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The history of the SIMD: From small molecules to metabolomics ☆

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Abstract

The Society for Inherited Metabolic Disorders (SIMD) recently completed its 28th annual meeting and requested that its birth and development be documented. Accordingly, this communication reviews the origins of the SIMD and considers its development over the past three decades. Each decade had growth and differentiation regarding policy making, international connections, highlights and tragedies. Past contributions are defined and future directions for the SIMD are subjected to prophesy.

Keywords: History; Society of Inherited Metabolic Disorders; SIMD

Introduction: the origins

The initiative to form a Society for Inherited Metabolic Disorders (SIMD) was traced to 1971 when the Food and Drug Administration (FDA) changed the classification of special formulas to treat disorders of amino acid metabolism from "drugs" to "foods for special dietary use" [1]. The FDA then contracted with the American Academy of Pediatrics to develop methods of implementing the necessary consultative human resources to diagnose, treat and consult on the use of these formulas and diets [2]. It became immediately apparent that there were limited number of "Metabolic" Physicians nationally and thus a subcommittee was formed from the Nutrition Committee of the Academy of Pediatrics to deal with "amino acid modified diets." This subcommittee was thorough, met three times annually and considered all aspects of nutritional therapy including industry, regulatory agencies, third party payers and professional staffing. Criteria for "Metabolic Centers" were established and National Centers were named (Table 1). These deliberations and those involved were published in 1976 [3,4]. Many members of that subcommittee of the AAP continued to lobby for and implement services, research and educational resources for inherited metabolic disorders. In many ways, support for newborn screening at a public health responsibility fulfilled today's paradigm for the discipline of medical genetics: presymptomatic screening, rapid follow-up, diagnosis, intervention and prevention of irreversible damage. Notable leaders during this gestational age of the SIMD were Donough O'Brien, Selma Snyderman and Charles Scriver.

The first decade

Through the pioneering efforts of Donough O'Brien and the naiveté of Skip Elsas, formalization of a Society was initiated at a meeting consisting of representatives of the Center Directors, FDA and formula industry. A follow-up meeting in San Francisco in 1977 established officers and bylaws that included Skip Elsas (President); Selma Snyderman (President Elect); Helen Berry (Secretary); Neil Buist (Treasurer) and three Directors-at-large: Harvey Levy, Rodney Howell and Donough O'Brien. The first official meeting was scheduled for Copper Mountain in 1978 and its first scientific program was organized by a young, postdoctoral fellow working with Steve Goodman in Denver, Ed McCabe. The first scientific presentations focused on small molecules, amino acids in particular and on efficacy

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Table 1

The Origins: 1972-1976

The First Metabolic Centers

George Donnell, M.D. California	Bob Ulstrom, M.D. Minnesota
Charles Scriver, M.D. Canada	Morey Haymond, M.D. and Richard Hillman, M.D. Missouri
Paul Wong, M.D. Chicago	Selma Snyderman, M.D. New York
Steve Goodman, M.D. Colorado	Charles Wharton, M.D. and Helen Berry, Ph.D. Ohio
Carol Shear, M.D. Florida (Miami)	J. R. Seeley, M.D. Oklahoma
OwenRennert, M.D. Florida (Gainesville)	Neil Buist, M.D. Oregon
Skip Elsas, M.D. Georgia	AndyDiGeorge, M.D. Pennsylvania
Joe Schulman, M.D. Maryland (Bethesda)	Rod Howell, M.D. Texas
Neil Holtzman, MD. Maryland	Peter Mamunes, M.D. Virginia
Harvey Levy, M.D. Massachusetts	Ron Scott, M.D. Washington
Richard Allen, M.D. Michigan	Stan Berlow, M.D. Wisconsin

