Editorial

The Days of Our Age: The American Journal of Medical Genetics in the Next Millenium

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"The days of our age are three score years and ten; and though men be so strong that they come to fourscore years; yet is their strength then but labour and sorrow; so soon passeth it away, and we are gone."

"So teach us to number our days: that we may apply our hearts unto wisdom"

Book of Common Prayer, 1662

'ERE WE ARE GONE

Prudence and common sense demand that an enterprise as complex and important as the *American Journal of Medical Genetics* be treated with the same care and respect as the health of a child, family or nation. The extraordinarily beautiful language of the Book of Common Prayer reminds us that our time is limited and our days are numbered. In the German Requiem Brahms paraphrased Ps 39:5–8 based on Luther's sonorous translation:

Herr, lehre doch mich,
Dass ein Ende mit mir haben muss,
Und mein Leben ein Ziel hat,
Und ich davon muss.
Siehe, meine Tage sind
Einer Hand breit vor Dir,
Und mein Leben ist wie nichts vor Dir"

[Lord, make it plain to me, That I must have an end And my life a purpose Before I am gone, Behold, my days are only as a width of hand before you, and my life as nothing before you.]

And as one much closer to threescore years and ten than to birth I have been anxious to assure a strong and successful future for the *American Journal of Medical Genetics* in concert with Colette Bean, Joe Ingram and Brian Crawford of Wiley-Liss, the members of the editorial board, and my colleagues at the University of Utah-foremost Professor Edward B. Clark, Chairman of the Department of Pediatrics, and Drs. John C. Carey and David H. Viskochil of its Division of Medical Genetics. A specific major concern has been my succession as editor, but more importantly the future of the Journal at a time of rapid, dramatic change in ge-

netic medicine and of major concerns about the entire publishing enterprise in biology.

As editor of this Journal for almost 23 years I have no intention of setting records of longevity in this job, only to maintain standards of quality until it is time to hand on the responsibility to someone else. Thus, I am retiring as editor at the end of the year 2000 together with the class 2000 editorial board members. Nominations for the class 2001 editorial board were solicited at the last editorial board meeting in San Francisco in October of last year and will be confirmed and announced later this year together with the new editor.

Thus, it seems appropriate, especially for one with a strong interest in the history of causal morphology and genetics, to take a brief look at our beginnings in order to attempt a look at the future.

BEGINNINGS

At a meeting in 1976, I was approached by a gentleman who introduced himself as the publisher Alan R. Liss of New York and who asked if I might be interested in editing a journal on medical genetics. Having proposed to do so on a prior occasion but running into considerable skepticism regarding the wisdom and need for such an enterprise from my colleagues in the field I thought I needed some time to reconsider, but promised Alan that I'd meet with him later in the year at the occasion of an NIH Study Section meeting to come to a conclusion, and to make plans in case we came to a meeting of minds. When the time for the NIH meeting arrived Alan and I agreed that we would meet that night in the lobby of my Bethesda Hotel to continue discussions over supper. My plane from Madison was late, but the taxi driver, newly arrived from Morocco, assured me he'd get me there avec toute vitesse. When we crossed a Potomac bridge for the third time with a full moon to my right it became clear to me that he was more lost than I. Finally arriving long after midnight, I found Alan soundly asleep in an armchair in the lobby. We found a diner open and on settling down for a truly wretched, cold meal Alan assured me about the reactions of my colleagues, several of whom having even "fingered" me to be editor. We sealed the deal and on March 23, 1977, we received our first manuscript by Kenneth M. Taylor, Uta Francke, Michael G. Brown, Donna L. George, and Marilyn Kaufhold of San Diego on "Inverted tandem ('mirror') duplications in human chromosomes: inv dup 8p, 4q, 22q"

which was published as paper number 1 in issue 1, volume 1, in 1977. That year saw the publication, in the old small format, with unjustified right margin of only 4 issues in one volume, a total of 480 pp. In 2000, with the new page format in place since 1989, we will publish, in the main journal, 6 volumes with 30 issues of 100 pp each, with one volume allotted to *Neuropsychi*atric Genetics (6 issues of 130 pp each) and another volume allotted to Seminars in Medical Genetics (4 issues of 64 pp each) for a total page budget of 4,036 for the year. In 1977, we received 77 manuscripts; in 1999, we anticipate around 900. In 1977, we rejected 17% of manuscripts; in 1999, probably 30%. Then as now, we asked two reviewers to go over each manuscript with care; however, with a smaller number of manuscripts we could afford to send out each for review, a luxury not possible anymore, a time when constraints on availability and energy of reviewers mandates pre-review of manuscripts to eliminate those with the lowest probability of acceptance. Other journals have had to adopt a similar practice.

