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William J. Whelan (1924–2021): Asking the right question
The origins of glycogen and a scientific legacy

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Dedicated to the memory of William Joseph Whelan (1924–2021), whose scientific curiosity continues to inspire generations of biochemists.

Summary

William J. Whelan was one of the leading carbohydrate biochemists of the twentieth century. His discovery of glycogenin, the self-glycosylating protein that initiates glycogen biosynthesis, resolved a longstanding paradox: glycogen synthase can extend a glucan chain but cannot create its own primer. The work completed a conceptual framework established by earlier pioneers including Carl and Gerty Cori and Luis Leloir. It also illustrates two qualities that characterized Whelan's science: recognizing a fundamental question hidden within an apparently complete pathway, and persistently testing an evidence-based interpretation despite prolonged skepticism. His influence extended beyond glycogen metabolism through scientific publishing, international biochemical organizations, education, and mentorship. Drawing on more than twenty-five years of personal acquaintance and collaboration, this article examines both his scientific contributions and the intellectual qualities that shaped them.

1. Asking the Right Question

Scientific history often celebrates discoveries more than the intellectual process that makes them possible. Yet major advances frequently begin not with better techniques but with recognizing that an accepted explanation is incomplete. The decisive contribution often lies in asking the right question.

William Joseph Whelan exemplified this approach. Throughout his career, he identified conceptual gaps hidden within apparently well-established biological mechanisms. This perspective culminated in the discovery of glycogenin, the protein that initiates glycogen biosynthesis [1–7].

The importance of this discovery becomes clear against the state of glycogen research in the mid-twentieth century. Carl and Gerty Cori established central features of glycogen breakdown and phosphorylase action [8–9], while Luis Leloir identified UDP-glucose as the activated glucose donor for glycogen synthesis [10–11]. Together with characterization of glycogen synthase and branching enzyme, these findings appeared to provide a nearly complete account of glycogen metabolism [12].

One crucial question, however, remained unanswered.

Glycogen synthase elongates an existing glucan chain but cannot initiate one de novo. Every known mechanism required a pre-existing glycogen primer whose origin remained unexplained. Many investigators regarded this as a minor detail. Whelan recognized instead that if the origin of the glycogen particle could not be explained, the entire pathway remained conceptually incomplete.

This distinction characterized his scientific thinking. Describing a biological process did not equal understanding it. Experimental observations had to fit into a coherent mechanistic framework capable of explaining both how a system functions and how it begins.

The discovery of glycogenin resolved the initiation paradox. Whelan and colleagues showed that glycogen synthesis begins with a self-glycosylating protein that generates the oligosaccharide primer required for subsequent glycogen synthase activity [1–7].

Subsequent studies have shown that glycogen accumulation may occur under certain conditions even without functional glycogenin-1, indicating alternative or compensatory priming mechanisms [13]. Rather than diminishing Whelan's achievement, these findings emphasize the lasting importance of the conceptual framework he established.

I knew Bill for more than twenty-five years as a scientist, editor, mentor, and friend. Our conversations ranged from glycogen metabolism to scientific publishing and the history of biochemistry. What impressed me most was not the breadth of his knowledge but the clarity of his reasoning. Discussions rarely ended with definitive answers; they usually concluded with another worthwhile question.

This article is therefore neither a conventional obituary nor a chronological biography. Instead, it examines the scientific philosophy underlying Bill Whelan's career. His greatest contribution was not simply discovering glycogenin but recognizing the fundamental question that others had overlooked.

