
GROWTH

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DR. ROBERT M. BLIZZARD - A LEGACY

Fima Lifshitz, MD

For the Editorial Board

Growth, Genetics and Hormones (GGH) has been published without interruption for the past 19 years. This journal was conceived and founded in 1984 by Dr. Robert M. Blizzard; the first issue appeared in March 1985. The goal set by him and the editorial board was to integrate reports of current advances in the fields of growth, genetics, endocrinology, metabolism and nutrition by bringing the most pertinent papers, with erudite editorial comments, to the attention of pediatricians, internists, pediatric endocrinologists, geneticists, nutritionists, nurses, and to others interested in these fields.

As Editor-in-Chief, Dr. Blizzard has worked tirelessly since the inception of the journal. He has been personally responsible for selecting, recruiting and stimulating the editorial board. He has elicited the best from all of us. Initially the editorial board consisted of Drs. David L. Rimoïn, Fima Lifshitz and Alan Rogol from the United States, Judith G. Hall from Canada, and Dr. Jürgen R. Bierich as a European representative. Subsequently other distinguished Pediatric Endocrinologists from Europe joined the editorial board, including Drs. Jean-Claude Job and James Tanner. The

current editorial board members, serving *GGH* since 1993, are Drs. William Clarke, William Horton, and Allen Root, plus founding members Judith G. Hall and Fima Lifshitz. Dr. Blizzard has spearheaded all aspects of the publication including the content, quality, and format.

Throughout the last 19 years *GGH* has exceeded his goals and has become a well established resource for all 6,000 of its current readers, many of whom cherish the journal and keep each issue in their reference libraries. As well, Dr. Blizzard has made sure that as the cycle of life continues there would be a positive and productive transition for *GGH*. During the past two years he has fostered a smooth passage to ensure that upon completion of his tenure as Editor-in-Chief the journal will continue to serve the needs of our colleagues and continue to grow. He personally has overseen all transitional aspects and bestowed responsibility for the future of *GGH* to me as Editor-in-Chief.

Dr. Blizzard requested that a short announcement be inserted about his retirement in this his last issue Vol. 19 No. 4. He wished to see that the many readers who have read *GGH* throughout the years were thanked and appreciation was expressed to all those who have contributed to *GGH* by writing lead articles and to those who have been consistent readers. We pass this message along for him, and the editorial board joins him in saying "thank you".

The editorial board, wishing to acknowledge the many years of service and the most important contributions of Dr. Blizzard, has prepared a brief outline of the accomplishments of this founding editor, teacher, pediatric endocrinologist, clinician, scientist, and man described below. This tribute to him is but a token way to bid him farewell and to imprint his legacy, so that future generations of our colleagues also may be inspired by him.

First and foremost, Dr. Blizzard will be remembered and recognized as a teacher and educator. He is an accomplished teacher, and his competence as an educator and preceptor is well known. He was trained (1955-1957) by Lawson Wilkins and he was "trained to

Highlights In This Issue

Newborn Screening by Tandem Mass Spectrometry	page 53
Clitoral Surgery in Intersex Conditions with Ambiguous Genitalia	page 54
Neonatal Exendin-4 Prevents Development of Diabetes in the IUGR Rat	page 56
Morbid Obesity & Mutations in Appetite Controlling Genes	page 57
Hypogonadism & Pubertal Development in Prader-Willi Syndrome	page 59
Growth & the Tyrosine Kinome	page 59
What Do Craniosynostosis & Kallmann Syndrome Have in Common? FGFR1	page 60
Clinical, Autoimmune, & HLA Characteristics in Type 1 Diabetes	page 61
TSHR Autoantigen in Graves Disease	page 62
Index Volume 19	page 64

