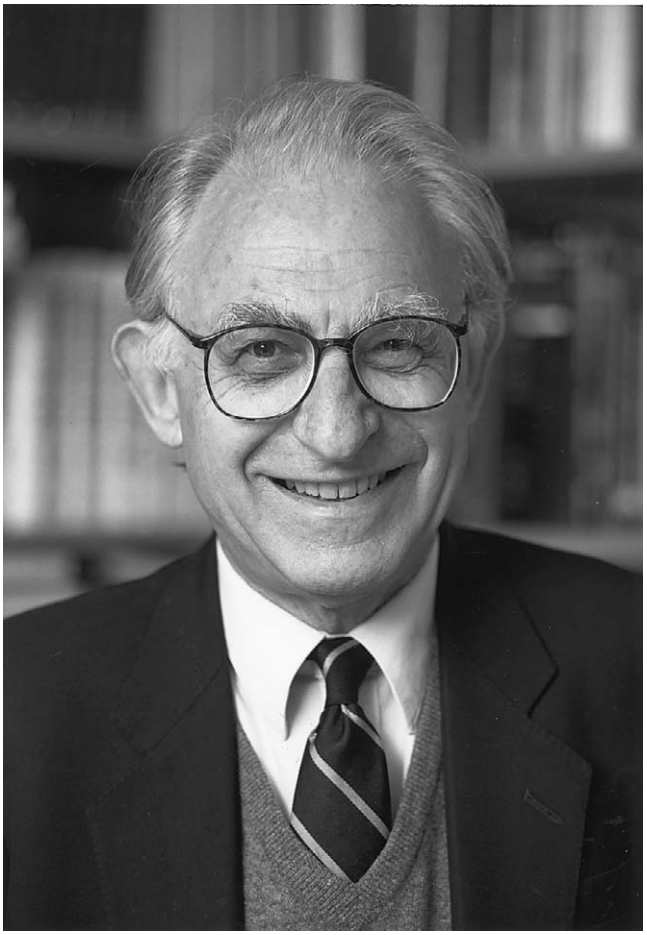
2001 WILLIAM ALLAN AWARD ADDRESS
Introductory Speech for Charles J. Epstein*

Arno G. Motulsky

Departments of Medicine and Genome Sciences, University of Washington, Seattle



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I am delighted to introduce this year's recipient of the William Allan Award—Charles J. Epstein. This prize is the major award of our society and is granted yearly to one (or two) scientists for substantial contributions to human and medical genetics that have been carried out over a lifetime of scientific and scholarly inquiry. I had the privilege of chairing this year's ASHG award committee. Charlie Epstein clearly emerged as our winner among many nominations.

I have known Charlie for almost 40 years. We were fortunate in Seattle that he decided to join our relatively new division of medical genetics for a postdoctoral fellowship in 1963. Charlie's credentials were outstanding. He had a B.S. in chemistry from Harvard College (summa cum laude), a Harvard M.D. degree (magna cum laude), followed by 2 years as house officer in internal medicine at Peter Bent Brigham Hospital in Boston.

Charlie then spent 2 years in Bethesda at the National Institutes of Health (NIH) with Chris Anfinsen, who later won the 1970 Nobel Prize in Biochemistry. There, Charlie received training on various aspects of protein chemistry and carried out research work in this area. A number of fine papers—often published in the *Journal of Biological Chemistry*—dealt with the genetic control of the three-dimensional structure of protein.

In planning his future life, a mere laboratory career in biochemistry did not attract Charlie. Nineteen sixty-three marked the beginnings of the golden years of human biochemical genetics, and clinical genetics had just started. In Seattle, we had initiated a genetics clinic and also saw patients with genetic diseases on the wards. We exposed our fellows to think along genetic lines and tried to fire them up with the great promises of genetic approaches to medicine, which did not seem quite as clear at that time as they are today.

Charlie's principal scientific problem in Seattle was posed by a patient: could Werner syndrome—an autosomal recessive condition with many features of premature aging—give us clues about the role of the Werner gene in the normal aging process? Charlie became the first author of a thorough synthetic analysis of the genetic and clinical manifestation of Werner syndrome, which remains a standard reference for this disease (Epstein et al. 1966). The genetic problems were clearly set out at that time, but it took almost 30 more years to identify the responsible mutation as a helicase gene, by Schellenberg's group in Seattle (Yu et al. 1996). Extensive work continues to be carried out in this field, par-

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Address for correspondence and reprints: Dr. Arno G. Motulsky, Departments of Medicine and Genome Sciences, Box 356423, BB-567 Health Sciences Building, University of Washington, Seattle, WA 98195. E-mail: agmot@u.washington.edu

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ticularly by Martin's group in Seattle (Martin and Oshima 2000). Charlie at all times pointed out that Werner syndrome should be considered a caricature of aging rather than a model for the aging process. Much work on the pathway from genotype to phenotype remains to be done, since we have few clues how a mutant helicase causes the characteristic clinical and laboratory findings.