of presymptomatic screening, dietary interventions and cognitive outcome. Vitamin dependency and the use of pharmacological doses of vitamin precursors for active cofactors were discussed such as B12, thiamin, biopterin and biotin for treatment in methylmalonic aciduria, Maple Syrup Urine Disease, Phenylketonuria and carboxylase deficiencies, respectively. The bylaws were submitted to the Internal Revenue Service and the SIMD was formally recognized under section 501 (C) (3) of the Internal Revenue Code as requested and signed by Neil Buist, Skip Elsas, Helen Berry and Rod Howell [5]. During the first decade, the Society was "restrictive" in membership. Charter members were comprised of previously designated Metabolic Center Directors and active investigators were invited by charter members (Table 1). There was considerable discussion among membership and other colleagues studying inherited metabolic disorders about this exclusionary origin and it was removed as the SIMD developed. The SIMD would foster six objectives through annual meetings and continued internal communication through its members (Table 2). The first decade laid the groundwork for the present day Society by maintaining a focus on both clinical and scientific advances and by generalizing from "inborn errors" to "inherited metabolic disorders," thus incorporating molecular genetics and protein structure–function relationships into the traditional Garrodian themes of blocked metabolic pathways. Scientific highlights in the first decade included emerging methods of quantifying analytes by ion exchange chromatography, gas chromatography coupled to mass spectrometry and high-performance liquid chromatography. Genes were cloned using the "forward" genetics format by isolating and sequencing the protein followed by cloning genes from cDNA and genomic libraries. Toward the end of the first decade, the polymerase chain reaction amplification of specific genes and mutations came into use and genotype, phenotype relations to disease expression were discussed. Collaborations were established to share in protocols and cell strains from scarce patients with rare disorders on a National basis.

In the first decade, most members were academicians assigned to Divisions or Sections of Genetics in Departments of Pediatrics (Table 3). Because the origins involved nutritional management of inherited metabolic diseases, academic nutritionists were important members of the SIMD and this traditional relationship continues to date. An exemplary center for this first decade is in Fig. 1. The Division of Medical Genetics, Department of Pediatrics, Emory University is pictured in 1980 and included clinicians, laboratorians, post-doctoral fellows and doctorate nutritionists with their RD trainees (Fig. 1).

During this first decade an interest in aligning the SIMD with international colleagues began and continues to date (Table 4). Funds were raised from NIH through grant proposals and were funded from NICHD and NIDDK. The first formal international meeting that involved the SIMD took place in Interlaken, Switzerland in 1980 where the Society for Inborn Errors of Metabolism (Britain), the European Society for Inherited Diseases and representatives from Japan, Saudi Arabia and Australia met and later formed societies in their respective countries. The International Congress for Inborn Errors of Metabolism (ICIEM) was established from participants. Consequent to this meeting, the SIMD was to host a future meeting that took place in Asilomar, CA, USA in 1990. Bob Desnick planned an outstanding scientific event for this fifth ICIEM (Table 4). Novel scientific topics concerning impaired protein targeting to subcellular organelles such as the peroxisome

Table 2

Primary Objectives of the SIMD

1. To increase knowledge of human physiology and biochemistry by the investigation of epidemiology, etiology, metabolism, pathogenesis, and prevention of conditions in humans which arise because of inherited defects in body chemistry collectively designated as inherited metabolic disorders.
2. To promote research in inherited metabolic disorders.
3. To bring into closer contact, investigators in the many general fields which involve inherited metabolic disorders.
4. To promote technological and therapeutic advances for effective detection, care and prevention of inherited metabolic disorders.
5. To maintain a core of qualified investigators and practitioners in the field of inherited metabolic disorders.
6. To promote public understanding of inherited metabolic disorders.

Table 3

SIMD MEETINGS AND PRESIDENTS

The First Decade

YEAR	PLACE	NAME
1978	Copper Mountain	Elsas
1979	Asilomar	Elsas
1980	Captiva	Snyderman
1981	Arkadelphia	O'Brien
1982	Asilomar	Howell
1983	Williamsburg	Hillman
1984	Mexico	Levy
1985	Asilomar	Goodman
1986	Charleston	Cederbaum
1987	Woodlands	Shapiro

Fig. 1. The Division of Medical Genetics, Department of Pediatrics, Emory University, ca. 1980. Some SIMD members include, first row, left to right: Dr. Paul Fernhoff (first), Dr. "Skip" Elsas (third), Dr. Phil Dembure (fourth), Dr. Dwain Blackston (fifth), Dr. Wilma Krause (sixth) and Dr. Jean Priest (seventh). Second row, peeking out behind Dr. Elsas is Dr. Phyllis Acosta with two of her nutritionists-in-training (Miss Margaret Halminski, front row second and Miss Mary Naglak fourth row, center). Also in photo is Dr. Dean Danner, fourth from right (second row).