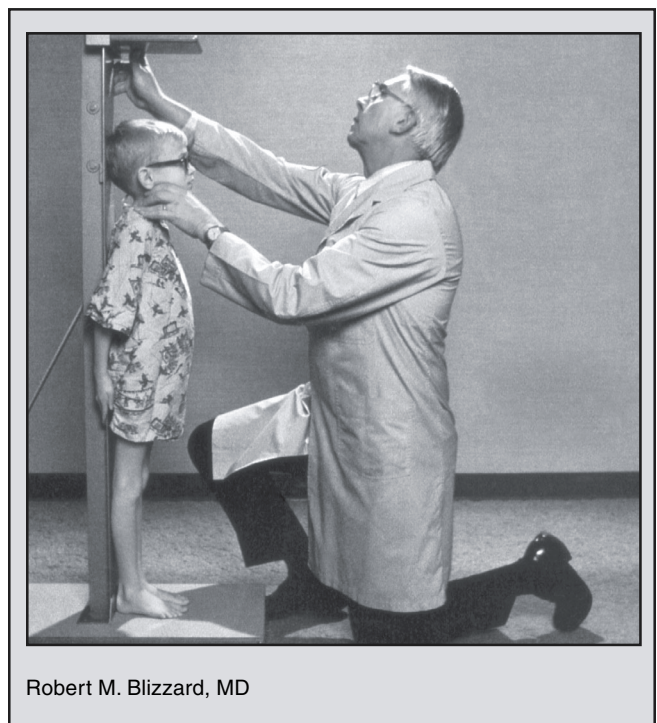
train”, when there were only approximately 20 pediatric endocrinologists in the country. He prides himself in being a pediatric endocrinologist for 48 years (1955-2003) and throughout his career he set the course for his students. Over 50 fellows, including myself and other members of the editorial board, undertook and completed their training with him. Forty-five of these are now in academic positions. Many are full professors including three deans, an associate vice president for health affairs, several chiefs of staff of children’s hospitals, and several pediatric department chairpersons in the U.S. and abroad. He is proud of the fact that most of his fellows have established their own pediatric endocrinology training programs, and thus provided an ongoing transmission of the teaching of Lawson Wilkins and himself to second and third generations of pediatric endocrine fellows. He has received multiple teaching awards including those from the Johns Hopkins Hospital, the University of Virginia, and other prestigious universities. Very possibly the teaching award of which he is most proud is his election to alpha omega alpha in 1970 by the members of the Johns Hopkins Alpha Omega Alpha (AOA) Society. His accomplishments as a student had not qualified him for AOA membership, and, therefore, his election by the student membership was particularly gratifying, since only one faculty member per year was elected to the society.

He also is proud of the opportunity to have served as Acting Chairman of the Department of Pediatrics at the Johns Hopkins University School of Medicine (1972 and 1973) and as Chairman of the Department of Pediatrics at the University of Virginia, School of Medicine (1974-1987). At these institutions he fostered 15 generations of pediatric residents who sought and attained their pediatric training in his departments. Most of them are now in academic and/or clinical practice in the US. A significant number are abroad. For his educational activities he has been honored with other prestigious awards. Among them are the Ayerst (1973) and Williams (1994) distinguished service and leadership awards bestowed by the American Endocrine Society. Recently he has been honored to be elected to the Johns Hopkins Society of Scholars (2002) and honored by the establishment (2002) of the Robert M. Blizzard Annual Lectureship at the annual meetings of the Lawson Wilkins Pediatric Endocrine Society (2002). He also has been honored by invitations to deliver over 150 named lectureships and visiting professorships at many national and international academic institutions. He was elected to the prestigious Hall of Fame of Miami Children’s Hospital in 1997. Those who attended the teachings of Dr. Blizzard have always recognized his talents in teaching, and most have asked for more!

However, his contributions as an educator transcend

the traditional teaching role through which he personally touched so many individuals and imparted his knowledge. Dr. Blizzard made major contributions to continuing medical education by serving on multiple editorial boards of journals, editing and publication of several textbooks, and by his 19 years of editorship of *GGH*. The number of physicians and other scientists whom he reached via this journal through the years cannot be easily counted nor measured, but *GGH* is currently read regularly, as previously stated, by over 6,000 colleagues world-wide. Thus, the impact of Dr. Blizzard as an educator can be summarized as “the teacher par excellence”.