THEN AND NOW

Far from being outdated stuff the contents of volume 1 make for fascinating reading and in fact allow the discernment of very important trends, and indicators of future directions.

Chromosome anomalies and the developmental effects of aneuploidy, inborn errors, segregating mendelian traits, syndrome delineation, prenatal diagnosis, mental retardation and syndromology were the dominant themes then and remain of central importance in medical genetics today.

Uta Francke, then still in San Diego, now at Stanford and President of the American Society of Human Genetics, wrote on inverted tandem duplications, the one of 8p remaining one of the commonest of these arrangements seen in mentally retarded individuals with multiple minor anomalies. We also accepted papers on the trisomy 4p syndrome, the risk of duplications in pericentric inversions, an unstable i(Yq), X/autosome translocations and isodicentric X chromosomes in the Ullrich-Turner syndrome.

Jürgen Spranger, recently retired as chair of Pediatrics in Mainz and as Editor-in-Chief of the European Journal of Pediatrics, defined mucolipidosis I as a sialidosis, Thad Kelly defining isolated neuraminidase deficiency as a lysosomal strorage disease; Charles Scriver, the distinguished senior editor of the Metabolic and Molecular Bases of Inherited Disease, defined hypophosphatemic nonrachitic bone diseases as an entity distinct from X-linked hypophosphatemia; Arbisser et al. delineated β-galactosidase deficiency; Montreal scientists reported on liver transplantation in Niemann-Pick disease Type A, and Len Pinsky and his coworkers analyzed 5α -reductase activity in male pseudohermaphrodites.

To pick only two papers on segregating mendelian traits, I'll mention the one by Riccardi et al. on the FG syndrome without embarrassment since I'm not a coauthor; the importance of this entity then considered rare and severe as one of the commonest of syndromes

in pediatric genetics is only now becoming apparent and is at the center of several intense research programs in the US and in Europe. The other is the still classic paper by Annemarie Sommer and her coworkers from Columbus, OH on the familial transmission of the Wiedemann-Beckwith syndrome through women, then interpreted as evidence for premutation, but now understood in terms of imprinting.

Also in Volume 1, Renata Laxová, my distinguished successor in Madison, published her beautiful paper on the causal analysis of severe mental retardation, an issue recently re-visited in the pages of this Journal by Cyndy Curry and a large committee of the American College of Medical Genetics, and by John Carey and Agatino Battaglia in ongoing collaborative studies in Pisa.

Judy Hall, then still in Seattle, but presently chair of Pediatrics in Vancouver, and her coworkers, published an influential and widely quoted study on the frequency and financial burden of genetic disease in a pediatric hospital, a study I was still quoting in the Montana legislature in support for requests for funding of the Montana Genetics Program a few years ago. Her conclusion, then considered quite radical, that only 46.6% of kids in such a Children's Hospital had nongenetic disorders, is, in light of more recent insights, an overestimate but an important early indicator as to the massive burden of genetically caused and predisposed disease in childhood years.

Len Pinsky's struggles with the syndromology of anorectral malformations and attempts, causally and pathogenetically to understand "associations" (pp. 461 ff) are as timely today as then. In continuing that line of thinking and analysis María-Luísa Martínez-Frías of Madrid and her coworkers have published severally in these pages using effectively an epidemiological approach to these problems.

The latest number of the Journal before me as I write is the last issue in Volume 86 published October 29, 1999. The cover is still blue and the focus is still medical, with papers on clinical aspects of known entities, prenatal diagnosis, cytogenetics abnormalities, metabolic disease, syndrome delineation, and genetic counseling, but with all signs of the intervening molecular revolution amply in evidence in papers on spinal muscular atrophy, SCN5A mutations in long QT syndrome, PABP2 mutations in Cajuns with oculopharyngeal muscular dystrophy, CALL gene haploinsufficiency in 3p-syndrome, and the high frequency of 167delT mutations in the connexin 26 gene in Ashkenazim with deafness.

This issue also manifests one of the strengths of the Journal which I hope it will retain in the future, namely of being a forum for the best of phenotype analysis (a science greatly denigrated by granting agencies over the last 50 years) and genotype—phenotype correlation, now belatedly recognized as of central importance in medical genetics as we struggle in our attempts to relate the tens of thousands of mutations possible and actually observed in humans to the very limited repertoire of developmental consequences imposed during evolution on higher metazoans.

STYLE AND SUBSTANCE

Over the years, this Journal has made a valiant and not always successful effort to foster and maintain certain rudiments of style, clarity and good writing against a rapidly increasing onslaught of professional jargon and technical obscurity which at times suggests pride in purposeful obfuscation.

