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FOREWORD—SPECIAL ISSUE IN MEMORY OF AVRAM GOLDSTEIN

Avram Goldstein: The Founder of *Molecular Pharmacology*[S]

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This special issue of *Molecular Pharmacology* is presented in honor of the founder of *Molecular Pharmacology*, Avram Goldstein, MD, who died on June 1, 2012, just a few weeks before his 93rd birthday. Avram strengthened the discipline of pharmacology during the second half of the last century by insisting on rigorous mechanistic explanations for the extraordinary variety of effects of chemical agents on biologic systems. Although he made major contributions to the field of opioid research, his reach extended beyond biomedical science to aviation, feminism, and a deeply felt sense of social justice that led him, later in his career, to advocate strenuously for a public policy that would treat heroin addiction as a brain disorder rather than a punishable offense. As all who knew him can testify, Avram could be a formidable opponent in a public or private debate, one who prized energetic discussion and logic above all other approaches. His reliance on close reasoning, normally a strength that served him well throughout his career, might have cost him the chance to identify the first opioid receptor, as explained below. The following brief summary of Avram's career and his role in establishing the new journal is based on his autobiographical essay (Goldstein, 1997) and the recollections of colleagues who worked with him at various points in his career. Additional biographical details can be found at http://www.inrcworld.org/news.htm and http://med.stanford.edu/ism/2012/june/obit-goldstein.html.

Avram was born in New York City in 1919. He majored in chemistry at Harvard and, after a period of travel, entered Harvard Medical School, from which he graduated in 1943. After serving in the US Army during the latter part of World War II, he returned to Harvard as an Assistant Professor in the Pharmacology Department, then chaired by Otto Krayer. His initial research focused on enzyme kinetics and the actions of inhibitors of cholinesterases, but he later turned to bacterial enzymatics and the problem of antibiotic resistance. This focus on factors altering drug responses later led to a long-term interest in the mechanisms of drug tolerance, dependence, and addiction. His research activities in these fields, supplemented by several trips and sabbaticals to active research laboratories in Europe, including Edinburgh (with John Gaddum), Bern (with Walther Willbrandt), Copenhagen (with Ole Maaloe), and Cambridge (with Arnold Burgen), led to an increasing interest in mathematical modeling of pharmacologic problems and in applications of the newly developing field of molecular biology in the study of drug action.

In 1955, Avram moved from Harvard to Stanford University, where he was asked to chair the Department of Pharmacology at the Stanford Medical Center, which was then transitioning from San Francisco to Palo Alto. This provided an opportunity to develop the strong basic science programs for which Stanford is known today. At Stanford, Avram became very active in recruiting others. He played a major role in bringing Arthur Kornberg, among others, from Washington University to form a new Biochemistry Department at Stanford. This influx of extremely productive faculty provided an optimum intellectual environment for the refinement of the discipline of pharmacology toward the more molecular science that was part of Avram's vision. During these years, Avram was a towering figure on the Stanford Medical School campus, both literally and figuratively. At this time, Avram also wrote a textbook on the application of statistics to biology that attempted to make the underlying statistical principles clear to nonmathematicians, although one of the authors (R.D.) found that converting an undergraduate understanding of statistics into a practical set of laboratory tools under Avram's tutelage proved to be both memorable and challenging. As the Chair of the Department of Pharmacology with responsibility for training medical students in the use of drugs, he was fascinated by the kinetics of drug action. He and his wife Dody developed the plateau principle, which emerged from the recognition that the time to steady state for any drug administered continuously or repeatedly was dependent only on its rate of elimination. These developments drove his increasing desire to see the discipline of pharmacology, both in research and in medical

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and graduate education, as a science with a strong mechanistic and theoretical underpinning.

