

The History of Pediatric Endocrinology at Brown University and in Rhode Island

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ABSTRACT

As is the case for the discipline of pediatric endocrinology, the Division of Pediatric Endocrinology at Brown University was borne of the field of metabolic and biochemical investigation. Its establishment dates to 1967 when Dr. Mary B. Arnold came to Rhode Island. The recruitment of Dr. Robert Schwartz in 1974 brought an expertise in pediatric diabetes. The unified Division of Pediatric Endocrinology and Metabolism was established in 1987. Since its earliest days, the division has graduated 31 fellows with board certification in pediatric endocrinology. The division's history is rooted in basic and clinical research, a hallmark of which has been the description and elucidation of novel clinical cases. At present, the division provides comprehensive and multidisciplinary clinical services to children and adolescents with endocrinologic disorders, including diabetes. Providing these services is a team of eight faculty members, three fellows in training and 15 staff encompassing the disciplines of nursing, diabetes education, nutrition, psychology, pharmacy, and social work.



Mary B. Arnold, MD

INTRODUCTION

Pediatric endocrinology is a relatively new discipline. It evolved from the era of metabolic and biochemical investigation to become a defined pediatric specialty in the 1930s and 40s.¹ The origin of the Division of Pediatric Endocrinology at Brown University precedes the establishment of the modern medical school at Brown. It also precedes the establishment of a pediatric endocrinology sub-board. The division's origin dates back to 1967 when Dr. Mary B. Arnold

[Figure 1] came to Providence. After completing a pediatric residency at New York Presbyterian Hospital-Columbia University, Dr. Arnold was a pediatric endocrinology fellow at the Massachusetts General Hospital with Dr. Jack Crawford, one of the founders of the field of pediatric endocrinology.²

Following her fellowship, Dr. Arnold moved to the University of North Carolina, where she came under the tutelage of Dr. Judson Van Wyk. Dr. Van Wyk had been a fellow at Johns Hopkins with another founder of the field of pediatric endocrinology, Dr. Lawson Wilkins.³ Working with Dr. Van Wyk, Dr. Arnold was only one generation removed from the inception of pediatric endocrinology as a specialty. In Rhode Island, Dr. Arnold became chief of the pediatric service at Roger Williams General Hospital (RWGH) and a faculty member at Brown University, teaching in Brown's "Masters of Medical Science" program. She also established a pediatric endocrinology clinic at RWGH, where she was regularly joined by an endocrine colleague, Dr. Jay Orson. Dr. Orson was a member of an established pediatric practice in Providence where he provided a combination of primary care and endocrinology consultative services.



Robert Schwartz, MD

The founding of the academic Department of Pediatrics at Brown was marked by the recruitment in 1974 of Dr. Leo Stern, a neonatologist, to serve as chair of the department. Dr. Stern's charge was to develop an academic department with a robust research enterprise. To that end, he recruited a small core of established academic pediatricians. Among them were Drs. Robert Schwartz [Figure 2] and William Oh. Dr. Oh, a neonatologist, and Dr. Schwartz, a metabolism specialist, were established physician-scientists. As they were preparing to come to Brown, they began to consider their mutual interests for the purpose of establishing a collaborative research program. Within several years, that collaboration had resulted in their securing NIH funding for a Child Health Research Center program project grant that focused on diabetes in pregnancy.

When Dr. Schwartz came to Brown in 1974, he brought with him Dr. Ken McCormick to serve as his first fellow in pediatric metabolism. Dr. McCormick spotted a pediatric resident, Dr. Philip Gruppuso, who had an interest in metabolism. Some behind-the-scenes activities resulted in Dr. Gruppuso being recruited to Dr. Schwartz's lab for research electives during residency. Following his chief residency year in 1980-81, Dr. Gruppuso became the division's first



Philip A. Gruppuso, MD

joint pediatric metabolism-endocrinology fellow. With the benefit of additional mentoring by Dr. Oh and Dr. John Susa, a PhD biochemist in Schwartz's group, Dr. Gruppuso [Figure 3] was appointed the first head of a joint division of Pediatric Endocrinology and Metabolism in 1987.

