Editorial

The first years of Indian Journal of Endocrinology and Metabolism

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The *Indian Journal of Endocrinology and Metabolism* finally came into being suddenly and without warning. One winter evening at the Annual Conference of the Society in Lucknow, I was asked, "Will you take it up?" "Yes", I replied, and so it began. The swift decision, verbalized by Prof RV Jayakumar (Quilon), Prof Kannan (Madurai) and Prof MV Muralieedharan (Thrissur) on behalf of members of the Endocrine Society of India ended in an anti-climax to long years of careful planning, thought and discussion, and with a substantial body of science in the form of unpublished manuscripts that lay ready for publication. It reminds one of the opening sentences from Goldsmith's "Vicar of Wakefield" in days when England needed more people than it had; Goldsmith marks the beginning of his novel with the words: "I was ever of opinion that the honest man who married and brought up a large family did more service than he who continued single and only talked of population".

With committed endocrinologists who have been publishing for years all over the world in prestigious journals deciding to stand behind the Society's own Journal, it was an auspicious beginning. Sure enough, the first set of manuscripts was received in order by registered post.

Publishing a Journal appeared much more sophisticated than my tryst with publication, which began in the mid 1980s. The hard copies of the articles for RSSDI's "*Diabetes Bulletin*" were delivered at the press at Delhi's South Extension. Pages were laboriously laid out in letter press, and the proofs provided in a couple of days. A couple of iterations later, the final copies were okayed.

Not the old days of letter press; with MS Word and Page Maker, all one had to do was key in the text, give it to the press, where it was swiftly composed and returned for proof-reading. It all seemed so advanced in the pre-email days. I only had to sit down at the end of day's work with a sheaf of papers, enter the text on my PC at the office, and go with the floppy to the press.

In the early days, the officials at the local post office courteously but firmly refused to accept the 450 or so envelopes containing the Journal for mailing the members. There were ways to overcome such obstacles though. Within a couple of issues, I was conversant with the geographical location of postboxes dotting the city. Carrying the journals in batches of 15 or 20, I would deposit them all over the town's postboxes.

For those of you who want to look at the early efforts, the present Editor and the Secretary had the Journal issues archived and uploaded at www.ijem.in.

The current online manuscript submission system has taken away a lot of tedium and perhaps some of the excitement of early days. More importantly, members submitted their manuscripts, although there was an unsaid yearning, "If only the Journal were indexed" in PubMed.

Presence of IJEM in PubMed is one of the outstanding accomplishments of the Journal. Appearance in PubMed and online submission system, I reckon, is flooding the current editor with manuscripts from all over the world. Such is the power of visibility and the open-access no-processing fees policy being followed by the Society.

The 2000 edition of the Journal was christened "Vision 2000".[1] In the first signed editorial, I prophesied the Human

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Genome Project (HGP) would transform endocrinology from a descriptive science to a systems biology enterprise. I must have hedged the prophesy with Maddox's words, "The most important discoveries of the next 50 years are likely to be ones of which we cannot now even conceive".

It is not 50 years yet since the Vision 2000 issue. What do we find now, 10 years into the HGP? Without doubt, there are few more spectacular events then HGP in terms of science, technology, ethics and hype. It was the biological equivalent of man landing on the moon. It brought together disparate fields together to find biological answers, and thereafter translational results in clinical medicine. Its progress has been spectacular: the budget for the original HGP was more than $3 billion dollars, it took 10 years and involved thousands of scientists the world over. Technology has advanced and the price has plummeted; one can now sequence a human genome in about a week at a cost of $10,000. The next aim is to be able to sequence a genome for under $1000.

Endocrine Society (USA) was one of the first medical disciplines to foresee the revolution the results of HGP would unfold when it organized the first Hot Topics symposium in 2001 at New Orleans.[2] The Endocrine Reviews carried a special feature on what HGP could be expected to do to the field of endocrine sciences.

Diabetes mellitus, which sits at the interface between lifestyle and genetics, is a prototype for studying the genomics of common diseases: it had been the prima donna at the four annual conferences, "Genomics of common diseases", alternately held at Hinxton UK and in USA jointly by the Wellcome Trust and Nature Genetics. From identifying putative genes to pathway analysis, the tenor and theme of research has evolved. Participants, who attended all the four, were struck by the remarkable evolution of knowledge.

