel room had a category for a double room for “myself and wife (or husband).” Jacqueline Verrett (U.S. FDA) noted above was the only invited woman scientist on the program.

Finally, reflective of the social milieu in which the Society was born, H. Bentley Glass [Martin, 2005], a former student of Muller’s and one of the leading public intellectuals of the day, gave the opening address. Glass at the time was the academic vice-president of the State University of New York at Stony Brook. His scientific work had been initially in *Drosophila* genetics but later addressed problems of blood group polymorphisms and effects of genetic mutation. He was a past-president of the Maryland chapter of the American Civil Liberties Union and had chaired the American Association of University Professors’ Special Committee on Academic Freedom and tenure, both of which opposed loyalty oaths during the McCarthy era and worked to assure unfair dismissal of suspected Communists. He was the subject of frequent investigations by the Federal Bureau of Investigation (FBI), largely because of his actions to eliminate racial segregation. The FBI continued to collect information on his views on genetic mutation and nuclear proliferation throughout the 1960s [Wolfe, 2018]. Thus, from the beginning, the society was not afraid to provide a forum for scientists/activists who pushed the boundaries of traditional scientists by arguing for social action. From its beginnings, the EMS articulated a social conscience, but one rooted in and derived from the science it fostered [Frickel, 2004].

EARLY SUCCESSES

Within just a few years of its founding, the EMS had accomplished most of its initial goals, including:

1. The establishment of the Environmental Mutagen Information Center (EMIC) at Oak Ridge in 1969. EMIC was the first electronically accessible, curated database of its kind and permitted the rapid growth of the field by making the literature in mutagenesis readily accessible to researchers. The EMIC database was subsequently incorporated into ToxLine at the National Library of Medicine.

2. The publication of a position paper advocating for the inclusion of mutagenesis testing of environmental chemicals for potential germ-cell effects. The EMS Committee 17 published a paper titled *Environmental Mutagenic Hazards* in *Science* [Drake et al., 1975] that outlined the research and regulatory needs for managing potential germ-cell mutagens in the environment. This high-profile publication provided guidance for future research and testing efforts as well as potential regulatory actions.

3. The establishment of a U.S. federal law providing for the mutagenicity testing of drugs and chemicals [Prival and Dellarco, 1989]. As described by Frickel [2004], EMS members played a pivotal role in helping to pass the 1976 Toxic Substances Control Act (TSCA), which empowered the U.S. EPA (established in 1970) to include mutagenicity data in regulatory decisions. Three EMS members, Samuel Epstein, W. Gary Flamm, and Lawrence Fishbein gave expert testimony at Senator Abraham Ribicoff's hearing on "Chemicals and the Future of Man" in 1971. President Alexander Hollaender convened a committee to evaluate the TSCA legislation prior to its final passage, and the recommendations from that committee were influential in the formulation of the law. In 2016 Congress amended TSCA to expand its testing authorities. (As the only remaining genetic toxicologist at the U.S. EPA who was involved in implementing the first TSCA through the U.S. EPA's Gene-Tox Program, I have had the privilege of helping the Agency implement this amended version.)

4. The establishment of the *EMS Newsletter* in 1969, the journal *Environmental Mutagenesis* in 1979 (subsequently renamed *Environmental and Molecular Mutagenesis* in 1987), and a book series on mutagenicity test methods beginning in 1971. Fred de Serres was the first Editor of the *EMS Newsletter*, and the *Newsletter* became a clearing house for all activities related to mutagenesis and to the new Society. (I was privileged to be among the EMS members who served as an editor of the newsletter, in my case from 1988–1991.) *Environmental and Molecular Mutagenesis* was founded as *Environmental Mutagenesis* in 1983 with Seymour Abrahamson as its founding editor; (I had the pleasure to be one of the Book Review Editors from 1990–1993) [Hoffmann, 2004]. The book series *Chemical Mutagens: Principles and Methods for Their Detection* was a 10-volume set first edited by Hollaender and later by de Serres and Hollaender [Hollaender, 1971–1986] that provided descriptions of a range of mutagenicity

assays. Volume 1 contained a chapter by Bruce Ames where he first introduced his *Salmonella* mutagenicity assay (as a spot test) using strains that he and Philip Hartman had isolated when they both were at the NIH [Ames, 1971].