Charlie went on to other pastures. His plan was to stay only a year in Seattle to be exposed to a human and medical genetics atmosphere before returning to NIH in Bethesda, where he continued productively with his work on various aspects of biochemical human genetics and took on the first small group of what later became a large number of both research as well as clinical fellows.

In 1967, Charlie moved to the Department of Pediatrics at the University of California in San Francisco, where his career blossomed with his work in the biochemical genetics of metabolic diseases. Note that he was always open to new challenges. After training in internal medicine, he now largely dealt with children and metamorphosed into a pediatrician. Charlie became the consummate physician-scientist, carrying out extensive work both in the biochemical-genetic laboratory and with patients. But that was not all! After realizing that elucidation of critical developmental processes and of pathogenesis could not be done with humans, Charlie extensively utilized the mouse as a model for his research. The early choice of this species turned out to be an inspired step, since it turned out that there were many genetic and functional similarities (as well as synteny) between mice and humans. At that stage of his career, the preimplantation mouse embryo became the focus of this work. One major research result was the determination of the timing of X-chromosome inactivation, as well as demonstrating that both X chromosomes were active during oogenesis.

Charlie also established a model system for clinical genetics in San Francisco. He was a pioneer in establishing criteria and standards of genetic counseling. He established satellite clinics to demonstrate that the benefits of genetic services and genetic counseling could be brought to outlying communities. Based on his biochemical skills, prenatal diagnosis of enzyme disorder became possible for a variety of conditions. Long before bioinformatics became a buzzword, he set up computer-based information systems for medical genetics.

Charlie's clinical activities motivated him to try to understand the pathogenesis of a common condition in clinical genetics: Down syndrome. Unlike the monogenic inborn errors that were relatively well understood based on the one-gene–one-enzyme paradigm, the developmental and clinical effects of an increased gene activity in trisomy 21 and other aneuploidies were not so readily apparent. Were all findings in trisomy 21 caused by increased dosage of various genes on the extra chromosome 21, or were there more nonspecific factors at work? Based on both a broad and in-depth analysis of phenotypes in various kinds of aneuploidy, Charlie published a book 15 years ago on *The Consequences of Chromosome Imbalance* (Epstein 1986), even before the full impact of the molecular revolution on genetics had occurred. Charlie's more recent outlook on the pathogenic mechanisms in Down syndrome is set out in his chapter of Scriver et al.'s *The Metabolic and Molecular Bases of Inherited Disease* (Epstein 2001). Charlie believes in a reductionistic model to elucidate the developmental and other phenotypic effects of the specific genes triplicated in trisomy 21. This approach led to convincing data for the role of specific genes in the pathogenesis of Down syndrome.

He drew on ingenious breeding schemes developed by others, as well as in his own laboratory, to create an ideal mouse model for Down syndrome. Knockout mice, transgenic mice, and segmental trisomic mice were employed to model the specific chromosomal segments that were triplicated in human trisomy 21. Many exciting experiments were done. His laboratory has also become much involved in studies on physiologic states and diseases regarding the role of the superoxide dismutases.

Charlie was never a slave to a single method but knew how to work with many collaborators who brought different skills and techniques to his studies. The important role of his immunologist wife, Lois—an expert on interferon—should be particularly acknowledged for his early work on Down syndrome.

As we meet here just a month after the worst terror attack ever launched against our country, let us recall that Charles Epstein was among the early targets of terror in the U.S.A. On June 22, 1993, possibly because of his visibility as the superb editor of *The American Journal of Human Genetics,* he was mailed a bomb by "Unabomber" Ted Kaczynski that almost killed Charlie and left him with residual injuries. This event affected Charlie profoundly but did not impair his scientific and scholarly vigor. The tragedy made him think deeply about the world, and he also started to write about societal and ethical aspects of work in human and medical genetics. I recommend his "1996 ASHG Presidential Address" (Epstein 1997), as well as a more recent article on ethical implications of the Human Genome Project (Epstein 2000). I also know that he is writing a book about his views on these matters. Dealing with terror may be affecting all of us in the future. We can look to Charlie as a guide in our efforts to help us come to grips with these challenges.

As a mentor, friend, and colleague, I am proud and delighted to present the 2001 William Allan Award to Charles Epstein for his pioneering role in scientific and scholarly inquiry complemented by his major impact

on many aspects of human and medical genetics. We all respect, revere, and love him!

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