What many of our coworkers in the field acknowledge cursorily without fully understanding is the impact of another revolution occurring in concert with the molecular one. What I am referring to is the Webinformation revolution responsible for the phenomenon of the cyberpatient (as it was called aptly by Bonnie Pagon) which frequently makes the patient/parent much better informed about a given condition than the consultant physician and has re-equilibrated the diagnostic process toward greater equality of, respect for, and involvement by patients/parents. These cyberpatients(-families) frequently arrive in the clinic with our published papers easily found though the internet and may ask embarrassing questions about meaning we left unclear, interpretations we omitted or implications we thought obvious. We owe it to our patients, colleagues, students and to ourselves to write clearly, correctly and succinctly with the absolute minimum of technical detail in text or appendix necessary to document materials, methods and results, making it our stylistic ideal to be understood unambiguously by the intelligent, educated lay person, an ideal already championed by Buffon in the late 1700s while writing the *Histoire Naturelle*. There is another important reason for considering or adopting this approach. In volume 1 the only foreign countries represented (besides Canada) were Germany and Switzerland. In 1998 and 1999 we received manuscripts from 52 foreign countries (excluding the UK, Ireland, Canada and Australia) and I understand that the Journal is read in many more. And as I have heard many times on my peregrinations through various parts of the world, the Journal is read not only for information, but also for style by scientists, scholars and physicians learning how to write a paper in English with a high likelihood of acceptance in our or any other editorial office. Thus, in this sense, the American Journal of Medical Genetics has had a very important teaching function. Also with respect to style patients and parents have told me time and again that necessary scholarly objectivity should not strive to be disrespectful or demeaning to the patients or persons described in our reports. I have been told, rightly so, that our use of certain adjectives is perceived as insulting; hence, I strike "male," "female" (as nouns) and replace with man, woman, boy, girl, as appropriate, etc. Objectivity in style does not mandate insensitivity, gracelessness, or a lack of humane concern.

However, beyond these obvious issues of stylistic aptness and grace, I am additionally concerned about a deeper, widespread and apparently unconscious epistemological ignorance or obtuseness which probably reflects our massive national cultural confusion between science and religion, the former functioning on the basis of skepsis, the latter by faith. When asked, many

authors really mean it when they state: We believe . . . " (e.g. this chromosome breaks disrupted gene X), when in fact science dictates another vocabulary, namely "we conclude . . . we infer . . . we interpret the data to suggest", etc. Other manifestations of this epistemological malaise are ways of speaking and writing which have become normal clinical argot by virtue of aping others with "authority" appearing to know what they are talking about: "Genitourinary exam is normal female". "Babinsky is negative", "family history is negative", etc, etc.

Hence, I have edited over the years (albeit not consistently successfully) in the firm conviction that avoidance of such degeneracy in style and confusion in epistemology aids clear thinking and makes a paper not just worthwhile, but a pleasure to read. Early on I was inspired by such masters of style in our field as Tony Murphy and Larry Karp whose manuscripts, as I recall, were among the very few in which I did not need to "fix" a single comma or split infinitive.

THE FUTURE

Appropriately so, the future of the American Journal of Medical Genetics is not in my hands. However, the startling similarity in themes between the oldest and the most recent of Journal issues noted above indicates a certain direction, focus and tradition of forum which my successor may consider an asset. These themes are: syndrome delineation and syndrome definition; nosology; pleiotropy (Plate, 1910); gene action in function and development—normal and abnormal; heterogeneity; modifications of gene action; allelic and non-allelic epistasis (Bateson, 1907); the epigenetic nature of development; genetic dissection of common complex, "multifactorial" disorders; the relationship between development and evolution; and the ethical, social, cultural, and historical aspects of our work.

In any event, extensive deliberations during 1999 by publisher, editor, editorial staff, editorial board members and Dr. Clark of the Department of Pediatrics at the University of Utah, worked out an approach towards the successful continuation, growth and function of the Journal as follows.

As of January 1, 2000, Dr. John C. Carey is appointed co-editor with opportunity of continuing as sole editor-in-chief (or as editor with co-editor) as of January 1, 2001 or of turning the responsibility over to a carefully selected successor should that be a mutually agreed-on desideratum. The editorial hub of the Journal will be in Salt Lake City with its editorial office connected electronically to the offices in New York and those of the Associate Editors who will be the hands-on daily decision makers working closely with the editor(s) and editorial staff in Utah. All manuscripts will be submitted as hard copy and as disc to the main office, posted via internet the day of receipt to the Associate Editors who will either accept editorial responsibility for the manuscript or suggest reviewers to the editor. If an Associate Editor accepts responsibility for a given manuscript, he/she will forward expeditiously

