



# Philip E. Cryer, MD: Seminal Contributions to the Understanding of Hypoglycemia and Glucose Counterregulation and the Discovery of HAAF (Cryer Syndrome)

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Optimized glycemic control prevents and slows the progression of long-term complications in patients with type 1 and type 2 diabetes. In healthy individuals, a decrease in plasma glucose below the physiological range triggers defensive counterregulatory responses that restore euglycemia. Many individuals with diabetes harbor defects in their defenses against hypoglycemia, making iatrogenic hypoglycemia the Achilles heel of glycemic control. This Profile in Progress focuses on the seminal contributions of Philip E. Cryer, MD, to our understanding of hypoglycemia and glucose counterregulation, particularly his discovery of the syndrome of hypoglycemia-associated autonomic failure (HAAF).



*Philip E. Cryer, as a mature professor and as a U.S. Naval officer.*

## Early Promise Fulfilled

Philip E. Cryer was born in 1940 in El Paso, IL, where his father was a country doctor. The founding of the American Diabetes Association (ADA) in the same year was an interesting coincidence, given his later career path in diabetes research and his leadership role in the ADA. An outstanding student, Cryer was valedictorian of his high school class in

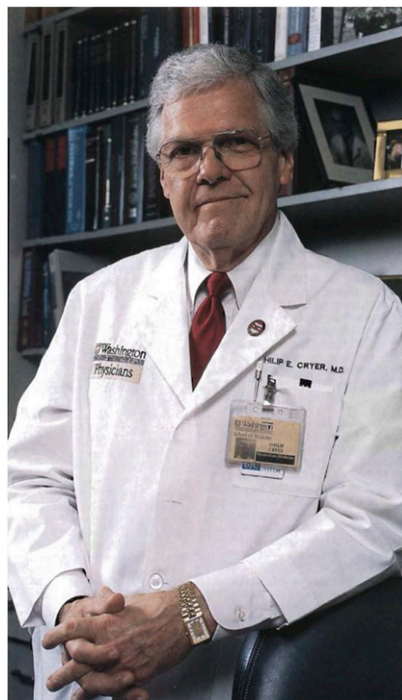
1958 and a Phi Beta Kappa graduate (1962) of Northwestern University in Evanston, IL. He obtained his MD (Alpha Omega Alpha) from the same institution in 1965, with "highest distinction." Cryer received clinical and research training in endocrinology

and metabolism under the direction of Drs. William H. Daughaday and David M. Kipnis at Barnes Hospital/Washington University School of Medicine in St. Louis (St. Louis, MO). After his completion of endocrinology training in 1969, he

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Cryer, Washington University School of Medicine in St. Louis (*Washington Magazine*, Fall 2002, p. 48).

served in the U.S. Navy at the Naval Medical Research Institute in Bethesda, MD, until 1971. After that, he returned to Barnes Hospital/Washington University School of Medicine in St. Louis, where he has spent his entire career.

Cryer rose to leadership positions at the Washington University School of Medicine. He was director of the Division of Endocrinology, Diabetes and Metabolism (1985–2002), director of the General Clinical Research Center (GCRC) for decades, and associate director of the Diabetes Research Center (2002–2014), among other roles. To his great credit, he led the GCRC through six successful competitive renewal applications to the National Institutes of Health over a period spanning 33 years. Cryer was named the Irene E. and Michael M. Karl Professor of Endocrinology and Metabolism at Washington University in St. Louis in 1995, a position he held until he became emeritus in 2014. Despite the numerous demands on his time, Cryer's major focus has been on patient-oriented, translational research. His research training in the late 1960s included experiences in both clinical research and then–state-of-the-art basic research. His first research publication, with Dr. Daughaday, was on the regulation of growth hormone secretion (1); his second article (with Drs. Jarett and Kipnis), titled “Nucleotide Inhibition of Adenyl Cyclase Activity in Fat Cell Membranes” (2), antedated the discovery of G proteins. Cryer's independent research work coalesced around the sympathoadrenal

system, glucose counterregulation, and hypoglycemia in general. In a career spanning more than four decades, Cryer has contributed three single-authored books, 94 book chapters, and 374 published articles to the medical literature.