The world of biology was also expanding rapidly during these years. Watson and Crick's 1953 article on the structure of DNA and its biologic implications made an enormous impression on Avram, as it did on the world of biology in general. Avram was present in Moscow in 1961 when Marshall Nirenberg described his elucidation of the genetic code. With these seminal developments, Avram concluded that the time was ripe for the establishment of a journal devoted to mechanistic aspects of drug action at a molecular level. He recruited a distinguished team of pharmacologists with a substantial international representation to serve on the editorial and advisory boards for the proposed new journal; 30% of board members were from outside the United States, with representatives from Australia, Canada, Denmark, France, Germany, Italy, Switzerland, the United Kingdom, and the Union of Soviet Socialist Republics. With this international support and a typically forceful argument presented in a 1964 letter to the American Society for Pharmacology and Experimental Therapeutics (ASPET) Board of Publications Trustees (reproduced in the data supplement), Avram was able to persuade ASPET to publish the new journal, which would be called *Molecular Pharmacology*. He notes (Goldstein, 1997) that he was later surprised and highly honored that the society chose to recognize his founding role by placing the legend "Founded by Avram Goldstein" on the cover of every issue. The Statement of Purpose in the first issue was explicit in emphasizing the mechanistic focus of the new journal: "Suitable papers are those which describe applications of the methods of biochemistry, biophysics, genetics and molecular biology to pharmacologic or toxicologic problems..... Observations of phenomena, that shed no light upon underlying molecular interactions, are not regarded as appropriate for publication." Avram served as Editor of *Molecular Pharmacology* for about three years and then, characteristically, passed the leadership role on to a distinguished list of successors.

Molecular Pharmacology was an instant success scientifically, with many pharmacologists from across the world seeking to publish their latest results in the journal. When journal impact factors began to be calculated, the journal was already one of the highest ranked pharmacology journals and for much of its existence has been the highest ranking of the primary journals in this field. Despite a highly selective manuscript acceptance policy, almost every issue contained more articles (and pages) than had been planned; thus, ASPET lost money on every issue. The journal did not actually break even until almost 40 years after its initial publication date, and the society continues to support the journal in recognition of its importance for the discipline.

At the same time as establishing the new journal, Avram, together with his Stanford faculty colleagues Lew Aronow and Sumner Kalman, were working on *Principles of Drug Action* (Goldstein et al., 1968), a pharmacology textbook that was new for its time in focusing only on basic principles underlying drug action and the longer-term responses of the body to the presence of drugs, while avoiding the extensive cataloging of the multitude of actions of all the major drugs that was the usual content of most pharmacology texts before that time. At the time of its publication, several new medical schools had recently opened, many medical schools were expanding their faculty, and many pharmaceutical companies were enlarging their pharmacologic research capabilities; as a result, there was a very large influx of young scientists into the discipline. The new journal and *Principles of Drug Action* arrived at the right time to have an important impact on these new recruits to the field, including one of the current authors (B.C.), who as a very junior faculty member in London, recalls being handed a copy of the 1968 first edition of the textbook by his department chair with the message that this was the way that pharmacology research would be moving in the future and anyone entering the field should be taking this approach. A second edition was published in 1974, and a third edition, now edited by William Pratt and Palmer Taylor, was published in 1990. Since that time, many other textbooks have concentrated on the basic principles underlying the chemical regulation of biologic systems, but this text was critical and novel for its time in the way that it expanded the horizons of many budding pharmacologists.

Avram's interest in academic pharmacology and the critical role of pharmacology in medical education remained important to him throughout his life. Avram was Chair of Pharmacology at Stanford at a time when students were becoming vocal critics of many aspects of their world, with campus uprisings at many universities, including Stanford, against the Vietnam War. Avram was actively critical of the Stanford administration at that time, supporting the protesting students and leading them in several antiwar marches. He was also disturbed by the under-representation of women in medicine in general and in academic medicine in particular. He played a significant role in increasing the enrollment of women into the Stanford medical school class and, later, in modifying the preclinical curriculum to increase its emphasis on scientific understanding as a critical underpinning of medical education.