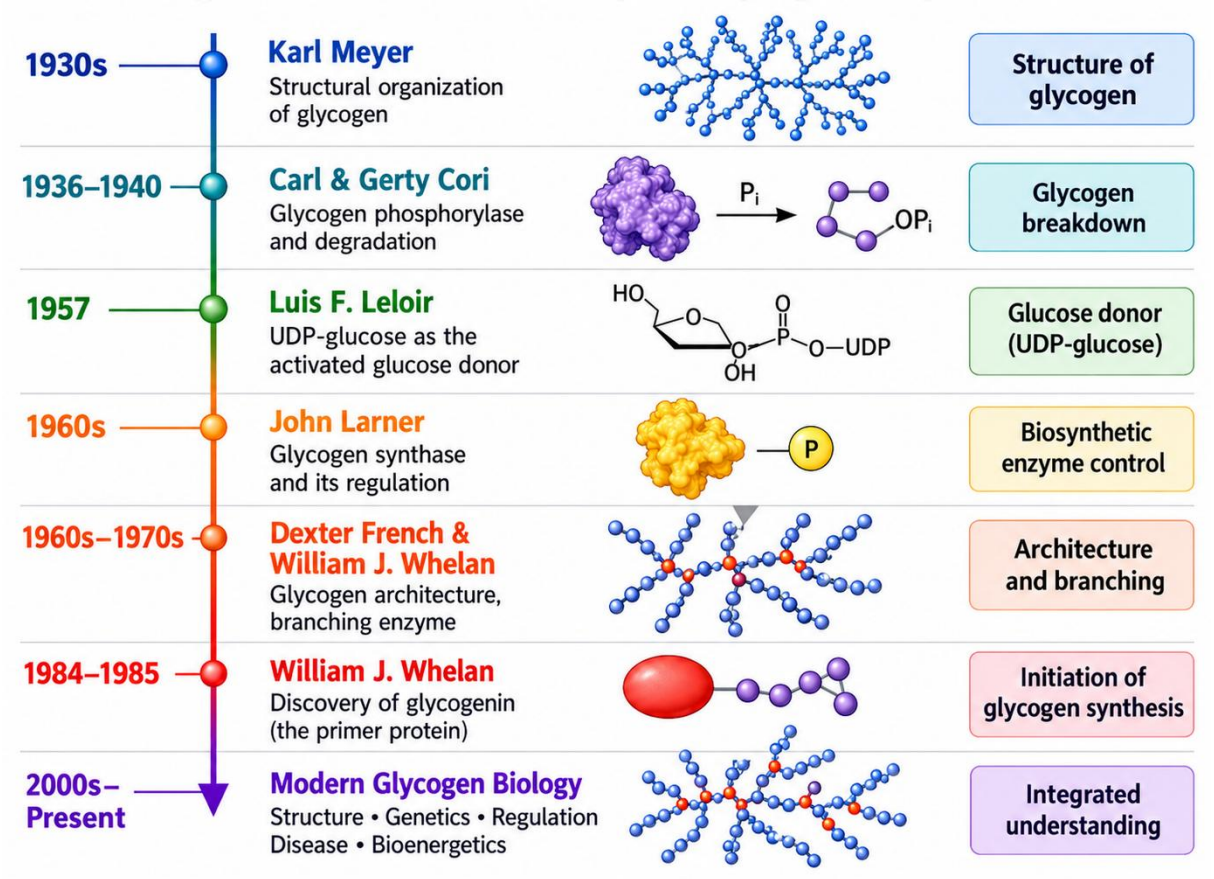


Figure 1. Evolution of Concepts in Glycogen Biosynthesis
Historical development of the concepts leading to modern glycogen biosynthesis. William J. Whelan's discovery of glycogenin completed the framework established by earlier pioneers.

2. Learning to Ask Fundamental Questions

The ability to formulate fundamental scientific questions develops through rigorous training, historical awareness, and a refusal to accept incomplete explanations. These qualities characterized Bill Whelan throughout his career.

Born in England in 1924, Whelan entered biochemistry during the rapid expansion of enzymology and molecular biology after the Second World War. Glycogen metabolism occupied a central place in this transformation because it was among the earliest metabolic systems investigated experimentally [10–12].

By the time Bill established his independent career, much of the enzymology of glycogen metabolism had been defined. He nevertheless became increasingly interested in the organization of the glycogen particle itself and in questions that the established enzymatic scheme did not answer.

A remarkable feature of Bill's scientific style was his appreciation of history. He regarded discoveries as successive stages in the evolution of ideas rather than isolated achievements. Conversations frequently moved from current experiments to the work of the Coris, Leloir, Meyer, French, and other pioneers. This historical

perspective encouraged him to ask not only what was known, but why important questions had remained unanswered.

The same philosophy shaped his mentoring. Bill rarely supplied solutions directly. Instead, he encouraged colleagues to identify the conceptual weakness in accepted explanations, believing that scientific independence begins with the confidence to question established assumptions.

Years of work on glycogen structure eventually focused attention on a deceptively simple question: How does a glycogen molecule begin? In retrospect the question appears obvious, but it had remained unresolved within an otherwise mature biochemical pathway.