The next year, the Division recruited Dr. Ian Ocrant. When Dr. Ocrant left after several years to

practice pediatric endocrinology in his home state of California, Dr. Gruppuso called his by-then friend and mentor, Dr. Van Wyk, who connected Dr. Gruppuso to his graduating fellow, Dr. Charlotte Boney [Figure 4]. Dr. Boney came to Brown in 1994. That same year, Brown and Rhode Island Hospital's Department of Pediatrics moved into its new home, Hasbro Children's Hospital.

Other faculty members who worked in the Division of Pediatric Endocrinology over the years included Drs. Gregory Goodwin, Penny Feldman, Rebecca McEachern, Cynthia Meyers-Seifer, Bracha Goldsweig, and Shara Bialo. All are highly skilled pediatric endocrinologists who made substantial contributions to the division's tripartite mission: clinical care, research and teaching. By 1996, the division was accepting a new fellow each year. Among them was Dr. Chanika Phornphutkul, who was a fellow from 1996 to 1999. Following her fellowship, Dr. Phornphutkul moved to the NIH to train in biochemical genetics with Dr. William Gahl. She was recruited back to RI in 1999. While she maintains her appointment and activities in pediatric endocrinology, in 2011 she was appointed director of the Division of Medical Genetics, a post that she holds to the present.

In 2005, Dr. Gruppuso was appointed Associate Dean for Medical Education at Brown. The division head position

was assumed by Dr. Boney, who recruited Dr. Jose Bernardo Quintos in 2007. Dr. Quintos trained at The New York Presbyterian Hospital-Weill Cornell Medicine under Dr. Maria I. New, one of the pioneers of pediatric endocrinology and a foremost expert in congenital adrenal hyperplasia. In 2013, Dr. Boney recruited Dr. Lisa Swartz Topor to the division from her position as a fellow then



Charlotte Boney, MD

junior faculty member at Boston Children's Hospital. Dr. Boney remained division head until 2014 when she left to be department chair in pediatrics at Baystate Medical Center and the University of Massachusetts. Dr. Quintos [Figure 5] became division head upon Boney's departure, a position he holds to the present.

RESEARCH

Shortly after his arrival in Rhode Island, Dr. Schwartz initiated a project aimed at testing the hypothesis that the fetopathy of diabetes in pregnancy was a direct consequence of fetal hyperinsulinism. To test this, Drs. Schwartz and Susa developed a primate model of primary fetal hyperinsulinemia. Fetal Rhesus monkeys were implanted in the latter stage of gestation with a subcutaneous osmotic minipump that secreted insulin for three weeks prior to delivery at term. In a series of papers, Schwartz's group showed that primary fetal hyperinsulinemia was associated with macrosomia, an increase in total body fat, increases in hepatic lipogenic enzymes, delayed lung maturation and erythropoietin-mediated polycythemia. In short, the model recapitulated the fetopathy of diabetes in pregnancy.⁴

While in Cleveland, Dr. Schwartz had established a collaboration with Dr. Kari Teramo, an obstetrician from the University of Helsinki. The collaboration continued at Brown, allowing studies that further supported a primary role for fetal hyperinsulinemia in the macrosomia seen in the offspring of diabetic pregnancies. Other lines of research led by Dr. Schwartz were carried out by his colleagues in neonatology – Drs. Jack Widness, Richard Cowett and William Oh – and in obstetrics – Drs. Donald Coustan, Marshall Carpenter and others. These collaborations made Brown an important center for fetal and maternal metabolic research.