### Sympathoadrenal System and Glucose Counterregulation

In the 1970s, Cryer developed a sensitive single-isotope derivative (radioenzymatic) assay for catecholamines (3). The advantages of that assay over the original double-isotope derivative method of Engelman et al. (4) included the use of smaller sample volumes and methodological simplicity. By dispensing with the need for internal standards (without compromising accuracy or precision), the Cryer assay also had an edge over the single-isotope derivative method of Passon and Peuler (5). With that tool, Cryer launched pioneering studies on the physiology and pathophysiology of the human sympathoadrenal system (6), as well as mechanistic studies on the metabolic actions of epinephrine in humans (7–10). The achievement of precision and efficiency in the measurement of catecholamines and other hormones enabled Cryer and his colleagues to chronicle the temporal pattern in the secretion of the glucose counterregulatory hormones during insulin-induced hypoglycemia. Those early studies set the stage for the discovery of the physiology of “glucose counterregulation,” a then-novel term that appeared as a running title of the 1976 publication authored by Alan Garber, Cryer, Julio Santiago, Morey Haymond, Anthony Pagliara, and David Kipnis (11).

### Hierarchy of Counterregulatory Responses

Subsequent work led by John Gerich and Cryer (12–15) discovered the principles of counterregulatory physiology by clarifying the hierarchy of changes in neuroendocrine hormones, symptoms, and cognitive function in response to decrements in blood glucose. In pivotal studies reported in 1979, Gerich and Cryer (12), along with their colleagues Jonathan Davis, Mara Lorenzi, Robert Rizza, Nancy Bohannon, John Karam, Stephen Lewis, Roy Kaplan, and Thomas Schultz, investigated the mechanisms for recovery of plasma glucose from insulin-induced hypoglycemia in healthy subjects and



Family portrait taken circa June 1997. Seated (center): Cryer and Carolyn Havlin-Cryer. From left: Mary Gudermuth Cryer (wife of Philip Clifford Cryer), Justine Laurel Cryer Dugan, Philip Clifford Cryer, Anthony Victor Havlin, Krista Victoria Havlin, and Rebecca Elizabeth Havlin Eberhart.

individuals who had undergone bilateral adrenalectomy. The study protocol included somatostatin infusion to inhibit glucagon and growth hormone secretion, with and without separate infusion of either hormone, to better understand the hierarchy of counterregulatory hormones. Those studies generated the now axiomatic knowledge that glucagon and epinephrine play critical roles, while the immediate contributions of growth hormone and cortisol are less critical, in the hierarchy of counterregulatory responses to acute insulin-induced hypoglycemia. The findings extended previous observations by Robert Brodows, F. Xavier Pi-Sunyer, and Robert Campbell (16) that demonstrated the neurohormonal control of counterregulatory responses during 2-deoxy-glucose–induced glucopeprivation in healthy subjects and patients with spinal cord transection.

### Hypoglycemia Unawareness

Elucidation of the hierarchy of counterregulatory responses soon was followed by the discovery (by Geremia Bolli, Gerich, Cryer, and colleagues) that these physiological defenses against hypoglycemia were compromised in people with type 1 diabetes (17,18). Those discoveries provided a conceptual framework for understanding hypoglycemia unawareness as the clinical expression of defective glucose counterregulation in people with diabetes. Probing the cause of the loss of glucagon response to hypoglycemia, insightful work from Cryer's group suggested that  $\beta$ -cell failure (and thus inability to modulate intraislet insulin levels) may be a mechanism for the aglucagonemic response to hypoglycemia (19,20). The neurogenic symptoms of hypoglycemia trigger a behavioral response (carbohydrate consumption) to abort hypoglycemia and restore euglycemia. Patients with hypoglycemia unawareness do not perceive neurogenic warning symptoms and thus are at risk for severe hypoglycemia, neuroglycopenia, coma, seizure, and even death. It had been generally believed that the neurogenic symptoms of hypoglycemia were of adrenomedullary origin (hence the term "adrenergic"). However, given the assessment of neurogenic symptoms, norepinephrine kinetics, and hemodynamic changes under clamped euglycemic and stepped hypoglycemic conditions in healthy

subjects and adrenalectomized patients, Cryer convincingly showed that the neurogenic symptoms of hypoglycemia are indeed largely the result of sympathetic neural, rather than adrenomedullary, activation (21). The clinical importance of these observations from studies championed by Cryer and colleagues is underscored by the demonstration that the combination of hypoglycemia unawareness and defective glucose counterregulation confers a 25-fold increased risk for severe hypoglycemia (22,23).