3. Understanding the Architecture of Glycogen

To appreciate why the discovery of glycogenin transformed carbohydrate biochemistry, it is first necessary to understand the organization of glycogen itself. Bill Whelan emphasized that biological function cannot be separated from molecular structure. In glycogen, architecture determines function. His studies of glycogen structure therefore extended beyond structural chemistry to explain one of evolution's most efficient solutions for biological energy storage.

Glycogen is the principal carbohydrate reserve of animals, providing a rapidly mobilizable source of glucose during fasting, muscular activity, and many physiological stresses. Unlike adipose tissue, which stores energy for prolonged periods, glycogen functions as a dynamic metabolic buffer capable of responding within seconds to changing energy demands. This remarkable flexibility depends directly on its molecular architecture [14–15].

The glycogen particle is a highly branched glucose polymer composed primarily of α-1,4-glycosidic linkages interconnected by α-1,6 branch points. This organization is functionally essential because each branch creates additional non-reducing ends where glycogen synthase and glycogen phosphorylase simultaneously add or remove glucose residues. Consequently, the efficiency of glycogen metabolism depends not only on enzyme activity but also on particle architecture [16].

This arrangement has important bioenergetic consequences. A linear polymer containing the same number of glucose residues would store equivalent energy but release it much more slowly because far fewer chain ends would be available for enzymatic attack. By generating numerous metabolically active termini, branching enables rapid glucose storage and mobilization. Glycogen is therefore optimized not simply as an energy reserve but as a highly efficient molecular system for energy management.

Bill Whelan recognized that this structural organization required explanation beyond individual enzymatic reactions. His laboratory made important contributions to understanding glycogen branching, chain-length distribution, and particle organization over several decades [16]. These studies helped establish glycogen as an ordered molecular structure rather than a random polymer.

His work also renewed interest in classical structural models. The Meyer-Bernfeld model provided an early conceptual framework, while French and subsequent investigators refined the description of branched polysaccharide organization [17–18].

Bill regarded structural models not simply as diagrams but as hypotheses capable of generating experimentally testable predictions.

As his understanding of glycogen organization deepened, Bill increasingly viewed glycogen metabolism as an integrated biological system. Glycogen synthase, branching enzyme, debranching enzyme, and glycogen phosphorylase functioned cooperatively to assemble and remodel a highly organized molecular particle whose structure determined its physiological behavior.

By the late 1970s glycogen metabolism appeared to be one of the best-characterized pathways in intermediary metabolism. Yet glycogen synthase elongated existing glucan chains but could not initiate them, and branching enzyme likewise required a pre-existing substrate [10–12,16]. The origin of the primer therefore remained unexplained.

For Whelan, this was not a minor technical detail but a logical gap in the pathway.

The question became: How does the first glucan chain arise?

4. The Discovery of Glycogenin: Solving the Initiation Problem

The discovery of glycogenin resolved the initiation problem by identifying a protein that acts both as enzyme and primer. Whelan and his collaborators showed that glycogenin transfers glucose from UDP-glucose to a tyrosine residue within its own polypeptide chain and extends the nascent glucan by self-glycosylation [1–7]. Glycogen synthase can then elongate the chain, while branching enzyme generates the characteristic architecture of mature glycogen.

This result emerged from a broader and partly parallel effort. Joseph and Wieslawa Lomako worked closely with Whelan on the self-glucosylating protein and its role as primer [1,3]. Independently, James Pitcher, Carl Smythe, and Philip Cohen demonstrated that glycogenin is the primer for glycogen biosynthesis [5]. The convergence of these studies placed the initiation mechanism on a firm experimental foundation.

The path to acceptance, however, was unusually difficult. As described in an earlier memorial account, NIH support for Whelan's work was repeatedly denied for approximately seven years, with a reviewer questioning the inference that glycogenin was the primer for glycogen synthesis. When Whelan identified the linkage between glycogen and protein as a novel glycosyl-tyrosine bond, the absence of precedent for such a bond was itself raised as an objection. Independent confirmation from Philip Cohen's laboratory helped settle the issue [19].

This episode adds an important dimension to Whelan's scientific philosophy. Asking the right question was only the beginning. He maintained an interpretation when the evidence supported it, but continued to refine and test that interpretation rather than treating it as established by conviction alone. His persistence was therefore inseparable from continued experimentation.

