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# Discovery and Resolve: The Human Genetics Society of Australasia Oration 2011*

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Human genetics spans every facet of biology from molecular science, through laboratory and clinical practice, to psychology and anthropology. In each of these areas, the history of human genetics has been punctuated by paradigm shifts in knowledge. Each such new concept has been received with skepticism, often with perplexity, and sometimes with frank incredulity. Such comprise the datum milestones along the path leading to our present corpus of genetic knowledge. In parallel to the personal threats to Copernicus and Galileo in the field of astronomy in the 17th century, almost all genetic discoveries of the 19th and 20th centuries were seen as challenges to the received wisdom, and sometimes the social order, of their time and place. Researchers, scientists and clinicians encountering such new and often-heretical paradigm shifts have required considerable resolve to promote and publish their work. Just as in the field of astronomy, new directions in genetics have threatened not only the reputations and sometimes the careers of scientists, but also have been challenges to fundamental religious and sociological beliefs in society more broadly. Examples followed the discovery of biological sexual dimorphism (in plants as well as animals) by Nehemiah Grew (1641–1712). Darwinian evolution, Mendel's First and Second Laws, the existence of mitochondrial genes, apoptosis and its genetic basis, and uniparental disomy are more recent examples. Many of these new revelations, which today have led to the current understanding of fundamental biology, were discovered by individuals working in relative isolation. To promote and publish findings that fundamentally challenge received wisdom continues to require considerable resolve, if not courage. Herein lies a message for all clinicians and researchers.

**Keywords:** history of genetics, genetic research, mitochondrial genes, Erasmus Darwin, apoptosis

*'It is in the darker regions of science that the great are recognized; they are marked by ideas which light up phenomena hitherto obscure and carry science forward'.*

Claude Bernard (1813–1878)
In: *An Introduction to the Study of Experimental Methods (Bernard)*[1]

New discoveries in science come about by small extensions of current knowledge; or by paradigm shifts that create a new fork in the road. Where that road leads cannot be seen at the time of its creation. But as Ralph Waldo Emerson's aphorism rightly said: 'Follow not where the path may lead; Go instead where there is no path and leave a trail' (Emerson, 2006).

Advancing scientific knowledge requires application, sheer hard work and the perspective of 'the prepared mind', which luck favours. In Pasteur's original quote, 'chance favours the prepared mind', the French word for 'chance' is 'hazard'. My personal experience and observation is that the proposal of new and sometimes heretical paradigms require considerable resolve and sometimes courage. Such can indeed be a hazard; and besides the *desiderata* of dedication and hard work, and indeed a measure of good luck, a quantum of stiff resolve is often necessary. The history of genetics provides many instances of this theme.

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## 'Cytoplasmic Inheritence'

In 1967, in the context of experimental studies on thalidomide teratogenesis (Pearn & Vickers, 1966), I talked with a good friend, Dr David Wallace, then Queensland's only full-time geneticist. He worked at the Queensland Institute of Medical Research and his laboratory was in an old wooden World War II army hut, sited on what today is the putting green of the Victoria Park golf course in Brisbane.

With considerable scientific courage, Dr Wallace was studying Leber's optic atrophy. One says 'courage', because even before the outbreak of World War II, at least 10 geneticists had postulated speculative but unconvincing theories about the (then) strange mode of inheritance of this perplexing disease (Davenport, 1930; Kawakami, 1926; Kitashima, 1930; Meyer-Riemsloh, 1925; Waardenburg, 1932; Yang, 1923). By 1967, another eight genetic studies of Leber's optic atrophy with its perplexing mode of inheritance had been published. None could provide any convincing explanation for its transmission (Colenbrander, 1962; Lundsgaard, 1944; Went, 1964).

Leber's optic atrophy was first described in 1871 (Leber, 1871). The clinical syndrome is characterized by the relatively sudden onset of optical neuritis, which progressed to atrophy and blindness; together with neurological features that variably include epilepsy, ataxia, spasticity, synkinesis, encephalopathy and psychiatric symptoms. After the sudden onset, most victims do not deteriorate further (Wallace, 1970a).

Several of the many perplexing features of the published family trees were:

- No affected male had ever passed the disease on to his descendents.
- Between 70 and 96% of the daughters of mothers known to be carriers, were themselves carriers of the disease.
- Not all women who on pedigree evidence were known carriers, manifested the disease; and
- Almost half (49%) of the sons and only 8–15% of the daughters of non-affected carrier women themselves manifested the disease (Van Senus, 1963).

This pattern of inheritance did not fit any conventional Mendelian or polygenic model of inheritance. The peculiar sex incidence of Leber's optic atrophy had a seductive resonance with both Lossen's Law and Kitashima's Law. Lossen's Law, formulated in 1877 (before the rediscovery of Mendel's 1866 papers in 1900) to describe the inheritance of hemophilia, noted that an affected male does not transmit his disease to his direct descendents (Imai, 1963). Kitashima's Law, propounded in 1930, noted that almost all normal females of affected kindred carried the disease (Kitashima, 1930).