### Hypoglycemia Begets Hypoglycemia: Early Clues to a Syndrome

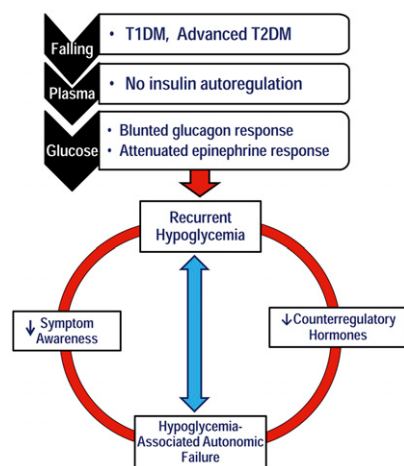
The benefits of glycemic control were clearly demonstrated in the Diabetes Control and Complications Trial (DCCT) (24), but the risk of iatrogenic hypoglycemia did not escape notice (24–26). The overall rates of severe hypoglycemia (including coma and seizure) were 61.2 per 100 patient-years versus 18.7 per 100 patient-years in the intensive and conventional treatment groups, respectively (25,26). DCCT participants who experienced severe hypoglycemia were at increased risk of subsequent episodes. Indeed, approximately one-third of the patients in each group experienced a second episode within the 4 months following the first episode of severe hypoglycemia (25,26). Analysis of several risk factors revealed that the number of prior episodes of hypoglycemia was the strongest predictor of the risk of future hypoglycemia (25,26). Elegant work in the late 1980s by Robert Sherwin and colleagues (27,28) (notably, Stephanie Amiel, Don Simonson, and William Tamborlane) linked strict glycemic control to impaired glucose counterregulation/hypoglycemia unawareness; however, a causal link between the latter and antecedent hypoglycemia had not been established at that time.

Indeed, conventional wisdom of that era had (mis)attributed the cause of hypoglycemia unawareness to diabetic autonomic neuropathy, until a convincing study in 1990 debunked that conclusion (29). Using an extensive battery of tests for autonomic function, Ryder et al. (29) observed that 12 patients with diabetes with hypoglycemia unawareness and 7 patients with defective

glucose counterregulation showed "little evidence of autonomic neuropathy." If not autonomic neuropathy, then what was the cause of impaired counterregulation and hypoglycemia unawareness? Extrapolating from their data, the extant literature (27,28,30), and clinical observations of pseudohypoglycemic symptoms in some normoglycemic (or even hyperglycemic) patients, Ryder et al. (29) speculated that "frequent hypoglycaemia might cause a downward resetting" of putative hypothalamic sites "to explain the hypoglycaemic counterregulatory defect." From about the late 1980s onward, Cryer's investigative efforts concentrated on the specific role of hypoglycemia in the etiology of hypoglycemia. Those efforts culminated in his maxim—"hypoglycemia begets hypoglycemia," quod erat demonstrandum! In 1991, Simon Heller and Cryer (31) demonstrated that a single episode of hypoglycemia in the afternoon impaired the hormonal, neurogenic, and neuroglycopenic symptom responses to subsequent hypoglycemia the following morning in healthy volunteers. Those findings were subsequently replicated in patients with type 1 diabetes who were carefully selected for the absence of autonomic neuropathy (32).