In this respect, Whelan's experience offers an illuminating parallel with Gaston Bachelard's epistemology. In Essai sur la connaissance approchée, Bachelard described scientific knowledge as progressive and provisional: established explanations are refined through successive correction rather than simply replaced by

final truths [20]. The Cori-Leloir framework was not overturned by glycogenin; it was extended at the point where its explanatory power ended.

The resistance to an unprecedented glycosyl-tyrosine linkage also recalls Bachelard's later concept of the obstacle épistémologique: assumptions embedded in established knowledge can themselves impede recognition of an observation that falls outside the familiar repertoire. In Whelan's case, the appropriate response to skepticism was not rhetorical resistance but stronger evidence. This distinction remains instructive for younger investigators: scientific independence requires openness to criticism together with the willingness to pursue a well-supported conclusion when novelty, rather than contrary evidence, is the principal source of doubt.

The mechanism itself was elegant. Initiation and priming were combined within a single molecule that became the structural core of the nascent glycogen particle. The discovery also placed glycogen biosynthesis within a broader biological principle: macromolecular assemblies often require specialized nucleation mechanisms.

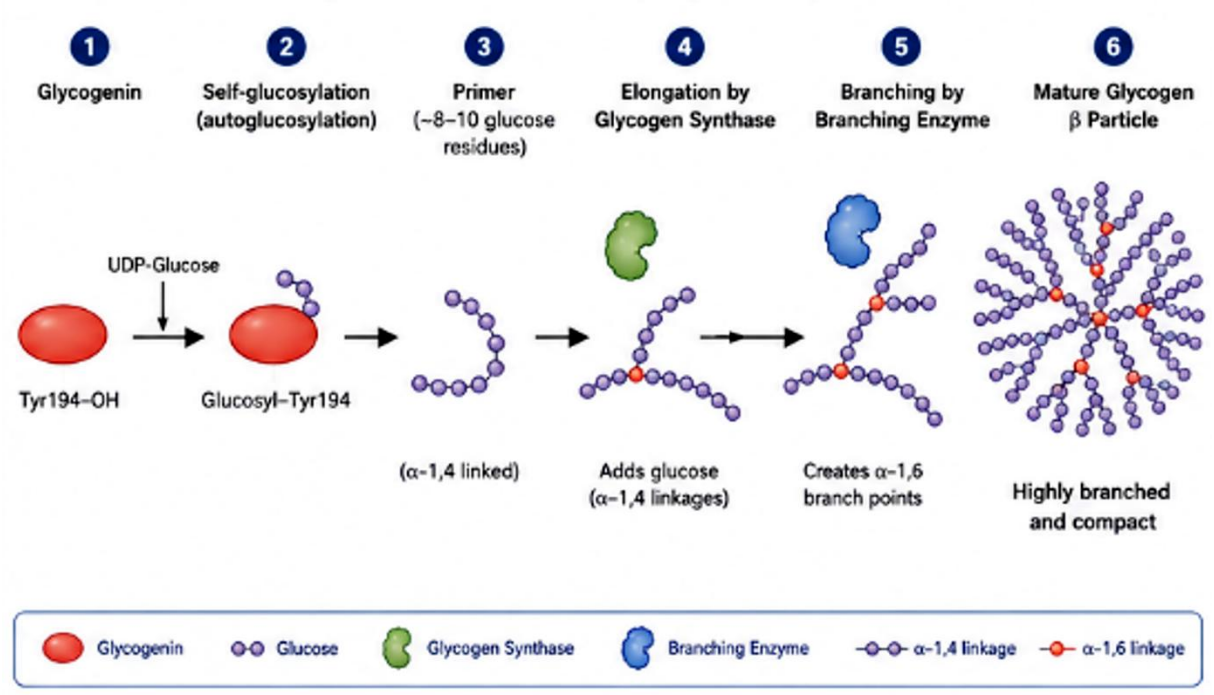


Figure 2. Initiation of Glycogen Biosynthesis
Glycogenin provides the first molecular explanation for glycogen initiation through autocatalytic glycosylation, after which glycogen synthase and branching enzyme construct the mature glycogen particle.