5. The establishment of the Gene-Tox Program, which could not have happened without EMIC. This program was initiated by EMS member Michael Waters and lasted 10 years, during which more than 150 scientists reviewed the entire literature in the field of chemical mutagenesis, producing 40 review articles and other papers [Waters, 1994]. It was the first and only effort to review the literature of an entire field and make recommendations about which assays and protocols were appropriate for continued use, what were the data needed to make a paper acceptable for publication, and what further research was needed. It formed the basis for the U.S. EPA's implementation of testing requirements under TSCA [Dearfield et al., 1991; Waters, 1994; Waters and Auletta, 1981] and contributed to the guidelines used by the International Agency for Research on cancer (IARC) in the evaluation of short-term tests for genetic and related effects. Through the contract efforts of EMIC, Gene-Tox created the qualitative Gene-Tox database, which is hosted by the National Library of Medicine's TOXNET [Cimino and Auletta, 1993]. Waters went on to develop the quantitative EPA/IARC Genetic Activity Profile (GAP) Database, which was used by IARC in the evaluation of carcinogenicity until the early 2000s. Through the application of tools such as Gene-Tox and GAP in chemical hazard evaluations, the number of genotoxicity tests in common use was gradually reduced from more than 200 to only a handful. During this period environmental mutagenesis *per se* became secondary to the detection of potential carcinogens. The Society's annual scientific meetings reflected this transition, and genetic toxicology was the Society's primary focus from the late 1970s until the advent of genomics.

6. The establishment of training programs in countries in which genetic toxicology had not yet been firmly established. Hollaender started these programs with an initial focus on Latin America [Olivero et al., 2010], which then expanded worldwide. After his death in 1986, Patricia Ostrosky-Wegman from Mexico re-initiated the Hollaender Courses in Genetic Toxicology starting in 1993, and they have been conducted annually worldwide since then; the programs can be found at https://www.EMS-us.org/page/hollaender-courses.

A collage of just some of the scientists mentioned in this review whose work was central in establishing the framework in which the EMS was born is shown in Figure 2. I apologize for omitting from the text and this picture so many scientists who played important roles in the history leading up to and initiating the EMS. Their collective efforts formed the cornerstone of genetics and environmental mutagenesis, leading to new insights and advances in cancer research, public health, environmental science, basic biology and molecular biology, and public policy and regulatory science that has spread worldwide. We owe them a deep debt of gratitude.

A LEGACY OF ACTION WITHOUT ACTIVISM: SEPARATION OF SCIENCE FROM POLICY

The exigency for the establishment of a scientific society such as the EMS came from many quarters, both scientific and political. However, the resulting organization was established firmly as a scientific society only, with no outward activist or political agenda whatsoever. Even the EMS Committee 17 paper in *Science* [Drake et al., 1975] was a statement of recommendations based on the available science. This clear separation between science and activism gave the EMS credibility from the beginning, enabling the Society to function as an advisory organization for all who needed help in the field of environmental/chemical mutagenesis and related areas [Frickel, 2001, 2004]. The objectivity that the Society has displayed for half a century assured that statements issued on behalf of the Society reflected an objective and dispassionate assessment of the current state of the science, giving EMS credibility on matters associated with environmental mutagenesis and genetic toxicity.

One of the primary goals of the Society was to gain an understanding of the extent to which environmental agents posed a threat to the human germline [Drake et al., 1975]. After 50 years, this important objective of the society has not yet been achieved. Most assessments have recognized that the failure to resolve this issue has been due largely to technical problems [Wyrobek et al., 2007]. Another factor was that the focus of the Society turned away from germ-cell mutation and towards cancer in the mid-1970s when data, initially from Bruce Ames' laboratory, began emerging that linked mutagenic and carcinogenic mechanisms. Nonetheless, efforts to identify human germ-cell mutagens continue through *ad hoc* committees and the efforts of individual research groups [Yauk et al., 2013a,b; 2015].

The need is greater now than ever for unbiased views on scientific matters of importance to society. This will become especially acute when (not if) the existence of human germ-cell mutagens is convincingly demonstrated. Most likely the first such agents will be tobacco smoke, air pollution, and ionizing radiation [Beal et al., 2017; DeMarini, 2012; Somers, 2011]. Although not foreseen in 1969, there is now compelling evidence of the critical role of environmental exposures to the germline resulting in heritable epigenetic changes [Escher and Robotti, 2019]; these, too, will need to be considered along with germ-cell mutations. The results of such discoveries will test the leadership of EMS and its members who will be called upon to explain the implications of such findings to physicians, policy makers, legislators, and the public.

