Trends in Pharmacological Sciences

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In Memoriam

Inimitable Paul Talalay (1923–2019)

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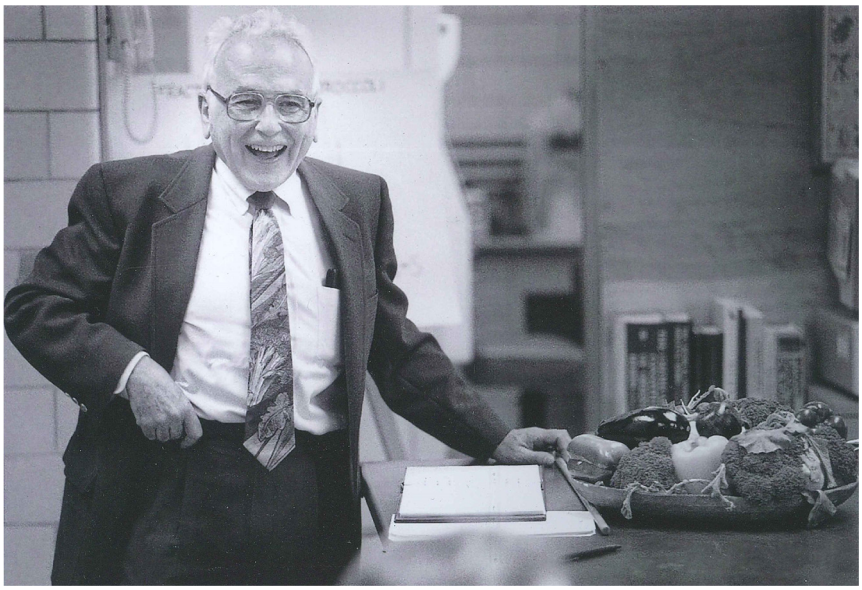
Pharmacology lost a pioneer and champion with the passing of Paul Talalay. A brilliant scientist and inspiring mentor, he had been the John Jacob Abel Distinguished Service Professor of Pharmacology and Molecular Sciences at Johns Hopkins Medical School. He died at age 95, after a full life, on 10 March 2019.



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Paul Talalay was a founder and international leader in the pharmacology of chemoprotection, the science of modulating the body's defense system against oxidative, inflammatory, radiation, or xenobiotic assault. His contributions, however, included much more than this. He initiated the field of steroid-metabolizing enzymes, described a quantitative method for assessing drug interactions, and was a highly successful program builder and educator.

As recounted in a poignant and gracefully written autobiography [1], Paul and his family came to the United States in 1940, after making serial moves across Europe to escape the Nazis. His education included undergraduate studies in biophysics at MIT, medical school at the University of Chicago and Yale, and surgical training at the Massachusetts General Hospital. After 13 years on faculty at the University of Chicago, he came to Johns Hopkins to direct, for 11 years, the Department of Pharmacology and Experimental Therapeutics. He remained at Hopkins, as the John Jacob Abel Distinguished Service Professor, for the rest of his life. Over his long career, Paul enjoyed many fruitful, sometimes decades-long collaborations, appreciatively described in his Reflections [1], so their names will not be cited here.

An Enduring Fascination with Enzymes

Paul Talalay's research interest in enzymes began in earnest when he was a medical student working in Charles Huggins's laboratories at the University of Chicago. Huggins and colleagues had shown that patients with metastatic prostate cancer could be improved dramatically by steroid hormone therapy, landmark studies recognized by the 1966 Nobel Prize in Physiology or Medicine. Notably missing at the time, however, was any understanding of the underpinning metabolism of steroids in cells. Paul, whose approach to science was deeply imprinted by Huggins, began this and every subsequent new endeavor by devising a simple, reliable, and quantitative assay to probe the problem. He isolated bacteria auxotrophic for testosterone [2] and began the first-ever isolation and characterization of enzymes that mediate chemical transformations of steroids [3]. His studies sketched the metabolic pathways of steroid metabolism, provided important new insights into the mechanistic workings of the component enzymes themselves, and afforded sensitive and specific new methods by which to quantitate steroid molecules [4].

Investigations into metabolism of the steroid A ring, and the desire to devise novel antitumor agents, led to studies of substrate analogs to inhibit methionine adenosyltransferase. An unexpected byproduct of these experiments, which included multiple inhibitors applied simultaneously, was the rational and simple Chou–Talalay equation for diagnosing drug interactions as additive, synergistic, or antagonistic. Described in some of the most highly cited publications in the scientific literature, this method has become a standard tool in molecular, animal, and clinical pharmacology [5].

Paul's favorite enzyme, ketosteroid isomerase, was described in more than 35 publications that ranged from characterization of its amino acid sequence to imaginative studies with irreversible suicide substrates that unambiguously identified the active site residues responsible for its remarkably brisk catalytic activity

[6]. It was this enzyme that linked Paul's work on steroid metabolism with chemoprotection against cancer. Efforts to purify this activity from mammalian tissues failed repeatedly until it was realized that catalysis was restored by add-back of discarded fractions. This led to the discovery that, in mammalian cells, ketosteroid isomerase is actually a well-known glutathione S-transferase, an inducible enzyme that protects cells against chemical damage, including carcinogenesis.

