Editor's note:
"Rare Diseases Column" is chaired by Dr. Zhanhe Wu from The Children's Hospital at Westmead, Australia, featuring articles related to rare diseases mostly genetic based, presented in early life disease, with chronic phase but frequently progressive, disabling and life threatening diseases. Article types of original articles, review articles, case reports, perspectives, etc. are welcomed to be submitted to the column.

Rare Diseases Column (Commentary)

Where will genetic research take us?

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When Watson and Crick published the structure of DNA in *Nature* in 1953, they anticipated that the structure would unlock huge scientific secrets allowing the treatment of a huge range of disorders. In their day, the range of disorders that could have a genetic basis would have been unfathomable and now include forms of cancer, diabetes, Alzheimer's and Parkinson's syndrome. The 1950's also saw tremendous progress in the understanding of biochemical disorders typified by Christian de Duve, Gerty and Carl Cori. The discovery of further intracellular organelles and the mechanisms of glycolysis led to the art of manipulation of the diet based upon biochemical understanding. Horst Bickel pioneered this in the 1950's for a condition called phenylketonuria (PKU). The timing of this dramatic intervention for a severe disorder was fortunate as soon afterwards Bob Guthrie discovered a rapid and cheap bacterial inhibition assay (BIA) that could reliably identify the condition. In the 1960's BIA was adopted as a newborn screening test for pre-symptomatic infants with PKU in several countries worldwide. This period, therefore was an era of time, when the basic biochemistry of physiological processes including the defining of the physical and biochemical structure of DNA, the biochemistry of metabolic processes and the manipulation of these to treat genetic disorders became many researchers primary objective.

After the turn of the millennium, the Human Genome Project helped to define a new era of genetic investigation. Now, the overall structure as envisaged by Watson and Crick has been built upon to help define a tremendously intricate structured genetic code. The questions we have now have evolved to what does this mean, how can we manipulate it and how does that code interact and change with environmental and genetic stressors? For many rare disorders, these are incredibly difficult questions to answer as there are insufficient data to test hypotheses. However, for PKU, a more common condition in Australia with an approximate incidence of 1 in 12,000, there have been treatment paradigms established from the 1960s for a large cohort of patients. Having a defined cohort allows further interrogation of the genetic basis of disease, genetic manipulation to alter disease, recreating genetic enzyme deficiencies using enzyme replacement therapies and managing affected physiology in novel ways. All of these approaches are discussed in detail by the research review by Hafid and Christodoulou in the paper in this issue titled, "Phenylketonuria: a review of current and future treatments" (1). These methods serve as a model for the scientific investigation of all rare disorders. In amongst this science, clinical description and definition of a case purported to have a genetic basis is paramount.

It probably would not have been clear to Watson and Crick in 1953, how far reaching their discovery would

be. Would they have, for instance, predicted the intricate transcription of the DNA they described, the translation into a mature protein and subsequent post-transcriptional modification? The couldn't have predicted the targeting and regulation of these proteins, the synthesis and breakdown of DNA, the way that errors became incorporated into discrete genes and the way repair mechanisms try to correct this. Could they have foreseen all the rare disorders identified, that drugs would be designed for specific mutations, that exons would be skipped, genes excised and replaced by gene therapy or that genetic products were synthesised *in-vitro* and replaced i*n-vivo*. It is clear to us now that hypon scientific rigor and international collaboration that phenomenal progress has been made in the last 60 years, meaning that we too now, do not know where the next discovery in genetic research will take us.

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Footnote

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1. Al Hafid N, Christodoulou J. Phenylketonuria: a review of current and future treatments. Transl Pediatr 2015;4:304-17.