In the field of endocrinology, he is particularly known for his contributions in the areas of growth and in autoimmunity, with over 200 original peer-review papers published in the literature. His picture is a clear testimony to his legacy as a clinician. He has always, in the Wilkins’ style, promoted accurate measurements of children in assessing growth. This is still the gold standard in the evaluation of children with short stature. Dr. Blizzard was a pioneer in this field, publishing his first studies on the action of human growth hormone in 1959, one year after the first publication by Dr. Raben of the use of human growth hormone in growth hormone deficient individuals. His interest continues in this field to this day. Dr. Blizzard, along with Dr. Joanne Brasel and Dr. James Wright in the early 1960s published several important papers that changed the approach to the diagnosis and treatment of growth hormone deficiency. Included were the observations that growth hormone deficiency can be manifested by delayed growth even in the first year of life, previously not thought to be the case, and that the



Robert M. Blizzard, MD

acute metabolic response to human growth hormone did not correlate with its growth promoting effects when growth hormone deficient children were treated. The search for reliable indicators to predict a quantitative response to growth hormone is still ongoing.

Subsequently, Dr. Blizzard authored or co-authored 56 publications in peer-review journals pertaining to growth hormone or growth factors. These studies clarified the role that growth hormone played in producing the adolescent growth spurt, and the phenomenon of growth hormone production and its relationship to steroid production during this stage of life. A series of articles published under his tutorage unequivocally demonstrated that growth hormone increases at the time of adolescence when testosterone is produced in males. These studies showed that growth hormone and testosterone each have separate mechanisms of action in promoting growth, as well as permissive actions in the relationship to the secretion of each other.

In 1971 Dr. Blizzard stimulated his associates to design a pump that would permit a constant withdrawal of blood over a 24-hour period, that would permit the measurement of integrated concentrations of circulating hormones. Dr. Avinoam Kowarski was successful in this endeavor, and he and Dr. Robert Thompson, Dr. Claude Migeon, and Dr. Blizzard first reported the determination of integrated concentrations of human growth hormone and true secretion rates of human growth hormone. The importance of pulsatility and the intricacies of growth hormone production at various stages of life were subsequently delineated using this technique in studies with Dr. Alan Rogol, Dr. Paul Martha, Dr. Nelly Mauras, Dr. Kathleen Link, and others at the University of Virginia.

While being a leader throughout his life and an innovative initiator of investigative protocols, he appropriately was appointed Director of the Clinical Research Center at the University of Virginia (1980-1983), while serving simultaneously as Department Chairman. He collaborated extensively with his colleagues in the Divisions of Endocrinology in Internal Medicine (Dr. Michael Thorner in particular among others). He coauthored 15 papers concerning the effect of growth hormone releasing hormone in humans - both as a diagnostic and therapeutic agent.

Although not as well known, Dr. Blizzard initiated and significantly contributed in elucidating the possible role of decreased growth hormone production during adult life in the aging process. He, his associate Dr. Ann Johanson, and his group initially demonstrated that older males secrete less growth hormone than do young males, and that older males receiving growth hormone retain nitrogen, comparable to that seen in growth hormone deficient young adults. They also reported that

growth hormone administered to older males generated insulin-like growth factor I, comparably to that generated in growth hormone deficient children. He subsequently described the changes in pulsatility of growth hormone secretion in older men and women as compared to younger subjects.

These studies led to the involvement of Dr. Blizzard in the first study to evaluate the effect of chronic growth hormone administration in older males. His research was not only at the intellectual/research level; he was the first of five males in a study which he initiated to receive growth hormone every day over a period of 30 months. He and his colleagues demonstrated that growth hormone had no significant effect upon skin collagen and its amino acid composition. He was obliged to stop the study in 1985 because of the report of possible contamination of native pituitary extracts by the prion producing Creutzfeldt-Jakob disease. However, the results of this project undoubtedly stimulated other investigators to assess the effect of growth hormone in the elderly.

Another major contribution of Dr. Blizzard was the concept that psychosocial dwarfism (also called emotional deprivation, maternal deprivation, the garbage can syndrome, and reversible hyposomatotropism) resulted from transient growth hormone deficiency. He insists that major credit in the concept be accepted by Dr. Dagfinn Aarskog, Dr. Gerald Powell, Dr. Salvatore Raiti, and others. The demonstration of the pathophysiology of such alterations gave great impetus to studying how the hypothalamus and its neurotransmitters are controlled by higher cerebro-cortical centers which has been the subject of countless studies. To date Dr. Blizzard continues to be considered a world authority on psychosocial dwarfism or reversible hyposomatotropism.