Around 1970, Avram's research interests began to focus on the pharmacologic bases of heroin addiction and in developing more rationally based therapeutic approaches to the treatment of this disorder. He has stated that this interest was triggered by a talk given at Stanford by Vincent Dole describing his studies on the use of methadone as a maintenance therapy for heroin addicts in New York City. In midcareer, Avram switched the focus of his laboratory from bacterial metabolism to quantifying the actions of opiate drugs. To exploit the new discoveries in opiate drug pharmacology in the clinical arena, he also created the first methadone treatment program in California in nearby San Jose. The emphasis was, from the beginning, on quantifying clinical outcomes and evaluating new therapies. Eventually, these basic and clinical research activities became integrated into a private nonprofit foundation, the Addiction Research Foundation (ARF), based in Palo Alto, which supported his research activities for the remainder of his scientific career.

The Foundation constructed new basic research laboratories in a building close to the medical school and, in a typical Goldstein gesture, painted the laboratories in a spectral array of colors, with room numbers determined by the wavelength of the predominant color in each laboratory. Administrative offices and treatment rooms for a new clinic devoted to evaluation of the use of *l*-alpha-acetyl methadol (LAAM), a long-acting analog of methadone, in the prevention of relapse to heroin use, were established on the floor above. Soon, patients were visiting to the clinic to receive LAAM

treatments, a development that caused some consternation to other tenants of buildings on the Stanford Business Campus. Eventually, this tension led to the closure of the clinic at this site; the clinic became the subject of a law suit claiming that the former heroin addicts attending the clinic presented a risk to the local businesses and discouraged potential customers. Avram was initially convinced that this claim was racially prejudiced in origin and unfounded in fact, but eventually his lawyers persuaded him that the case would not be thrown out before trial, leaving him with possible responsibility for very substantial damages. The case was settled before coming to trial with an agreement that former drug-using clients would no longer be brought to the ARF clinic after the current cohort of subjects enrolled in the clinical trial of LAAM had completed the trial protocol. The study showed that LAAM had many advantages over methadone as a maintenance therapy to reduce relapse to illicit opiate use, but eventually the drug had to be withdrawn because of hepatic toxicity in a few patients.

These years were particularly rich scientifically, with work that laid the conceptual basis for identifying opioid receptors, the discovery of dynorphin, and its role as a selective agonist of kappa opioid receptors. Avram's increasing emphasis on the processes underlying various forms of drug addiction and the importance of scientific advocacy and the education of politicians, a role in which Avram himself excelled and that he regarded as critical to the future of a rationally based health care delivery system. During this period Avram outlined the criteria for biochemical identification of opioid receptors, based on saturable and stereospecific binding of a radioligand to brain tissue fractions. He had a healthy start on the competition in searching for the elusive receptor. However, his strategy used the radioligand levorphanol at a concentration of 2 μM or higher, reasoning from his own measurements that this is the brain concentration required to produce analgesia in the mouse (Goldstein et al., 1971). We now know that nonspecific binding predominates at this high concentration under the conditions used in their biochemical assays. His strategy for identification of opiate receptors was exploited two years later by others to demonstrate the presence of opioid receptors in brain, which ushered in a new era that emphasized the biochemical study of receptors. Avram's personal tragedy is that a departmental graduate student had raised the theoretical problem of low specific radioactivity with him during a departmental seminar meeting, but the warning had been disregarded on the basis of his reasoning that study of ligand concentrations much lower or higher than the pharmacologically active concentration is likely to be irrelevant.

Avram's interests were not confined to the laboratory and the academy. He loved to fly small planes. Following his teaching instincts, he became a certified flight instructor and then an instrument flight instructor. As a consequence, he taught flying and published four instructional and pilot safety handbooks. One of the authors (R.D.) remembers, as a graduate student, a thrilling ride over the Sierras from Palo Alto to Phoenix. He was asked to navigate from the right seat, peering at the map spread on his lap, trying to glimpse landmarks below through the clouds, and hoping that Avram was not relying too much on his directions. Others in the laboratory were sometimes surprised and usually delighted to be invited to travel with Avram in his plane to scientific meetings held within flying distance of Palo Alto, and on occasion, the families of laboratory members were treated to low-level flights around the San Francisco Bay area. Another transcontinental trip from Palo Alto to Cape Cod by J.S.H. sticks in the memory.