Scientific understanding has continued to evolve. Glycogen accumulation can occur under some conditions without functional glycogenin-1, suggesting alternative or compensatory initiation mechanisms [13]. These findings refine rather than erase the conceptual advance represented by glycogenin: they reopen, at a deeper level, the same question of how polymer synthesis is initiated.

The discovery's influence later extended to glycogen storage diseases, muscle physiology, diabetes, structural enzymology, and metabolic regulation [6–7,21–25].

Before glycogenin, the pathway explained how glycogen grew; the discovery supplied the first molecular explanation for how it began.

5. Building Modern Biochemistry

Scientific discovery alone does not build a discipline. Whelan also helped construct the institutions through which modern biochemistry communicated, organized itself, and trained younger scientists.

His engagement with scientific publishing began early: The Biochemical Journal invited him to serve as an editor in 1952 [19]. As the first Secretary-General of FEBS, he promoted the creation of FEBS Letters; the first issue appeared in 1968, with Prakash Datta as managing editor. He later became editor of Trends in Biochemical Sciences and was involved in Applied Biochemistry (now Biotechnology and Applied Biochemistry), IUBMB Life, and BioFactors. In 1984 he founded BioEssays, and from 1987 to 1996 he served as the first Editor-in-Chief of The FASEB Journal [19].

These activities reflected a consistent editorial philosophy. Bill considered journals not merely repositories of observations but instruments for improving scientific understanding. I frequently discussed with him the responsibilities of editors and reviewers, the need for conceptual clarity, and the value of criticism that strengthens rather than merely judges a manuscript.

His organizational influence was equally extensive. Whelan helped establish FEBS and served as its first Secretary-General. After moving to Miami, he helped create the Pan-American Association of Biochemical Societies and later served as General Secretary and President of the IUB/IUBMB [19]. These roles allowed him to promote international exchange at a time when communication and travel between laboratories were far less routine than today.

At the University of Miami he founded the Miami Winter Symposia, bringing leading investigators into direct contact with students and faculty. The Wood-Whelan Research Fellowship, established in 1985 in honor of Harland G. Wood and Whelan, supported short laboratory visits that enabled biochemists to perform experiments or learn new techniques [19].

The same philosophy characterized his mentorship. Bill challenged younger scientists without discouraging them. Rather than supplying ready-made answers, he encouraged them to identify weaknesses in accepted explanations and to formulate better questions. His influence therefore operated through individuals as well as institutions.

A striking parallel connects these activities with his laboratory science. In glycogen research he sought the missing foundation of a biosynthetic pathway; in scientific life he helped build journals, societies, meetings, and fellowships that provided foundations for communication and discovery. In both settings, he understood that lasting progress depends on structures that allow good questions to be pursued.

6. The Scientist and the Man

Scientific publications preserve discoveries but rarely reveal the character of those who made them. Those who knew William J. Whelan remember not only his scientific achievements but also the personal qualities that made him an exceptional colleague, mentor, and friend. The same intellectual honesty, generosity, and curiosity that defined his research also shaped his relationships with others.

I had the privilege of knowing Bill for more than twenty-five years. During that time our professional interactions developed into a lasting friendship. We met at scientific meetings, exchanged numerous letters and e-mails, discussed manuscripts, debated scientific questions, and reflected on the changing landscape of biochemistry. Looking back, I realize that these conversations influenced my understanding of science as much as many published papers.

One of Bill's most remarkable qualities was his ability to listen. He never hurried to express an opinion. Instead, he listened carefully, asked a few deceptively simple questions, and only then offered his perspective. Those questions often proved more valuable than immediate answers because they encouraged one to reconsider assumptions, clarify ideas, and recognize aspects of a problem that had previously gone unnoticed.

Equally memorable was his generosity. Younger investigators quickly discovered that Bill was approachable, encouraging, and genuinely interested in their work. He understood that scientific confidence develops through constructive criticism rather than intimidation. Many scientists who later became leaders in their own fields undoubtedly benefited from his quiet encouragement.

Humility was another defining characteristic. Despite international recognition and numerous honors, Bill never projected the authority of a celebrated scientist. Conversations with him remained informal and relaxed. Reputation meant little compared with the quality of ideas and the strength of experimental evidence. This absence of pretension made collaboration with him intellectually rewarding and personally enjoyable.

His understated sense of humor further distinguished him. Often expressed through a brief observation rather than an anecdote, it lightened even demanding scientific discussions. Bill understood that research inevitably involves uncertainty, failed experiments, and unexpected results. Humor provided perspective without diminishing scientific seriousness.