Although currently known by young pediatric endocrinologists and academicians more for his work in the field of growth, he contributed significantly in other fields of endocrinology. In 1959 he initiated a study to determine aldosterone excretion in virilizing adrenal hyperplasia. He was the lead author of an article in the *Journal of Clinical Investigation* demonstrating that salt-losing congenital virilizing adrenal hyperplasia was due to decreased aldosterone secretion.

Between 1955 and 1980 Dr. Blizzard was a leading international investigator and authority on autoimmune endocrine diseases. He suggested that many endocrine diseases characterized by glandular atrophy, including adrenal insufficiency, hypoparathyroidism, premature ovarian failure, and insulin dependent diabetes mellitus were of autoimmune origin. He studied this model in his laboratory over the next 25 years and applied his

findings in the clinic setting which led to publications of 27 papers in peer-review journals.

In his laboratory with the assistance of Dr. Robert Chandler, he was one of the first investigators to demonstrate that Addison's disease was frequently of autoimmune origin and the first to elucidate the physical and biochemical characteristics of the antigens involved. In 1966 he reported that hypoparathyroidism was also related to antibody formation. In 1960 he had demonstrated that there was a high incidence of antibodies against thyroid microsomes and thyroglobulin in the serum of mothers of athyreotic cretins. Dr. Blizzard postulated that autoimmune thyroid disease in the pregnant woman might be the etiology of at least some cases of congenital athyreotic cretinism. At the Pediatric Endocrine Research Meetings in May 1987, Dr. Dussault of Canada presented confirmatory evidence of this hypothesis, and acknowledged that the concept and early data had been presented by Dr. Blizzard years previously.

In the early 1960's he proposed that some cases of insulin dependent diabetes mellitus were probably of autoimmune origin with destruction of the beta cells of the pancreas. This observation was based on his earlier papers reporting the associations of diabetes mellitus with Addison's disease and hypoparathyroidism. In 1961, he submitted a grant to the National Institutes of Health (NIH) proposing to study this concept. The grant was rejected stating that the concept was preposterous; subsequently it was demonstrated that indeed many patients with insulin dependent diabetes mellitus had antibodies to beta cells and the role of autoimmunity in insulin dependent diabetes mellitus was firmly established.

Even subsequent to 1979, when Dr. Blizzard was devoting the majority of his investigative time to problems of growth, he published major papers concerning autoimmunity. These papers further elucidated the associations of various types of autoimmune diseases, and particularly clarified the associations of the various types of polyglandular autoimmune adrenal disease with other endocrine disorders. At an international autoimmune conference held in Pisa, Italy, in 1979, Blizzard proposed a classification of polyglandular autoimmune diseases, which was accepted internationally and continues to be used today with only minor modifications.

Blizzard has recorded many other "firsts" in the field of pediatric endocrinology, including, with the collaboration of Dr. Ann Johanson and Dr. Harvey Guyda and other fellows, the elucidation of the intricacies of luteinizing hormone and follicle stimulating hormone secretion during childhood and puberty, and the abnormalities

found in sexual precocity. In his laboratory, along with Dr. Robert Penny, he demonstrated that gonadotropin levels were elevated in hypothyroid children who have associated sexual precocity. He reported with Dr. Johanson that patients with gonadal agenesis or Turner syndrome grew significantly when treated with anabolic agents.

Other firsts included a description and report of the Johanson-Blizzard syndrome of congenital anomalies in congenital hypothyroidism and a description of the syndrome of congenital adrenal cortical-unresponsiveness to ACTH with Dr. Claude Migeon. In addition, Dr. Blizzard actively contributed to and participated in the treatment and research of patients with central sexual precocity utilizing gonadotropin releasing hormone agonists (GHRHa) to block pubertal development. Dr. Blizzard was proud of his capability to work collegially and collaboratively with others to promote multicenter investigation. An example was his collaboration over several years with Dr. Paul Boepple, Dr. William Crowley, and others in Boston in studying the role of GnRH analogues.