Avram made several speaking trips to Beijing, and after his retirement, he arranged to have a great deal of scientific equipment and furniture transferred from the Addiction Research Foundation to the fledgling Neuroscience Institute at the Peking University Health Sciences Center. A plaque on the wall acknowledges this gift and its impact in the formative years of the Institute, and Avram's desk is still in use in the Director's office.

Avram was given many awards. He was elected to the National Academies of Science and the Institute of Medicine and received the Sollman Award from ASPET. Many scientists, from the United States and countries worldwide, were attracted to work with Avram, and the training that they enjoyed is reflected in their continuing analytical approach to the discipline. These former students continue the attempt to teach others in the same rigorous approach to the discipline. This special issue of *Molecular Pharmacology* contains short reviews from former colleagues, collaborators, and friends of Avram's. For those of us who had the privilege of working with him, Avram was an inspirational mentor, a man who had little use for discussions meant to obfuscate rather than clarify issues. We hope that the contributions to this special issue will convey to others something of his scientific charisma and enthusiasm and foster the continued development of the discipline to which he was so devoted.

Authorship Contributions

Contributed to the writing of the manuscript: Cox, Han, Dingledine.

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SUPPLEMENTAL DATA

The following memorandum dated June 23, 1964 was written by Dr. Avram Goldstein to ASPET's Council and Board of Publications Trustees and was published in *The Pharmacologist*, volume 7, number 1, pp. 35-36, Spring 1965 in an article by Dr. Walter F. Riker, the then Chair of the Board of Publications Trustees, announcing the launch of *Molecular Pharmacology*.

THE JOURNAL OF MOLECULAR PHARMACOLOGY

The recent explosive progress in molecular biology has created a crisis for pharmacology.

Only 12 years ago Sanger culminated his studies on insulin with publication of the first complete amino acid sequence of a protein. Now the structures of a growing number of other proteins are yielding to similar attacks, and the details of secondary and tertiary structure are also being elucidated. In 1953 the Watson-Crick double-helical structure of DNA was proposed, certainly one the most fundamental concepts of modern biology. These two achievements led with extraordinary rapidity to the emergence of a whole new field of research, now known as molecular biology.

The years 1961–1964 have witnessed further startling developments. Jacob and Monod advanced the messenger-RNA hypothesis, which was soon amply confirmed, thus completing the link between the storage of genetic information in DNA and its translation into protein structure. Using synthetic messenger-RNA in a cell-free system, Nirenberg discovered the main features of the code. Repression and derepression (induction) were given a firmer basis through elucidation of mechanisms controlling and modulating the transcription of the genome into messenger-RNA. Thereby not only enzyme induction but the phenomena of cytodifferentiation began to yield to the new experimental attacks. Benzer's resolution of gene fine-structure to the level of base-pairs, his demonstration of "hot-spots" for mutation, and the introduction of specific chemical mutagens opened the way for a much deeper understanding of mutational events. The consequences of mutation for the structure and function of proteins were clarified by numerous studies, especially those initiated by Pauling and Itano with sickle-cell hemoglobin and carried to fruition by Ingram, and more recently the proofs of colinearity between base sequence and amino acid sequence by Yanofsky and others.

At the same time the more traditional lines of biochemical inquiry, especially enzymology, made rapid progress. A concrete picture began to take shape, of protein tertiary structure and its role in specific interactions with small molecules, as exemplified by the Kendrew-Perutz models of hemoglobin and myoglobin, or Koshland's conformational analysis of enzyme active centers. Also noteworthy are the findings, in a number of cases, that the biology activity of a protein may depend upon the association of two or more polypeptide chains, and that reversible transitions between inactive and active forms of enzymes may be influenced by small molecules. Most re-

cently Monod and his colleagues have formulated the concept of allosteric proteins, which promises to be useful in interpreting certain aspects of the interactions between agonist or antagonist drugs and their receptors.