Dr. Schwartz urged Dr. Gruppuso, upon completion of his fellowship, to pursue laboratory research full time. To this end, they solicited the support of Dr. John Fain, the head of Brown's Section of Biochemistry. A resulting NIH career development award allowed Dr. Gruppuso to work with a new faculty member at Brown, Dr. David Brautigan. In Dr. Brautigan's lab, Dr. Gruppuso developed expertise in signal transduction research. Melding this new interest with his background in metabolism, he embarked on a project aimed at characterizing the metabolic and growth phenotype of rat fetal hepatocytes. This proved to be a fruitful area of research, resulting in funding of an NIH R01 grant from 1989 until 2023. The work done under the auspices of this project evolved to focus on epigenetic regulation of hepatic gene expression, liver progenitor cells and their capacity to repopulate an injured liver, and liver carcinogenesis.⁵⁻⁷ From the start of this project, a key researcher in the lab was Joan Boylan, who served as lab manager in the division while holding a position as research associate at Brown University. One of the graduate students who came through the



Jose Bernardo Q. Quintos, MD

laboratory was Dr. Jennifer Sanders, who obtained her PhD in 2005. She subsequently completed a postdoctoral fellowship at Brown, then moving on to a faculty appointment in pediatrics. Dr. Sanders directed the Pediatric Endocrinology Laboratory and Brown's Pathobiology Graduate Program.

During her fellowship, Dr. Boney had done research aimed at understanding the role of the insulin-like growth factor (IGF) system in fat cell biology. Upon her arrival at Brown, she established a basic research program focused on cell signaling by IGF and insulin and their role in adipogenesis. The work, which established a primary but distinct role for both hormones,⁸ had implications for the development of adipose tissue, and the factors leading to obesity and insulin resistance. Boney had the opportunity to pursue this topic in collaboration with Dr. Betty Vohr, director of the neonatal follow-up program. Together, they published a seminal paper⁹ that established the link between maternal obesity, gestational diabetes and development of metabolic syndrome during childhood in the offspring.

When Dr. Phornphutkul returned to Brown, she pursued a project that also focused on mesenchymal cell differentiation. She focused on chondrogenesis, a subject that had direct relevance to childhood growth. Dr. Phornphutkul demonstrated that chondrogenesis at the growth plate involves the integration of insulin, IGF and nutrient signaling.¹⁰ Her work contributed to our understanding of the mechanisms by which nutritional status affects long bone growth.

UNUSUAL CASES AND RESULTING SCHOLARSHIP

The Division of Pediatric Endocrinology has made meaningful contributions to scientific knowledge through careful clinical observations and related laboratory investigation. Not long after his arrival in RI, Dr. Schwartz was asked to see a 12-year-old girl who had been evaluated at another endocrine program and diagnosed with "pre-diabetes." He involved his then fellow, Dr. W. Patrick Zeller, who confirmed that the girl had impaired glucose tolerance associated with elevated levels of immunoreactive insulin. Her case, which included an evaluation of her family and a careful analysis of circulating proinsulin and proinsulin conversion intermediates, was published in the *New England Journal of Medicine* as only the third known case of hyperproinsulinemia.¹¹ Further evaluation for a mutation in the proinsulin gene revealed that the patient's metabolic abnormality was due to a point mutation in the region of the insulin gene that encodes the insulin B-chain, resulting in impaired proinsulin-to-insulin conversion.¹²

This case spurred further work on proinsulin carried out by Drs. Gruppuso and Schwartz in collaboration with Drs. Bruce Frank and Mary Root at Eli Lilly. Studies in pregnant Rhesus monkeys showed that proinsulin, like insulin, does not traverse the placenta, but that immunoreactive fragments of the connecting peptide released during

proinsulin-to-insulin conversion, C-peptide, do cross.¹³ Other studies focused on the ability of proinsulin and conversion intermediates to interact with the insulin and IGF receptors.¹⁴ This work was important at the time because Eli Lilly was moving toward the development of proinsulin as a therapeutic agent for use in diabetes.