The remarkable leadership, vision, organizational skills, and persistence of the founders of the EMS represent striking examples of how scientists working in concert from disparate fields can shape the direction of science and public policy and influence succeeding generations to explore the issues of concern that they identified more than half a century ago. Although much has been achieved, much more needs to be done if the original mission of the Society is to be completed. There is a need for a deeper understanding of basic mutational mechanisms and of DNA repair; of the role of epigenetic mechanisms with regard to heritable effects; and the role of environmental exposures on both mutational and epigenetic effects, both in somatic and germ cells.

The development of new tools in genomic science prompted the Society to change its name from EMS to EMGS [DeMarini and De Flora, 2010; Wilson et al., 2013]. These scientific developments will make what was impossible finally possible and should reinvigorate the Society to tackle the remaining problems in environmental mutagenesis and genetic toxicology to help improve public policy and public health. If Shakespeare was right that the past is prologue, then EMS is well-positioned to provide such leadership now and into the future. EMS still has a vital mission to complete for science and society; the Eagle has not yet landed*.

RESOURCES ON THE HISTORY OF EMS

In constructing this history, I acknowledge the scholarship of John Wassom, Scott Frickel, Errol Zeiger, Phil Hanawalt, and many others who have chronicled the origin and early years of the EMS, genetic toxicology, and DNA repair. The history of the EMS is all the richer for their efforts to document what transpired so that we can be inspired to complete the mission envisioned by so many concerned scientists. I thank them, and others listed below, for their contributions to science and the history of this society. I take responsibility for any errors and the many omissions (due to space and time) that no doubt are present in this review.

In addition to the references in this article, I also acknowledge the important contributions to the history of the field provided in books by Auerbach [1976] and Frickel [2004], and most recently the e-book edited by George Hoffmann [2019] that is a compilation of >40 *Reflections* articles by scientists in the field of mutagenesis that Hoffmann procured during his 21 years as Editor of the *Reflections* series in *Mutation Research—Reviews*, which I had the pleasure of editing, along with Michael Waters, for 21 years.

I also recommend for interested readers and historians, philosophers, and sociologists of science the additional articles, written or edited by ~70 scientists, nearly all EMS members, who took the time to record the history of this special organization and the field. These are in Special Issues of *Environ Mol Mutagen* celebrating the 20th, 25th, and 40th anniversaries of the society and the 25th anniversary of *Environ Mol Mutagen*:

[Vol 14 (Suppl 16) 1989]: Rosalie Elespuru, Richard J. Albertini, John S. Wassom, James F. Crow, John W. Drake, William L. Russell, Liane B. Russell, Evelyn M. Witkin, Donald G. MacPhee, Philip E. Hartman, Michael J. Prival, John Ashby, David Brusick, Bruce N. Ames, William Lijinsky, James G. Burkhart, Heinrich V. Malling, Philip C. Hanawalt, William R. Lee, J. Justin McCormack, and Veronica M. Maher;

[Vol 23 (Suppl 24) 1994]: J. Patrick O'Neill, Marvin S. Legator, Frederick J. de Serres, John W. Drake, David Brusick, Richard J. Albertini, Liane B. Russell, Michael D. Shelby, John A. Heddle, Anthony V. Carrano, Sheila M. Galloway, R. Julian Preston, George R. Hoffmann, Michael D. Waters, James T. MacGregor, Philip C. Hanawalt, James M. Gentile;

*Reference to the first words uttered by Neil Armstrong upon landing the lunar module (the Eagle) on the surface of the moon in 1969, "Houston, Tranquility Base here. The Eagle has landed."

[Vol 51 (8–9) 2010]: Suzanne M. Morris, Robert H. Heflich, George R. Hoffmann, Errol Zeiger, and Heinrich V. Malling [Vol 44 (5), 2004]; and Suzanne M. Morris, Anane Aidoo, Vasily Dorbrovolsky, Robert Heflich, Mugimane Manjanatha, Jack Bishop, Barbara Parsons, John S. Wassom, Heinrich V. Malling, K. Sankaranarayanan, Po-Yung Lu, Diana Anderson, Ofelia A. Olivero, Marcelo Larramendy, Sonia Soloneski, Carlos F.M. Menck, Jaime Matta, Gustavo A. Folle, Enrique Zamorano-Ponce, Graciela Spivak, Kristine L. Wit, Patricia G. Moorman, Olga Kovalchukk, Nina Holland, Gladys Block, Paul R. Andreassen, Errol Zeiger, Lynn H. Pottenger, B. Bhaskar Gollapudi, Ronald D. Snyder, James D. Tucker, Vasily N. Dobrovolsky, Daishiro Miura, Robert H. Heflich, Stephen D. Dertinger, Barbara L. Parsons, Meagan B. Myers, Fanxue Meng, Yiying Wang, Page B. McKinzie, Joe Shuga, Yong Zeng, Richard Novak, Richard A. Mathies, Pierre Hainaut, Martyn T. Smith.