But what does it mean to clinical care? A recent article provided some answers.[3] The sample comprised subjects who were enrolled for the Diabetes Prevention Program (DPP). The answers were available: who progressed to develop diabetes, who regressed to normal glucose tolerance and who stayed as they were. The current investigators used the most advanced genetic tools that were known to be associated with type 2 diabetes mellitus, applied them to the DPP sample and assessed what the genetic score did in predicting the clinical outcome(s). The results were interesting.

Among 2843 participants in the DPP, genotyping was done for 34 type 2 diabetes associated variants, and a genetic risk score (GRS) was constructed; each risk allele was weighted by its reported effect size on type 2 diabetes, risk and summing the values.

The results did not throw radical surprises: individuals having the highest GRS had diminished pancreatic beta cell function and impaired insulin processing (the latter measured as proinsulin-to-insulin ratio). Surprisingly, they also had better metabolic profile in terms of central obesity and insulin resistance. The apparent dichotomy in genetic factors predicting the progression to diabetes was because both comparative groups were similar (viz., they had impaired glucose tolerance, which was already a high risk for future diabetes development).[4]

The genes most at risk, predictive of type 2 diabetes, were related to beta cell function, and not so much to insulin resistance. Even on constructing a multivariable model using clinically measurable variables, GRS was not an independent predictor of diabetes. What it means is, clinical risk factors already known and easily measured capture most of the predictive information: it is not that we do not have the knowledge that we find it difficult to put it into practice.[5]

What this study suggests though is that individuals at (genetic) risk may be captured earlier on in the course of disease, even before they develop Impaired glucose tolerance (IGT), and lifestyle modification can then prevent the march to diabetes.

The study builds upon earlier studies which used DNA variants in predicting the risk of developing diabetes mellitus: the Scandinavian study reported that when compared to clinical risk factors alone, "common genetic variants associated with the risk of diabetes had a small effect on the ability to predict the future development of type 2 diabetes".[6] Another study published back to back on the Framingham Heart Study sample concluded that a genotype score based on 18 risk alleles "provided only a slightly better prediction of risk than knowledge of common risk factors alone".[7]

These studies led to comments, "disproportionate attention and resources dedicated to finding the genes are skewing priorities away from what we can currently accomplish".[8] The authors of the article responded that identifying people at increased risk of disease was only one goal, which is interesting. The other goals were to identify novel pathogenic pathways, and they mentioned *TCF712*, the strongest gene for T2DM, which was unknown until genetic research brought it out in 2006.[9]

True enough in the current study, even though GRS did not improve on the clinical risk factors, it brought out the importance of defects at the level of insulin production by the beta cells as crucial to pathogenesis. In practical terms, it also clearly demonstrated that genetic risk was not immutable; lifestyle modification was effective in reverting high genetic risk individuals back to normal glucose tolerance.

A recent policy forum feature summarized the perils of imputing genetic risk to common diseases:[10] common diseases by definition are common and result from interplay of environment and genes. It would be unwise to expect genetic risk factors to really change the development of the disease. Second, it is difficult to change the behavior, and hence the hope that finding genetic risk could push at-risk individuals to embrace a healthy lifestyle. Paradoxically, those identified as being genetically "low risk" might be lured into abhorring healthy lifestyle!

So currently, where does genomics stand in relation to clinical diabetes? Is it all blabber, of wasted time, effort and money? Or are we on the Holy Grail?

True, information about genetics of common-garden type 2 diabetes has not yet penetrated into clinical practice, except in rare instances: in identifying forms of MODY, where the risks of long-term vascular complications are low, and in diagnosing rare forms of neonatal diabetes mellitus that may respond to sulfonylurea drugs.[11]

In the decade since, the Journal has swiftly taken off under the leadership of successive editors who led with commitment, flair and erudition. The members of our Society as authors, on their part, have continued to put their faith in making the Journal truly representative; the reviewers and members of the editorial board have continued to give direction.[1] The Journal has moved "beyond survival to the next level of success".[12]

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