Table 4

SIMD GOES INTERNATIONAL WITH THE INTERNATIONAL CONGRESSES FOR INBORN ERRORS OF METABOLISM (ICIEM)

Meeting date	Country	Host
1977	Israel	DeVries
1980 *	Interlaken	Aebi
1984	Munich	Zollner
1987	Sendai	Tada
1990	Asilomar	Desnick
1994	Milano	Giovannini
1997	Vienna	Widham
2000	Cambridge	Fowler
2003	Sydney	Wilcken
2006	Tokyo	Eto
2009	San Diego	TBA

*Our first NIH funded travel

and mitochondria were presented for the first time. The mitochondrial genome, maternal inheritance and an array of inborn errors of oxidative phosphorylation were defined from mutations in mitochondrial DNA. Progress in enzyme replacement therapy and gene therapy were summarized [6]. In addition, satellite conferences were held on "Treatment of Genetic Diseases" and on "Selected Problems in Newborn Screening" both held sequentially in San Francisco, CA, USA. As can be seen in Table 4, this pivotal, hosted congress laid the groundwork for future international meetings and provided some capital for future SIMD development. The SIMD will once again host an international meeting in San Diego in 2009.

The second decade

The second decade saw an ever-broadening definition of "Inherited Metabolic Disease," international visibility and multidisciplinary membership (Table 5). Membership became "inclusionary" and the members became more involved with public policy. Asilomar remained the most favored place for meetings and the SIMD held some of its annual meetings in conjunction with the ICIEM. Notable joint sessions were accomplished in Milan, Mexico and Vienna. The Society was involved with national, political and social issues and members spearheaded and supported the Orphan Disease Act, the National Organization for Rare Diseases, and expanded newborn screening with the genetics section of HRSA's Maternal and Child Health Agency. Members helped the American College of Medical Genetics develop CPT codes for services in biochemical genetics and wrote a wide range of position statements.

One major highlight in the second decade was the offer and acceptance by Ed McCabe and the SIMD for his journal, Molecular Genetics and Medicine as the official journal of the SIMD. Over the next decade and into the future, this journal has and will publish the social, scientific and political activities of the SIMD. The expanding scientific ideas of

Table 5

SIMD MEETINGS AND PRESIDENTS

The Second Decade

YEAR	PLACE	NAME
1988	Asilomar	Valle
1989	Orlando	Scott
1990	Asilomar	Desnick
1991	Santa-Fe	H. Berry
1992	Callaway Gardens	Sweetman
1993	Asilomar	Shih
1994	Milan	Kerr
1995	Perdido Beach	Gahl
1996	Mexico	Batshaw
1997	Vienna	Rosenblatt

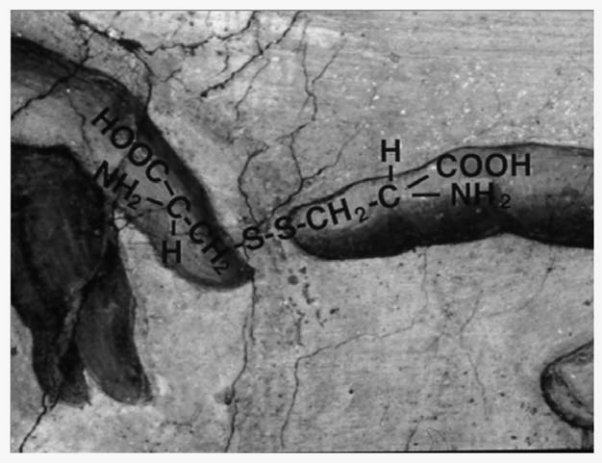

Fig. 2. The Cystine Chapel. Depicting the transition of thought and scientific interest from small molecules to the totality of protein function in humans. From reference [7].

Fig. 3. Members and presidents of the SIMD from its origins to present day. Left to right, Greg Grabowski, Neil Buist, Donough O'Brien, Parvin Justice (Front), Harvey Levy (Behind), Steve Goodman, Ron Scott, Greta Seashore, Selma Snyderman, Steve Cederbaum, Mendel Tuchman, Lew Barness (Front), Jean-Marie Sandubray (Behind), Phyllis Acosta (Front) and Tony Velazquez.

the SIMD membership were quixotically viewed by Bill Gahl in Fig. 2. Its beginnings were constituted by centers for diagnosing and managing small molecules accumulated in the presence of classic Garrodian errors of metabolism (such as cystinuria). The Society was now involved in the genetic control of macromolecular functions as well. Topics of interest included protein trafficking to subcellular organelles and their assembly (peroxisomes, mitochondrial OXPHOS complexes and lysosomes) as well as endocytosis, regulation of degradative processes of proteins and cellular signaling. This figure depicts cystine, a small classical molecule, whose impaired membrane transport by epithelial cells ignited Garrod's thought processes. A century later lysosomal storage of cystine was recognized and lead to an understanding of its efflux from lysosomes [7] (Fig. 3).

Although comparing the origins of the SIMD to creation of man is admittedly grandiose, our society progressed from its origins to encompass the assembly and function of subcellular organelles and prepared for research on the molecular effects of variations in whole cell metabolism in the post-genomic era.