### Hypoglycemia-Associated Autonomic Failure

Cryer coined the term hypoglycemia-associated autonomic failure (HAAF) in a review article in 1992 (33) and subsequently used it as the title of the description of the syndrome in a 1993 publication (32). As originally proposed (32,33), the concept of HAAF in diabetes posits that recent antecedent hypoglycemia causes both defective glucose counterregulation and hypoglycemia unawareness during subsequent hypoglycemia, thus creating a vicious cycle of recurrent hypoglycemia (Fig. 1) (34). The syndrome of HAAF was demonstrated in subjects without diabetes (31), in patients with type 1 diabetes (32), and in those with advanced type 2 diabetes (35). Rodent models of HAAF soon appeared (36), and additional features (including decreased baroreflex sensitivity and muscle sympathetic nerve activity) were described following recent antecedent hypoglycemia in humans (37). An important question is whether HAAF is adaptive or maladaptive. Clearly,



**Figure 1**—Schematic representation of the concept of HAAF. Adapted with permission from Awoniyi et al. (34). T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

the vicious cycle of severe iatrogenic hypoglycemia triggered by HAAF is maladaptive. However, HAAF appears to protect against brain damage (38) and fatal cardiac arrhythmias (39) from subsequent severe hypoglycemia in rats, findings that raise the possibility of an adaptive response, somewhat akin to ischemic preconditioning (40). Recurrent hypoglycemia and HAAF also increased gene expression of GAD and levels of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) in rat neurons (41).

Although recent antecedent hypoglycemia was pivotal in the initial description of HAAF, prior exercise (42) and sleep (43) were demonstrated to induce similar syndromes, thereby linking defective glucose counterregulation to the well-known increased vulnerability to hypoglycemia after exercise and during sleep. Indeed, the demonstration of sleep-induced HAAF by Salomon Baner and Cryer (43) helps explain the predilection of most episodes of severe hypoglycemia for nocturnal hours (25). Although insulin action is highest at nighttime (44), that factor alone ought not pose a particular hazard for hypoglycemia if counterregulatory function were intact. Cryer often stresses that HAAF is pathophysiologically distinct from classic diabetic autonomic neuropathy—a structural disorder characterized by nerve fiber loss. The veracity of that assertion is underscored by the discovery by Fanelli et al. (45), Amiel and colleagues (46), and Cryer and colleagues

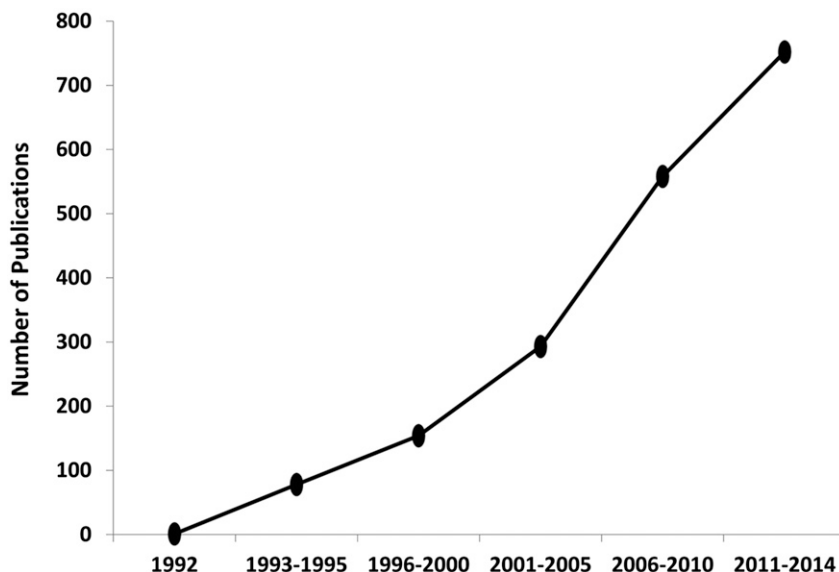
(47,48) that components of the HAAF syndrome are reversible in as little as 2–3 weeks of scrupulous avoidance of iatrogenic hypoglycemia. It is now standard clinical practice to recommend cautious relaxation of glycemic control and strict avoidance of hypoglycemia as a therapeutic strategy in patients with recurrent hypoglycemia and HAAF (49,50). Seldom has a research finding found its way so quickly into clinical practice.