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recommendations on acceptance/non-acceptance and suggestions for revision to the main office in Utah where all manuscripts will be edited. Editor and Associate Editors will have the benefit of advice and guidance from a distinguished group of Advisory Editors some of whom have guided the Journal from its beginnings. The editorial board has been metamorphosed into a small group of very active collaborators who will review in a timely manner a minimum of 20 manuscripts per year, will submit some of their best work and that of their students and coworkers to the Journal, write an occasional editorial or contribution to the Seminars in Medical Genetics and will solicit submissions of first-class material from colleagues for the Journal. These members of the Editorial Board serve staggered 1-5 year terms with possibility of reappointment as such on mutual agreement. Dr. Clark has accepted appointment as an Advisory Editor and has expressed strongest support for the Journal through the University of Utah; in fact a future faculty member of the Department of Pediatrics may be appointed with a specific (part-time) supportive or coeditor role vis-a-vis the Journal.

VALE ET GRATIAS AGO

I am also not the one to allot my remaining days, but am extremely conscious of the need "to number" my days so as to apply my heart (and mind) increasingly "unto wisdom." I am very glad that now I may leave without regret and without hesitation about the future of the Journal. In doing so I am conscious of the language from the Latin version of the preface to the mass, "Vere dignum et justum est, aequum et salutare nos tibi semper et ubique gratias agere..." [It is just indeed and fitting, right and for our lasting good, that we should always and everwhere give thanks . . . "], and of my need to express my deep gratitude to the many friends, colleagues and coworkers who have had such a massive effect on the quality of the science and scholarship in this Journal, who helped shape it and confirmed it in its unique role, who have reviewed and helped in handling the thousands of manuscripts we have received between 1977 and now, and who have produced each issue and gotten it to readers and subscribers on time. This includes:

- The publishers: beginning with Alan Liss and including Eric Swanson, Brian Crawford, Joe Ingram, Colette Bean and the production editors in the New York offices, latest and most spectacularly Swapna Padhye and Joe Gill;
- The Associate Editors: beginning with Jürgen Herrmann of Milwaukee, a virtual co-founder of the Journal, and including Jim Reynolds and John Johnson of Helena, Giovanni Neri of Rome, Norio Niikawa of Nagasaki, Terry Hassold at Case Western Reserve University in Cleveland, John Carey and Dave Viskochil of Salt Lake City;
- The Senior, Section and Special Features Editors: particularly Ming T. Tsuang and Stephen Faraone, who have made the section on Neuropsychiatric Genetics such a spectacular success;
- The three hard working Assistant Editors who have

- born the daily frontline brunt of "running" the Journal and the editorial office devotedly and effectively for 22 years, they are LaVelle M. Spano of Helena, and David Kirkpatrick and Shauna Huffaker of Salt Lake City.
- All former and present members of the Editorial Board, some of whom have served for many years, but with all providing the service, help and advice without which no Journal can operate for long, retiring members being recognized for the first time by the awarding of a special certificate of appreciation beautifully designed by Brennan Travis in Colette Bean's office. The retiring editorial board members are:

Ségolène Aymé Gideon Bach Christos Bartsocas Kurt Benirschke Keith R. Benson Suzanne B. Cassidy Eduardo E. Castilla Andrew E. Czeizel Gian-Antonio Danieli Vazken M. Der Kaloustian Robert J. Desnick Harry C. Dietz Sherman Elias Robert C. Elston Beverly S. Emmanual Mark I. Evans Andreas Gal George S. Gericke Richard Gitzelmann Thomas W. Glover Michael R. Hayden Wolfgang Holzgreve Rhiannon Mary Hughes-Benzie Alasdair G.W. Hunter Laird G. Jackson Eric Juengst Helena Kääriänen Bruce Kovacs Cyril Legum Fredrick P. Li R. Brian Lowry Losif W. Lurie Henry T. Lynch Cynthia Morton Steven A. Narod Norman C. Nevin Leena Peltonen Lothar Pelz Eugene Pergament Jean H. Priest Antonio Richieri-Costa Havnes B. Robinson Wendy P. Robinson Stuart Schwartz Christine E. Seidman Mary J. Seller

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Charles F. Sing M. Anne Spence Louise C. Strong Lisbeth Tranebjaerg Catherine Turleau Margot I. Van Allen Daniel L. Van Dyke Kenneth Ward Stephen Warren Benjamin S. Wilfond Orsetta Zuffardi

- All reviewers whose knowledge, wisdom and integrity is the sine qua non of any peer-reviewed journal and the cornerstone of the peer-review process; and, last but not least.
- The authors whose work fills each issue, who gener-

ate new and review and revise old knowledge, facts, and data, and who, on the whole, strive very hard to comply with the editorial process knowing that virtually every manuscript can be improved once more upon submission for peer review. Your continued support and efforts to submit your best will guarantee the future success of the *American Journal of Medical Genetics*.

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