These remarkable developments have opened the way to understanding all aspects of cellular function in molecular terms. They have not only shed light upon basic problems of biological function, they have also begun to yield deeper insights into mechanisms of drug action than could be attained through the methods of "classical" pharmacology. This is by no means to demean investigations that lack a clear biochemical basis. On the contrary, it is only through excellent research at other levels (physiological, behavioral, clinical, and so on) that the relevant parameters of drug action can be discovered, defined, and isolated. But it has always been clear that no drug action can be understood completely until it is pursued to the level of molecular interactions, and now such pursuits can increasingly become realistic goals of research.

Modern pharmacology thus faces an opportunity and a danger. The opportunity is to provide a more favorable environment *within* our field, in which the attitudes and experimental approaches of molecular biology and modern biochemistry may flourish, and in which these will be applied to elucidating mechanisms of drug action. We must ensure that the intrinsic fascination of pharmacology will draw into our field a fair share of the rapidly increasing numbers of students and young investigators who are being attracted to molecular biology as a career.

The danger is nothing less than the disintegration of our discipline. The same years that have witnessed the emergence of molecular biology as a fresh field have seen pharmacology undergo further fragmentation. We have long suffered a process of centrifugal depletion whereby whole areas of subject matter that were traditionally in our domain have been lost. Chemotherapy is only the most glaring example. This subject should be a central theme in pharmacology, yet nearly every fundamental development of the past quarter-century has taken place and been published outside of our discipline. The major contributions to elucidating the modes of action of the sulfonamides and of penicillin were not published in a pharmacological journal. And currently the mechanism of action of one antibiotic after another is now being clarified at the molecular level (e.g., actinomycin, puromycin, streptomycin, chloramphenicol) but none os [sic] this work has been conducted under the auspices of a pharmacology department or been published in the pharmacological literature.

What has been said of the antibiotics is also apposite to other areas that used to be (or should be) pharmacology. Recent advances have begun to reveal the molecular basis of hormone action, of chemical mutagenesis, of the action of teratogens, of chemical carcinogenesis, of numerous toxicologic phenomena, of the effects of radiation-sensitizing drugs (to cite only a few instances), yet most of this work is done and published entirely outside our field.

Another factor tending to weaken our field has been a tendency to view pharmacology as a convenient umbrella that will cover any sort of investigative activity. This breadth of scope is in many way appealing, but the definition of pharmacology as 'anything a pharmacologist does' leads to a fuzzy image that, in my opinion, impedes recruiting. Pharmacology is the study of drug action. This has broad enough implications. For those of us who are biochemically oriented, there is, I believe, an obligation to study the molecular basis of drug effects. Departments of

pharmacology should not be merely places where biochemists (and others) pursue their own interests, while mechanisms of drug action are investigated elsewhere.

This is not the place to present a detailed program of remedial action. Much could be done in our Society and at its scientific sessions, and in our graduate recruiting and training programs. I hope that bringing this problem into the open will evoke discussion among our officers and members that could lead to steps which will strengthen the position of pharmacology and of our Society.

There is one thing, however, that can and should be done now. I propose the immediate establishment of a new journal, of very high standards, devoted exclusively to molecular pharmacology. I have in mind a publication not unlike the *Journal of Molecular Biology*, but devoted to theoretical and experimental papers which represent significant contributions to our understanding of drug action at the molecular level.

I am willing to set the wheels in motion for initiating this journal, and I am also willing to undertake its editorship and to recruit and editorial board. I think it would be best if such a journal were operated by our Society, so I invite the Council and the Board of Publications Trustees to accept its sponsorship.