A search of the medical literature showed just one article with specific reference to HAAF in 1992; the term has since appeared in the title, subtitle, or text of several thousand articles (Fig. 2). Twenty-five years ago, few would have imagined that an episode of hypoglycemia could elicit such a panoply of neuroendocrine, electrophysiological, cardiovascular, genomic, biochemical, neurocognitive, and behavioral responses! Cryer opened a Pandora's box: his healthy infatuation with the mechanisms of hypoglycemia stretched a field far beyond its traditional boundaries, opening up new vistas for inquiry and discovery. Unraveling the intricacies of this new physiology is an ongoing effort in numerous laboratories. To begin with, we do not yet have a unifying mechanism for the myriad manifestations of HAAF. Several groups, including Cryer's, have been testing a number of interesting potential mechanisms of HAAF (41, 51–55). These studies suggest possible contributions from glucocorticoids (52), inhibitory thalamic centers (53), altered

gene expression in GABAergic neurons (41), and excitotoxicity pathways (55), among others, as possible mechanisms underlying the syndrome of HAAF. The field opened up by Cryer and a coterie of dedicated hypoglycemia researchers no doubt will continue to intrigue and attract creative minds well into the future.

### Case for a New Taxonomy

As originally proposed by Cryer, HAAF is characterized by a clinical or subclinical event (recent antecedent hypoglycemia), biochemical features (defective glucose counterregulation, evidenced by attenuated glucagon and epinephrine responses), and subjective manifestations (absent or impaired awareness of neurogenic symptoms, arising from attenuated sympathetic neural responses to hypoglycemia) (32,33,51,54). Subsequent reports have identified additional features associated with recent antecedent hypoglycemia, including decreased baroreflex sensitivity and muscle sympathetic nerve activity in humans (37). Furthermore, HAAF is associated with neurocognitive/antiarrhythmogenic preconditioning (38,39) and increased GABAergic (41) tone in rodents. The etiology of the syndrome itself has expanded to include exercise (42) and sleep (43); thus, induction of HAAF is no longer restricted to the stimulus of recent antecedent hypoglycemia. Although his disquisitive reviews (51,54) now recognize the diverse causes of HAAF (51,54), Cryer would admit



**Figure 2**—Publications with HAAF in the title, subtitle, or text, 1992–2014 (source: Google Scholar).

that, semantically, HAAF has become somewhat of a misnomer for a functional autonomic disorder that is inducible by nonhypoglycemic stimuli. The taxonomic mismatch is likely to widen in the future, as additional inducers of HAAF are recognized. Perhaps it is time to consider “Cryer syndrome” as a descriptor for the foundational construct of a reversible autonomic disorder characterized by defective glucose counterregulation, hypoglycemia unawareness, and increased risk for severe hypoglycemia that is induced by antecedent hypoglycemia, prior exercise, sleep, or other putative factors.

Admittedly, the use of eponyms in medicine is in decline, after having peaked in the 1950s (56). Yet, eponyms do have certain advantages, including succinct communication, nosologic synthesis, and diagnostic parsimony. Consider the example of Cushing syndrome: Affected patients could present with weight gain, bruising, striae, osteoporosis, facial plethora, depression, diabetes, hypertension, and hirsutism, among other features. The underlying etiology could be an adrenal tumor, a pituitary tumor, exogenous glucocorticoid exposure, or ectopic ACTH or CRH secretion. Yet, the term Cushing syndrome is immediately informative and directs clinical behavior along established paths. Adoption of Cryer syndrome could deliver a similar parsimonious taxonomy for a complex disorder of diverse etiologies characterized by functional autonomic failure and myriad neuroendocrine, physiological, behavioral, and clinical manifestations. As already noted, the features of Cryer syndrome are reversible (45–48), making it a clinically relevant and treatable syndrome. Pragmatically, a patient with diabetes with a history of severe or recurrent hypoglycemia and hypoglycemia unawareness can be presumed to have Cryer syndrome. Given the impracticality of routine documentation of defective counterregulation in the clinic, a history of hypoglycemia unawareness can be used as a surrogate for defective glucose counterregulation in the setting of recurrent antecedent hypoglycemia. Fortunately, self-reported hypoglycemia awareness status is reliable, as evidenced by assessment of symptom scores during stepped hypoglycemia clamp (47).