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Figure 1.
Earthrise taken by Apollo 8 astronaut Bill Anders in December 1968. https://www.bing.com/images/search?view=detailV2&id=6CC3DD930DF26BC50F172145598C494C5D984CD1&thid=OIP.116vh8vI2hDA4cbKbFG4WgHaHa&mediaurl=https%3A%2F%2Fupload.wikimedia.org%2Fwikipedia%2Fcommons%2Fthumb%2Fa%2Fa8%2FNASA-Apollo8-Dec24-Earthrise.jpg%2F1024px-NASA-Apollo8-Dec24-Earthrise.jpg&exph=1024&expw=1024&q=Original+Apollo+8+Earthrise&selectedindex=0&ajaxhist=0&vt=0&eim=1,2,6

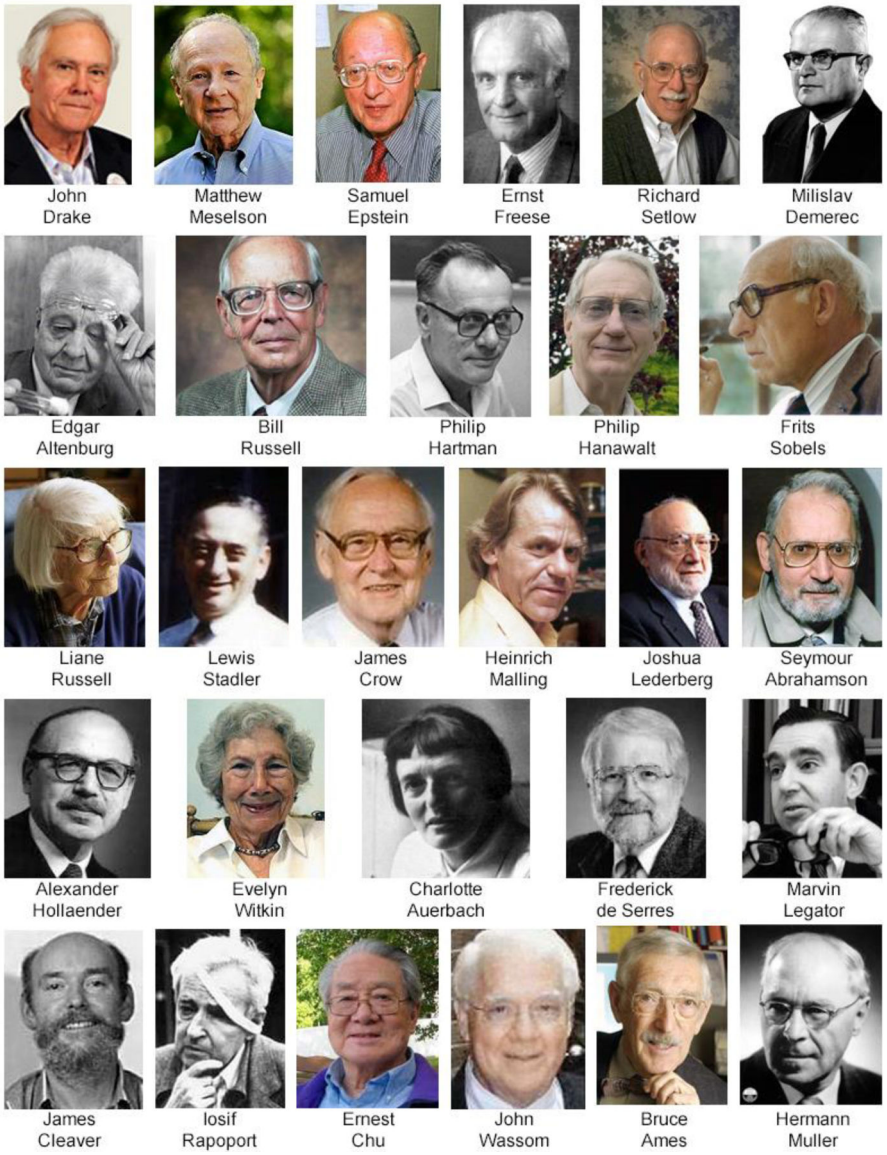

Figure 2.

Collection of some of the key scientists whose work contributed to the basis for founding the EMS.

TABLE I.