The present decade

The third decade saw expansion of the SIMD membership, rapidly increasing interest in intermediary metabolism in a post-genomic era and financial stability for the society (Table 6). Asilomar remained the most popular meeting place, and is searching for increased space to accommodate the growing membership. From 1999 to 2004, membership climbed from 192 to 342 [8]. This 43% growth now includes 285 members with doctoral degrees (M.D. or Ph.D.), 15 non-doctoral; 15 from developing nations; 22 with emeritus status and 5 post-doctoral trainees.

The SIMD's financial stability is seen by comparing the Treasurer's financial statement over the past decades. In 1978, the annual budget was $3359.03 and in 1979, $8152.72. These sums were raised primarily from dues and minor support from the nutritional industry. There were "no costs" during the first decade according to Treasurer, Neil Buist because all functions of the SIMD were "volunteered" or "pay-as-you-go" to meetings. Although the "pay-as-you-go" concept persisted for meetings, the SIMD now has significant savings and interest to support executive personnel, awards for science, student travel, a website and liability insurance for its board members. According to last year's Treasurer's report, the SIMD had approximately $217,000 in capital savings.

Scientific highlights in this third decade included the use of new methods for comparative microarray analysis at the genome, transcriptome and proteome levels. "Discovery-driven" science was not immediately acceptable to the hypothesis-driven membership of the SIMD. However, as linkage association developed new candidate genes for metabolic systems, interest was kindled. More progress was made in the arena of practical diagnostics including the use of tandem mass spectroscopy to expand public health-related, newborn screening to over 40 defined disorders of

Table 6

SIMD MEETINGS AND PRESIDENTS

The Third Decade

YEAR	PLACE	NAME
1998	Asilomar	Seashore
1999	Lanier	Grabowski
2000	Cambridge	Buist
2001	Miami	Buist
2002	Asilomar	Velazquez
2003	Australia	Velazquez
2004	Orlando	Tuchman
2005	Asilomar	Tuchman
2006		

metabolism. There was some conflict with members and friends from public health departments over the delay to incorporate this new technology into public health-based newborn screening.

Tragedy punctuated the new genomic era. The death of Jessie Gelsinger during gene therapy for ornithine transcarbamoylase deficiency placed the SIMD in mourning. All members of the SIMD as well as other scientists involved in human research were impacted by the tragedy of the death of a young volunteer. The aftermath resulted in cessation of human research in gene therapy, pending fundamental experiments to find better vectors and proof of efficacy in experiments involving large animal models. Despite this major setback, clinically oriented SIMD members progressed with other research approaches for therapy.

Stem cell transplantation for progressive neurodegenerative metabolic disorders continued [9]. The concept was published of chemical chaperones to alter aberrant folding of mutant proteins [10]. Inhibitors of metabolic pathways came to clinical trials to reduce accumulation of pathologic substrates that injured the brain [11] or provoked hepatocarcinoma [12]. The use of small molecules to provide alternate pathways was studied in urea cycle patients [13] and homocystinuria [14]. Transplantation of liver, kidney and hematopoetic stem cells were implemented and the outcome of these approaches to therapy will be the subject for future SIMD meetings.

The future

Under its current visionary guidance, the SIMD is positioned to lead in the post-genomic era and will progress into systems biology. Eight meetings have been accomplished (Table 6). However, the SIMD recognizes that extraordinary effort is required to define all of the interacting functions of genome transcription, translation and post-translational regulation. Those metabolic pathways defined in humans with evolutionary conservation will use model systems for research into systems biology [15–17].

The concept and knowledge will continue such that rare, inherited metabolic disorders offer windows of opportunity to understand how the cell and organism survive after perturbation by returning to homeostasis. The yeast is one model system in which this research approach to "metabolomics" was initiated for the human disease, galactosemia [15–17]. Each evolutionary-conserved step in the galactose metabolic pathway was blocked genetically and the effects of this single gene impairment on the organism's transcription and translation were studied [17]. This Herculean "discovery-driven" science, though impressive still required previously published, focused efforts by SIMD members for interpretation where microarray methodology was associated with biochemical analysis of involved analytes. Using hypotheses derived from comparative microarrays and clinical and laboratory observations, at least one patho-physiological mechanism was supported [15,16]. As these approaches are applied to other inherited metabolic disorders, new signaling pathways will be discovered and novel approaches to intervention will be applied. The SIMD will continue to provide leadership in service, education and research into disorders of metabolism as our interest and technological capabilities expand to systems biology or "metabolomics" of the whole cell and organism.

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