A second high impact case report followed several years later. Members of the division had been following a child with Albright's Hereditary Osteodystrophy pseudohypoparathyroidism. His clinical manifestations, including multi-hormone resistance, asthma and subcutaneous ossifications, were particularly severe. An endocrinologist at Johns Hopkins, Dr. Michael Levine, was working to identify the G-protein mutations that were presumed to account for this disorder. The Rhode Island patient became the first individual with a defined mutation accounting for pseudohypoparathyroidism.¹⁵

A third case report that had a particularly high impact within and outside our division was that of a teenager who had been followed since birth with a disorder of sexual development (DSD). At the time, the standard of care for newborns with DSDs was based on the principle that an assigned gender, appropriate to the specific disorder, would be accepted by the patient as long as there was consistency on the part of the parents. The significance of the case was that, as a teenager, the patient rejected his assigned female gender. This coincided nearly exactly with the emergence of the "John/Joan" story, which also highlighted that gender assignment was rejected by a boy with an assigned female. The RI case, published in *Pediatrics*,¹⁶ was part of a change to a new standard of care that includes avoidance of early surgery and greater inclusion of parents and patients in decision-making. As a result of involvement in this case, Dr. Gruppuso went on to contribute to a change in the taxonomy¹⁷ that resulted in the standard use of the DSD terminology and a move away from terms such as "pseudohermaphrodite."

A case exemplifies the impact that case reports can have on basic research. In 2013, Dr. Quintos met a 5½ year-old with the unusual clinical constellation of short stature with an advanced bone age. A genetic analysis revealed a missense mutation in the gene that encodes the intercellular matrix protein aggrecan.¹⁸ Other kindreds had been described with similar presentations,¹⁹ but the molecular basis for the growth abnormality had not been identified. Hypothesizing that the aggrecan mutation affected the development of growth plate chondrocytes, endocrine fellow Dr. Juanita Hodax carried out studies on chondrogenic cells made null for aggrecan production. Her studies²⁰ showed that aggrecan participates in the normal process of chondrocyte differentiation, a novel finding, such a role not having been attributed to this matrix protein.

Throughout the history of the division, faculty and fellows have made scholarly contributions in the form of case reports^{21,22} and case series,²³⁻²⁵ and original clinical research

in diabetes and endocrinology.²⁶ While many have focused on diagnostic and therapeutic observations, more recent reports have taken advantage of contemporary molecular analyses to define the genetics of specific disorders.^{18,22,27,28}

PEDIATRIC ENDOCRINOLOGY TRAINING

A training fellowship at RI Hospital preceded the establishment of a specialty board in pediatric endocrinology. Over the 45 years since inception of the academic department, the division has graduated 31 fellows [Table 1]. Of these, most provide direct patient care, while others are primarily researchers or working in industry. Fellowship graduates include dozens of faculty members of academic departments across the United States, including many who have served in academic and educational leadership positions.

Among the Division's fellowship graduates, three currently reside and practice in Rhode Island. One, Dr. Gregory Fox, has made an important contribution by serving as the physician for the RI diabetes camp, Camp Surefire, and the president of its supporting foundation. Dr. Meghan Fredette, a 2019 graduate of the fellowship, is a faculty member in the Division. The third graduate of the fellowship program practicing in Rhode Island is Dr. Phornphutkul who, following training at NIH in clinical genetics, came back to Rhode Island to lead the Genetics Division in the Department of Pediatrics.

The fellowship program, directed by Dr. Lisa Swartz Topor continues to recruit and graduate one fellow per year. Of the approximately two thousand pediatric endocrinologists who have been certified by the American Board of Pediatrics since the inception of its specialty board, more than a third are over the age of sixty.²⁹ Brown University's fellowship program will continue to play an important role in sustaining the discipline of pediatric endocrinology

disorders. Given the nature of this population, a substantial proportion of the Division's clinical efforts have been directed to the care of pediatric patients with diabetes. Dr. Schwartz established a diabetes clinic when he came to Rhode Island. During the first several years, some eighty patients were referred to him by primary care providers. This small clinical service grew gradually over the subsequent several decades such that by 2020 the Division was caring for over 1,000 pediatric diabetes patients. With the advent of current diabetes management technologies, including insulin pumps and continuous glucose monitors, the management of type 1 diabetes involves multi-disciplinary specialty teams. These patients are being managed by a team of physicians, diabetes nurse educators, registered dietitians, and social workers.