One drawback is that eponyms can be fraught with rancorous priority disputes. Witness the eponym in Graves disease, which has been variously substituted with the names of Parry, Basedow, March, Parsons, Flajani, Begbie, and others (57,58). Although Parry first described the condition in 1825, 10 years before Graves and Basedow (57,58), Robert Graves was the first to convincingly link the major diagnostic features of goiter, palpitations, and exophthalmos. The triumph of Graves over other eponyms illustrates Sir Francis Darwin’s dictum that “in science the credit goes to the man who convinces the world, not to the man to whom the idea first occurred” (59).

### Back to Cryer

Cryer has had a global impact on the diabetes field through his direct work and the work of the more than 40 fellows he has mentored. The many honors he has received in recognition of his contributions include the Banting Medal for Distinguished Scientific Achievement and the Albert Renold Award (for mentorship), both from the ADA; the Claude Bernard Medal from the European Association for the Study of Diabetes; the Kellion Award from the Australian Diabetes Society; the Rorer Clinical Investigator Award from the Endocrine Society; the David Rumbaugh Scientific Award from JDRF; and an honorary doctorate from the University of Copenhagen, among others. Cryer is the only person in the 75-year history of the ADA to receive its Banting Medal for scientific achievement, serve as editor of its prestigious journal *Diabetes*, and be elected president of the Association. An advocate for people with diabetes, Cryer frequently reminds his professional colleagues that “hypoglycemia is the limiting factor in the glycemic management of diabetes.” That was the theme of his Banting Lecture (1994) and his Claude Bernard Lecture (2001). Cryer consistently acknowledges the contributions of collaborators and trainees and expresses high regard and gratitude for their collaboration.

Formerly married to Susan Shipman Cryer, Cryer married Carolyn Havlin-Cryer in 1994. Their blended family includes five children—Philip Clifford Cryer, Justine Laurel Cryer Dugan, Anthony Victor Havlin, Krista Victoria Havlin, and

Rebecca Elizabeth Havlin Eberhart—and six grandchildren—Kacy Elizabeth Cryer, Benjamin Philip Cryer, Matthew Philip Dugan, Emma Inez Dugan, Mollie Breanne Havlin, and Max Havlin Eberhart. At the time of his retirement from Washington University in St. Louis in 2014, Cryer was greatly honored by the decision of the William and Elaine Wolff Family, including their son Gary Wolff, to endow the Philip E. and Carolyn E. Cryer Professor of Endocrinology and Metabolism Chair at Washington University in St. Louis.

Albeit as a listener and no longer a performer, Cryer is a fan of the tight, four-part harmony of barbershop quartet singing, a classic American art form; he even knows the meaning of the acronym SPEBSQSA! He also enjoys nonmedical reading, mostly of histories and biographies, and counts the American writer and humorist Mark Twain (Samuel Clemens, 1835–1910) and the British mathematician, philosopher, and social critic Bertrand Russell (1872–1970) among his favorite authors. Indeed, Cryer frequently prefaces his lectures with a quote from Russell’s *The Conquest of Happiness*, first published in 1930: “One of the symptoms of an approaching nervous breakdown is the belief that one’s work is terribly important” (60).

### Summary

In closing, work championed by Cryer and others clearly established the legitimacy of a syndrome of functional autonomic failure, defective glucose counterregulation, hypoglycemia unawareness, and increased risk for recurrent severe hypoglycemia. The syndrome is inducible by recent antecedent hypoglycemia, prior exercise, or sleep. Finding a parsimonious descriptor for such a multifarious syndrome that captures the foundational construct and current (and potentially future) diverse etiologies has become a challenge in medical taxonomy. The proposed term Cryer syndrome is an apt, succinct, and attributively congruent solution.

**Acknowledgments.** S.D.-J. was a research fellow in metabolism in Dr. Cryer’s group from 1990 to 1992 and subsequently served as a faculty member in the Division of Endocrinology, Diabetes and Metabolism at the Washington University School of Medicine in St. Louis from 1992 to 2000.

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