In 1961, in association with Dr. Alfred Wilhelmi, Chairman of the Department of Biochemistry at Emory University, the National Pituitary Agency was established. The purpose of this agency was to collect human pituitaries at autopsy examination, extracting their hormones, and to distribute these hormones on a national basis for investigation and therapy. He organized this collection and distribution program under the auspices of the (NIH), and was the Director of the agency until 1967. Dr. Blizzard inspired and led a lay group of individuals to develop an organization of parents and others to assist in the collection of human

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pituitary glands. Their success led to the establishment of the Human Growth Foundation in 1965. The scope of this organization grew and eventually became a support source for families of children with growth disorders with chapters across the country and with an ability to fund research in the area of growth disorders. After the National Pituitary Agency and The Human Growth Foundation were firmly established, Dr. Blizzard was followed by Dr. Salvatore Raiti, one of his former fellows, as director. It was this program that led to, and made possible, all of the investigation pertaining to pituitary hormones that occurred in humans in the subsequent 24 years (1961-1985) before synthetic growth hormone became available.

In 1993 he was asked to establish the Genentech Foundation for Growth and Development, a grant awarding organization separate from Genentech Inc., with an independent board and decision making authority. In the 8 ½ years of its existence under his leadership this foundation provided more than \$18 million dollars in grants to clinical investigators, to basic science investigators, to physicians receiving training in the fields of growth and development, and to support professional and personal education of growth and development in these fields.

Discussing the many contributions of Dr. Blizzard to

pediatrics and to science is an easy and enjoyable endeavor, particularly because he always attempted to recognize the contributions of those with whom he worked professionally. Examples of his appreciation for professional collegiality and recognition are cited in the text above. A major professional colleague of Dr. Blizzard and contributor to the success of Growth, Genetics & Hormones for 19 years is Ms. Juanita Bishop, his trusted and dependable assistant of over 20 years.

Describing the human qualities of Dr. Blizzard also is an easy and enjoyable endeavor. He is an exceptional human being, and it is worth noting the comforting way he talked to his patients and families and his ability to put them at ease despite their difficult problems. He has a special skill to develop closeness with others lasting a lifetime, and to nourish and support his patients, students, fellows, and associates. This is what I and his other associates appreciate the most!

The cycle of life continues, with the publication of this issue Dr. Robert M. Blizzard has officially retired from the editorship of *GGH*. He has had a most prestigious and distinguished career with enough accomplishments for many lifetimes. He now plans to enjoy more time with his family. We anticipate he will continue that which he does best, inspiring and teaching. As he has thanked so many of us, we thank him for all!

Abstracts from the Literature

Screening Newborns for Inborn Errors of Metabolism by Tandem Mass Spectrometry

Newborn screening for inborn errors of metabolism has been in place in many countries for many years. Strong arguments have been made for screening not only for improving care of patients identified through screening, but also for reducing the cost of this care. Indeed, there are numerous examples, PKU most notably, of how early diagnosis and treatment have prevented serious illness or death from these disorders. However, as Wilcken and colleagues point out, formal evidence for the clinical effectiveness of screening is lacking, especially for rarer diseases, such as inborn errors of metabolism. Randomized, controlled trials of screening have been very limited because of the rarity of these disorders and also because of the strong conviction based on clinical experience that there is a benefit from early diagnosis.

Against this backdrop Wilcken et al compared the effectiveness screening for inborn errors of metabolism in all newborns with tandem mass spectrometry from 1998 to 2002 to conventional biochemical screening performed because of clinical suspicion from 1974 to 1998. The study population lived in New South Wales (Australia) and the Australian Capital Territory and totaled six million. Thirty-one disorders were selected for study. PKU and pterin disorders were excluded

because effective screening by other methods had been in place for many years; also excluded were disorders known to be benign or of maternal origin.

The diagnosis rates were reported in four-year brackets, i.e., 1974-1978, 1978-1982 ... 1998-2002, etc. During the six four-year periods preceding the implementation of tandem mass spectrometry screening, 22-34 cases were diagnosed per period giving rates from 6.6 to 9.0 cases per 100,000 births. Diagnoses were made at different ages depending on the age of clinical presentation. There were no trends toward increased overall rates of diagnosis between 1982 and 1998 even though some of the 31 disorders were first recognized during these periods.

Between 1998 and 2002, when all infants were tested between 48 and 72 hours after birth, 57 infants were diagnosed with one of the 31 inborn errors or 15.7 diagnoses per 100,000 births. Of these, 48 infants were diagnosed by screening, while six were diagnosed clinically before or at the same time as the screening result became available, usually within 24 hours of testing. Two patients, siblings with ornithine transcarbamylase deficiency born to a mother with known risk, did not undergo screening. Seven patients