Some Key Environmental Events of the 1960s[a]

Year	Event
1960	1. U.S. Public Health Service initiates 2-year study of air pollution due to automobile exhaust
	2. Jacques Cousteau and Prince Rainier II of Monaco help stop French plan to dump radioactive waste into the Mediterranean Sea
	3. Alaska Conservation Society established to oppose Edward Teller's Project Chariot to use nuclear weapons to modify the Alaskan landscape
	4. Three operators killed during a nuclear reactor meltdown and explosion in Arco, Idaho
	5. Two Mark 39 hydrogen bombs accidentally dropped over Goldsboro, NC
	6. International Clean Air Congress held in London
	7. World Wildlife Fund and African Wildlife Foundation were formed
1961	Thalidomide removed from the U.S. market due its teratogenic effects.
1962	1. Conference on Conservation held at the White House
	2. Publication of *Silent Spring* by U.S. author Rachel Carson
	3. London smog 4–7 December worst since 1952. Although 750 die, it is less than the 4,000 in 1952 due to Clean Air Act of 1956
1963	1. Berne Accord to protect Rhine River from pollution
	2. U.S. Senate creates Subcommittee on Air and Water Pollution
	3. Nuclear Test Ban Treaty between the U.S. and U.S.S.R.
	4. Canadian author Farley Mowat published "Never Cry Wolf"
1964	1. U.S. Congress creates National Wilderness Preservation System
	2. Citizens for Clean Air is organized by Hazel Henderson in New York
	3. Tom Lehrer records his song *Pollution*
	4. U.S. president Lyndon Johnson and his Environmental Pollution Panel of his Science Advisory Committee Issue a report "Restoring the Quality of Our Environment" that warns of increasing atmospheric CO_2 levels
	5. U.S. Congress passes Water Quality Act, Noise Control Act, and Solid Waste Disposal Act
	6. Weather inversion creates 4-day air pollution killing 80 in New York City
	7. Collapse of UK's Sea Gem off-shore oil drilling rig kills 9
	8. "Birth of environmental law" with U.S. federal court decision to block construction of a utility project
1965	Ralph Nader published *Unsafe at Any Speed*, which critiqued the auto industry
1966	1. Barry Commoner established Center for the Biology of Natural Systems at Washington University, St. Louis, MO
	2. U.S. Senator Edmund Muskie holds hearing on leaded gasoline, with UCLA scientist Clair Patterson exposing the fraudulent science of the petroleum industry. Leads to considering of establishing new environmental regulatory agencies
	3. France begins nuclear weapons testing in South Pacific
	4. Fermi No. 1 nuclear reactor in Detroit, MI partially melts down
	5. Collapse of coal mine waste in Aberfan, Wales kills 116 children and 28 adults
1967	1. Outer Space Treaty signed preventing nuclear weapons in orbit

Year	Event
	2. Treaty of Tlatelolco signed preventing nuclear weapons in Latin America
	3. Environmental Defense Fund established
	4. U.S. Congress passes Air Quality act/Clean Air Act
	5. Torrey Canyon oil tanker crash, polluting coastlines of England and France
	6. Greenpeace founded in Vancouver, Canada
	7. Lynn White published *Historical Roots of Our Ecological Crisis* in Science 155:1203
1968	1. Redwood National Park established in California
	2. U.S. Congress passes Wild and Scenic Rivers Act and National Trails System Act
	3. Meteorologist Elmer Robinson (Stanford Research Institute) warns American Petroleum Institute of rising atmospheric CO_2
	4. David Brower leads effort preventing dams in the Grand Canyon
	5. First ice core drilled in Antarctica to study historical climate changes
	6. Friends of the Sea Otter founded
	7. Garret Hardin publishes *Tragedy of the Commons* in Science 162:1243
	8. Apollo 8 astronauts take first photo of earthrise
	9. Paul Ehrlich publishes *The Population Bomb*
1969	1. Oil well blowout off the coast of Santa Barbara, California
	2. U.S. Federal Coal Mine Health and Safety Act passed
	3. U.S. National Environmental Policy Act passed
	4. Friends of the Earth founded
	5. Cuyahoga River near Cleveland, PA catches on fire from oil and chemical pollution
	6. Nuclear bomb detonated underground in Colorado to free natural gas (fracking), but the freed gas was too radioactive to use
	7. Victor Sheffer published *The Year of the Whale*, starting the save-the-whale movement
	8. DHEW report recommends genetic toxicity testing of pesticides
	9. Environmental Mutagen Society is founded.

[a]Adapted from http://environmentalhistory.org/20th-century/sixties-1960–1969/