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Editorial

Paediatric Endocrinology and Inborn Error of Metabolism Disorders in Hong Kong: Some Historical Perspectives to Shed Light on Our Way Forward

A century ago the first Nobel prize of Physiology and Medicine[1] in the Hormone field was awarded to the Swiss surgeon Theodor Kocher in 1909 for his work on the physiology, pathology and surgery of the thyroid gland. He was instrumental in establishing the causal link between thyroid deficiency and cretinoid clinical features through insightful observations of his patients for whom he did superb thyroidectomy.

In 1977, another Nobel prize in Hormone was awarded to an American scientist, Rosalyn Yalow (incidentally, she is one of the very few female scientists awarded Nobel prizes in history so far), for developing radioimmunoassay (RIA). Her work actually originated from analysing patients with diabetes mellitus who developed insulin antibodies after receiving bovine/porcine insulin injections (see below). The ability for clinicians to efficiently determine thyroid hormone levels underscored the successful universal newborn screening for congenital hypothyroidism in most developed countries/affluent communities including Hong Kong.[2] The Hong Kong programme was pioneered by Prof JH Hutchison in late 1970s and eventually matured into a territory wide effort.

The 1977 Nobel prize was shared by a French American, Roger Guillemin and another Polish American, Andrew Schally, for the discovery of pituitary and hypothalamic peptide hormones: ACTH, TSH, LH, FSH, CRF, TRF and LHRH. One of Guillemin's few prime fellows at Salk institute, Nicholas Ling, was a Hong Kong Chinese American scientist. It was through Nicholas that seven paediatric patients with growth hormone (GH) deficiency (GHD) underwent a clinical trial of pulsatile subcutaneous GHRF infusion in mid 1980s in Hong Kong,[3] when cadaver-derived GH was discontinued for causing Creutzfeldt-Jakob disease.

On the other hand, in 1923, Canadian clinician Federick Banting and medical physiologist John Macleod were awarded a Nobel prize for identifying insulin and consequently producing animal pancreatic extracts for treating type I diabetes mellitus patients. The antibodies against the foreign bovine/porcine insulin developed in some IDDM patients indirectly contributed to the invention of RIA. Numerous Nobel prizes were awarded for the various major advances in molecular biology, which led to the landmark application of recombinant DNA technologies in producing the first therapeutic polypeptide insulin for clinical

trial in the summer of 1980. Around that time, similar success was enjoyed by recombinant human growth hormone, rendering the clinical trials of using GHRF to treat GHD not as crucial.

Clinical endocrinology is often exemplary of how revolutionary change in health care stemmed from integrating good clinical and basic sciences, the dynamic interactions of which continues to flourish. The saga of diabetology recently extends into the newly defined field of metabolic syndrome with obesity being one of the most important phenotypic components. Numerous novel hypothalamic and gut hormones underlying the functional neuroendocrine & gastro-neural circuitries governing eating/feeding behaviours and related elements of metabolism[4,5] have been unraveled. These groundbreaking discoveries are foreseeable targets for Nobel prizes in the near future. Hong Kong is beginning to take on the brunt of the world epidemic of obesity[6] and metabolic syndrome and it is extremely important for us to keep abreast with the advancing knowledge in this subject area to contribute to improving the preventive and clinical care of these patients.