The conditions for which patients are most commonly referred to pediatric endocrinologists include short stature, delayed pubertal maturation, and thyroid disease. The Division also cares for a population with a broad scope of rare and serious endocrine disorders. The division's expanding clinical service, which has included the establishment of four satellite clinical locations, led to the recruitment of new faculty members in recent years. Dr. Monica Serrano- Gonzalez who trained at Children's Hospital of Los Angeles, was recruited in 2017. Dr. Meghan Fredette joined the division as a faculty member upon the completion of her fellowship in 2019, Drs. Kate Millington and Kevin Scully joined in 2022 after completing their training at Boston Children's Hospital, and Dr. Jonathan Tatum who was recruited in 2024 after finishing fellowship at Cincinnati Children's Hospital. Among the current staff are several individuals who have been with the division for over a decade, Maryann Johnson, RN, Terri Hamm, RN, CDE and Jean Bisordi, RN, CDE. The contribution they have made to the care of our patients is incalculable.

Table 1. List of Pediatric Endocrinology Fellows

Year	Fellow
1983	Philip Gruppuso, MD
1985	Vincent Nishino, MD
1987	Michael Sarris, MD
1992	Luis Aparicio, MD
1996	Suleiman Mustafa-Kutana, MD
1997	Lauren Lipeski, MD
1999	Chanika Phornphutkul, MD
2000	Penny Kadmon, MD
2001	Anil Kumar, MD
2003	Gregory Fox, MD
2004	Nikolaos Kefalas, MD
2005	Molly Harrington, MD
2006	Valerie Auyeung, MD
2007	Eda Cengiz, MD
2008	Mimi Kim, MD
2009	Katarina Gambosova, MD
2011	Otilia Neacsu, MD
2011	Mia Pingul, MD
2012	Sujana Reddy, MD
2013	Sunita Cheruvu, MD
2014	Angela Ganán Soto, MD
2015	Shara Bialo, MD
2016	Sungeeta Agrawal, MD
2017	Serife Uysal, MD
2018	Juanita Hodax, MD
2019	Meghan Fredette, MD
2020	Ugen Lhamu, MD
2021	Anna Chin, MD
2023	Avani Ganta, MD
2023	Sabitha Sasidharan Pillai, MD
2024	Sujatha Seetharaman, MD MPH (completed training at UCSF)

THE CLINICAL MISSION

Throughout the history of the Division, its core mission has been to provide clinical care to the population of pediatric patients in Rhode Island and southeastern New England with endocrine

CITIZENSHIP AND PROFESSIONAL SERVICE

Since the inception of the Division, its members have served in a variety of local and national positions. One of the earliest and most important contributions was Dr. Arnold's contribution

to the establishment of the neonatal thyroid screen in the late 1970s, work that she did through her work for the New England Regional Newborn Screening Program. Since 1989, Dr. Gruppuso has served on federal and non-federal committees and grant review panels. He was a member of the board of the RI affiliate of the American Diabetes Association from 1990 to 1996 and was its president from 1992 to 1994. His patient advocacy activities included membership on the medical advisory board of the Intersex Society of North America. He has served as a member of the editorial boards of *The Journal of Clinical Endocrinology and Metabolism* and *Pediatric Research*. Dr. Quintos serves on the endocrinology sub-board of the American Board of Pediatrics. Dr. Quintos was Chair of endocrinology sub-board of the American Board of Pediatrics from 2023–2024, a position also held by Dr. Boney while she was a member of the Division. More recently, Dr. Quintos contributed to the development of the Pediatric Endocrine Society's Task Force on Consensus Guidelines for Growth Hormone Therapy,³⁰ and Dr. Topor is serving as the chairperson of the Pediatric Endocrine Society Training Council from 2024–2026, working with fellowship directors across the US and Canada.

SUMMARY

The clinical field of pediatric endocrinology is one that is still relatively new. The recruitment of specialists in this discipline coincided with the founding of the medical school at Brown University and of its academic department of pediatrics. While only 45 years have lapsed since the division's inception, it has made substantial contributions to the care of infants, children and adolescents in Rhode Island, to the training of pediatricians and endocrinologists, and to scholarship related to the clinical and basic science of endocrinology. The division is committed and able to continue making these contributions for the foreseeable future.

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