One small episode remains especially vivid. During the final years of his life, Bill asked whether I could enlarge the font of my e-mails because reading on his iPad had become more difficult. It was a simple practical request, yet it revealed something essential. Even as age imposed physical limitations, his desire to read, discuss, and think about science never diminished.

That brief exchange captured Bill's character. Scientific curiosity was not merely his profession but part of his identity. Long after many would have withdrawn from active scientific life, he continued reading manuscripts, corresponding with colleagues, and engaging in thoughtful discussion. Physical limitations never reduced either his intellectual generosity or his enthusiasm for discovery.

7. A Legacy Beyond Glycogen

The history of science often associates individuals with a single discovery. Bill Whelan will rightly be remembered for glycogenin, but reducing his legacy to one protein would underestimate both the breadth of his contributions and the originality of his scientific vision.

His work demonstrated the value of recognizing conceptual inconsistencies, pursuing them experimentally, and remaining open to refinement when new evidence appears. Subsequent discoveries of glycogenin-independent glycogen accumulation make that lesson particularly appropriate: important mechanisms are not final answers but frameworks from which better questions emerge.

His institutional legacy is equally durable. Through FEBS, IUB/IUBMB, scientific journals, the Miami Winter Symposia, and international fellowships, Whelan helped shape the community in which modern biochemistry developed [19].

For younger scientists working amid increasingly sophisticated technologies and enormous quantities of data, his example remains relevant. Advanced methods matter, but they do not substitute for identifying the question that the existing explanation has failed to answer.

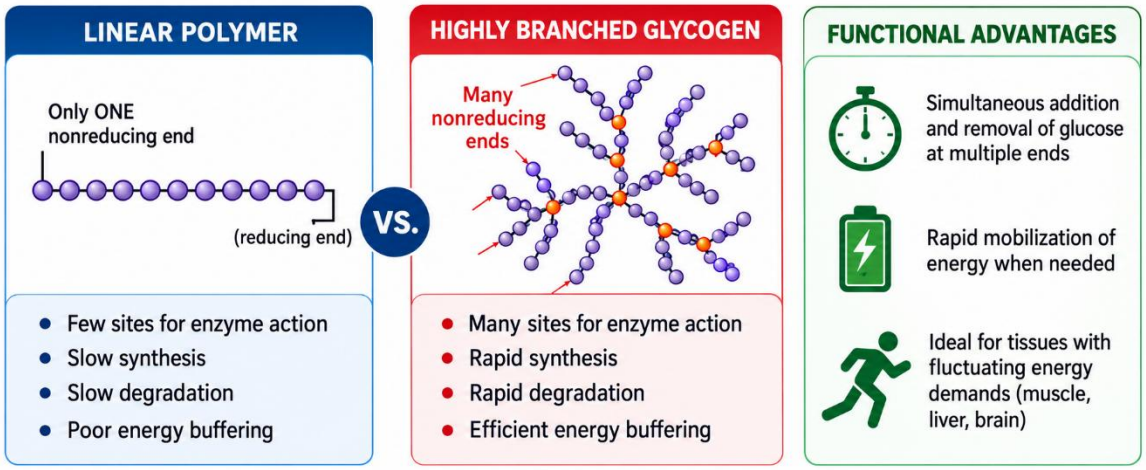


Figure 3. Functional Advantages of Glycogen Branching
Branching increases the number of non-reducing ends, allowing simultaneous glucose addition and removal, thereby maximizing the rate of glucose storage and mobilization.

Epilogue

For more than twenty-five years I had the privilege of knowing Bill Whelan as a scientist, colleague, mentor, and friend. What remains most striking is the consistency between the scientist and the man: intellectual rigor, curiosity, generosity, modesty, and a willingness to listen before reaching a conclusion.

The discovery of glycogenin solved an elegant biochemical problem, but the history of that discovery also reveals something broader. Bill recognized an unanswered question, persisted when his evidence met skepticism, welcomed independent confirmation, and continued to regard scientific knowledge as open to refinement.

Our conversations often ended not with certainty but with another question worth exploring. That habit of mind may be the most enduring part of his legacy.

Bill Whelan never stopped asking the right question. That is why his answers continue to matter.

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