Historical perspectives in Paediatric Endocrinology would not be complete without examining the story of congenital adrenal hyperplasia (CAH).[7] Around 90-95% of CAH are due to 21-hydroxylase deficiency, which is one of the commonest inborn error of metabolism (IEM) disorders involving adrenal glucocorticoid biosynthesis. Most ethnic groups shared similar incidence of around 1:10,000 to 20,000 newborn babies being affected. The 1950 Nobel prize was awarded to American Scientists, Edward Kendall & Philip Hench, and Swiss scientist Tadeus Reichstein, for their discovery of adrenal cortical hormones, their structure and biological effects. With the biosynthetic enzymatic defects of CAH delineated, the availability of RIA measuring 17-α-hydroxyprogesterone in amniotic fluid and the documentation of genetic linkage of CAH to HLA types, prenatal diagnosis for CAH readily became one of the very first successful examples of such clinical practice. Naturally it also made the first successful antenatal therapy of an IEM disorder, allowing prevention of ambiguous genitalia formation in affected female fetuses with maternal dexamethasone treatment. Such antenatal therapy was further aided by relevant molecular biology tests as CYP21B genetic mutations were delineated in greater details. In Hong Kong, we have made the first attempt to adopt non-invasive fetal DNA assays for CYP21B gene mutation analysis using pregnant maternal plasma, to guide the antenatal therapy for a pregnancy from a family with prior affected offspring.[8]

In addition, the high incidence of CAH and the potential fatal outcome especially in affected male babies has rendered it another successful target for newborn screening. Paradoxically, Hong Kong is distinctly lagging behind most developed countries and even Shanghai by not having CAH detection integrated into our neonatal screening programme.

Along this line, it is relevant to ponder about our care for the general spectrum of IEM. Most paediatricians are well aware of the simple but compelling concept that though the incidence of each individual IEM is rare, the combined incidence of IEM is significantly high. Furthermore the prevalence of IEM increases as better diagnostic acuity and supportive care in neonatal and paediatric ICUs all contribute to the culmination of longer term survivors, making them more visible to medical professionals, parents and the society.

At least it is comforting to realise, with the articles in this issue of the Journal, that IEM is drawing more attention in Hong Kong. One must admit, however, that the true impact of IEM in our Society has not been and will never be revealed until more comprehensive screening is performed to detect these babies and children. A lesson we have learnt is the assumption of phenylketonuria being exceptionally rare or did not exist in Hong Kong is wrong. This assumption has been questioned in view of significant incidence of PKU documented in Beijing, Shanghai, Taiwan and even Guangzhou. Indeed we recently confirmed the diagnosis of the BH4 deficient variant of PKU in three Hong Kong children with biochemical and molecular genetic mutation analyses.[9] In fact comprehensive newborn screenings for a good representative range of IEM disorders have been developed at reasonable and affordable cost and provided by various regional or national centres in developed countries.

Concerned paediatricians do feel perplexed, inadequate and anxious in not seeing more visible impact of translational efforts in applying mature advanced technological breakthroughs like tandem mass spectroscopy, MR spectroscopy, and molecular genetic diagnosis to advance Paediatric Health Care in Hong Kong in the dawn of the new millennium. Suggestions to focus on any "less attended" medical problems are often met by mundane responses with un-inspiring explanations, citing lack of resources or difficulty to apportion resources fairly

amongst matters of equal priorities, and other administrative considerations as major deterring factors.

It is hard not to attribute this at least in part to the diffuse and diluted spread of the paediatric services in Hong Kong where, with a population of about 6.8 millions, not a single children hospital is in sight. The current establishments pose obvious obstacles to promoting the acquisition and development of skills to manage rare disorders, of which IEM is but one category, which demand concentrated technological supports, innovative clinical approaches and more importantly, the joint efforts from multiple expertise. The recent formation of a Hong Kong Society of Inborn Error of Metabolism indirectly speaks for the acknowledgement within the paediatric community to rally more attentions and to consolidate commitments to tackle this domain. This is commendable and would be supported by all conscientious Professionals. More fundamental structural re-organisation of the current Hong Kong Paediatric Services, however, would need to be addressed in parallel to provide the crucial alignment of clinical patients and expertise with research development. One of the top priorities should be the development of full range of comprehensive core sub-specialties at designated Paediatric Hospitals/Health Centres, before it is too late to keep Hong Kong on par with the forefront Medical Practice of the International Paediatric Community.

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PT **Cheung** and LCK **Low**
Guest Editors