Paul's major awards and honors (including lifelong Professor of the American Cancer Society, fellowship in the American Academy of Arts and Sciences, membership in the National Academy of Sciences, and election to the American Philosophical Society) were based largely on his elegant and rigorous studies of steroid-metabolizing enzymes. These accomplishments not only prepared him to see the medical promise of chemoprotection but also brought immediate and substantial credibility to his efforts in a groundbreaking new field.

An Unexpected Pivot to Chemoprotection

Despite the risk, which he clearly recognized [1], Paul seized the serendipitous opportunity to transition his focus from steroid enzymes to enzyme induction for cell protection. He recognized early that a wide variety of chemical agents, including dietary phytochemicals, induce a cytoprotective response in mammalian cells. Reflecting his training as a physician, he also realized that upregulating a cytoprotective response could impact not just the risk of cancer but also the risk of other chronic diseases. His subsequent research spanned the full range of pharmacology, from structure–activity relationships of novel phytochemical (and synthetic) inducers [7] to large interventional field trials [8]. His work was supported by longstanding NIH grants, and by the philanthropic generosity of Lewis B. and Dorothy Cullman. The latter funding afforded flexibility to shift quickly in response to new discoveries and to explore high-risk ideas.

To delve into the science of cytoprotection, Paul first focused on the induction of Phase 2 drug-metabolizing enzymes (e.g., the glutathione S-transferases) and the protection this afforded against carcinogens. Typically, he started by inventing a simple and robust *in vitro* bioassay for quinone reductase as a sensitive reporter for enzyme induction [9]. Thirty years later, this foundational assay continues to contribute to significant research worldwide. It underpinned the landmark discovery of sulforaphane, one of the most potent naturally occurring Phase 2 enzyme inducers, in broccoli [10,11]. This finding captured popular imagination, leading to his identification as the 'Broc Doc', a nickname he both relished and regretted. Collaborative studies then identified cysteine-rich Keap1 as the intracellular sensor that triggers migration of Nrf2 into the nucleus, where it binds to the antioxidant response element and induces synthesis of cytoprotective proteins [12]. Translational studies documented the efficacy of broccoli sprout extracts in animals and evaluated their safety, metabolism, and pharmacokinetics in humans.

To demonstrate efficacy in humans, Paul turned to indications with timelines shorter than that for carcinogenesis. One fascinating and important mechanism-driven inquiry showed that social and behavioral symptoms of autism can be reduced by regular ingestion of a broccoli sprout extract [13], a remarkable finding for an intractable condition, and one that has since been corroborated by others. Studies in China have shown that administration of broccoli sprout extract improves biomarkers for both liver cancer and air pollution injury [8]. Numerous Phase II placebo-controlled trials of broccoli and sulforaphane efficacy in humans, undertaken in the final years of Paul's life and still ongoing, have brought his work squarely into the clinical setting, a fitting capstone to his exceptional career.

Convinced his discoveries could help people at risk of cancer and other conditions, mindful of the largely unregulated health food market, and fueled in part by tremendous public interest in cancer prevention by broccoli and sulforaphane, Paul realized the need for a company to make high-quality sulforaphane-rich broccoli sprouts available [14,15]. He cofounded Brassica Protection Products 'to develop chemoprotective foods and extracts', a company that now provides a market source for broccoli products and well-characterized material for laboratory and clinical trials. Talalay himself never profited from this company.

Lasting Impact

Paul Talalay's legacy comprises not just his impactful discoveries. The pharmacology department at Hopkins, illustrious in its early years, had declined by the time he arrived as director in 1963. With a keen eye for talent, he hired a series of splendid young faculty who entirely revitalized the department: Snyder, Coffey, and Cuatrecasas, all of whom themselves became distinguished. With great foresight, he purchased the first mass spectrometer in any medical school. He was a quiet but effective champion for women, nominating Gertrude Elion for the Nobel Prize, appointing Catherine Fenselau to the Hopkins faculty (the second woman to become full professor in the basic sciences after Florence Sabin in 1917), and from the start enrolling a high proportion of women in training programs.

Paul was mindful of history and indeed wrote histories of pharmacology and clinical pharmacology at Hopkins, but his eye was firmly on the future. He relished nothing more than meeting with and advising young colleagues, hearing their

latest discoveries and celebrating their accomplishments. Students of his own trainees were greeted as his 'intellectual grandchildren'. He founded the MD/PhD Medical Scientist Training Program at Hopkins. With classic Talalay charm and resourcefulness, in 1978 he established a Young Investigators' Day celebration at which outstanding trainees receive prizes from endowments he gathered from grateful families of former trainees. Fittingly, the event now includes a Talalay prize.

Paul was known for his brilliance, humor, and judgment, which combined to make him a peerless confidant and advisor to international committees, deans, department chairs, faculty, trainees, and housekeeping staff alike. His prodigious memory and quick wit were legendary; his kindness was instinctive, unobtrusive, and effective. After the 2011 tsunami, he sent money and laboratory supplies to a colleague in Japan, declaring that if red tape got in the way he would deliver this personally (and there is no doubt he would have). His beloved family includes Pamela, his wife of 66 years, a Cambridge-trained PhD and scientific editor supreme, and their four children, Antony, Susan, Rachel, and Sarah, all respected professionals in their own rights.

Science and scientists have been impacted by the elegance and rigor of Paul Talalay's work; by his optimism, warmth, and uncanny wisdom; and by his visionary leadership. He has left all of us a wonderful and lasting legacy.

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