Neither of these 'laws', or monogenic inheritance (either autosomal or X-linked) explained the inheritance observed in the dozens of published pedigrees of Leber's optic atrophy. Numerous modified theories were put forward to preserve the inviolability of Mendelian monogenic inheritance, the nuclear DNA of today. These included suggestions of a combined autosomal and X-linked inheritance, and a proposal that unknown factors rendered all spermatozoa of affected males non-viable (Wallace, 1970b). Another ingenious hypothesis suggested a differential and selective sex hormonal influence on the gametes of the two sexes (Waardenburg, 1932). Another was a postulated selective effect related to cyanide metabolism (Wilson, 1963).

The 1960s were also the era of Gajdusek's work on kuru (Gajdusek et al., 1966; Richmond, 2009). It was also a time when speculative theories, including novel genetic models, were raised to explain the bizarre sex and age differential of the familial occurrence observed in kuru victims. Kuru, invariable fatal, afflicted almost exclusively adult women and children of both sexes. Against this background, Dr David Wallace told me that the hitherto inexplicable inheritance pattern in Leber's optic atrophy could be explained by some type of cytoplasmic inheritance; specifically, 'a transmissible self-replicating entity'. He told me that it was too radical to propose that genes might be in the cytoplasm. Nevertheless, in 1970 he showed considerable resolve in proposing that another cytoplasmic intergenerational transmissible agent, today called a slow virus, could explain his observed genetic data (Wallace, 1970b). The existence of a new class of infectious agents, slow viruses, had recently been described by Gajdusek in the context of his work on scrapie, Aleutian mink disease and kuru. David Wallace was working in an internationally famous virus laboratory, was familiar with other examples of intergenerational transfer of disease-causing agents, and was influenced by the role of viruses in human disease. In his theory of a transmittable cytoplasmic agent, Wallace drew parallels with the vertical transmission of avian leucosis virus and 'congenital' (e.g., transplacental) infection as described per mouse lymphocytic choriomeningitis (Wallace, 1970b).

Ten years later, in 1978, Fine published in the *Lancet* the characteristics one would predict for a disorder resulting from a mutation in a theoretically proposed mitochondrial chromosome (Fine, 1978). By 1981, mitochondrial chromosomes had been sequenced at Cambridge by Dr Sanger and his team (Anderson et al., 1981). By 1982, the first suggestion that the 'cytoplastic inheritance' of Lever's optic atrophy might be due to mutations in the mitochondrial gene was proposed. Victor McKusick noted that two conditions, Leber's disease and chloramphenicol resistance in cultured cells, might be the result of cytoplasmic genes (McKusick, 1982). Twenty years after Wallace's paper, Holt and colleagues demonstrated that deletions in the DNA of muscle mitochondria caused myopathy (Holt et al., 1988). Immediately, the inheritance pattern of Leber's optic



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atrophy became obvious. Mutated mitochondrial genes were the cause; but the concept of a cytoplasmic gene had hitherto been too radical to contemplate.

Today, mitochondrial diseases are recognized as major causes of morbidity (DiMauro & Schon, 2003; Schapira, 2006). The rate of clinical mitochondrial diseases occurring in the general population is known to be 1 in 10,000, with a further 1 in 5,000 at risk of the carrier state (Schaefer et al., 2004). The human mitochondrial genome is contained in a small circular molecule of 16,569 base pairs, consisting of 37 genes (Kirkman et al., 2008).

The point of this anecdote is that however radical, heretical or counter-intuitive a hypothesis might be, if it explains the observed facts, much is to be achieved if one lets it have full reign. Such often produces ridicule, or worse, as Galileo found to his cost. But for those who are eventual 'winners', much is to be gained and scientific understanding advanced.

## 'Breaking the Mould'

Much courage is required in exposing one's theories or beliefs to one's peers; and even more so to the broader community. Prior to the rediscovery of Mendel's work in 1900, Copernicus and Galileo in astronomy, and Nehemiah Grew and Darwin in genetics, had all felt the odium and in some cases the threat of physical danger from those whose beliefs were challenged by new theories — theories nevertheless based on sound and ultimately irrefutable observational or experimental evidence.

In his 2003 Harveian Oration delivered to the Royal College of Physicians in London, the Nobel Laureate, Sir Paul Nurse, well described:

> The delay between discovery and recognition…(which) I think reflects the general resistance of biologists to abstract thinking because of their greater reliance upon more empirical approaches. (Nurse, 2003)

In the history of genetics, there are many examples of those who, at considerable personal risk, felt they had to maintain personal integrity by proposing unifying theories which would explain their observed data.

## Nehemiah Grew (1641–1712)

In the history of genetics, a pioneer of particular resolve was Nehemiah Grew, a London surgeon-physician with a passionate interest in plant anatomy. Grew had allowed his scientific curiosity full reign, and manifested the courage to publish his work. Further, he manifested a resolute self-discipline to stand firm by his scientific observations, in the face of odium and the criticism of many of his contemporaries. Grew's botanical discoveries were significant. He showed that cotyledons were the first leaves of germinating seedlings; that thorns are derived from leaves or shoots and that bulbs might be underground buds. Grew's greatest discovery was that of the sexual anatomy of plants.

The idea that plants might have sex organs — in today's concepts that they might manifest genetic dimorphism — had been suggested to Grew by Sir Thomas Millington of the Royal Society. Grew investigated this and showed that the stamen (with its pollen) is the male sex organ and that the pistil corresponded (in seventeenth century concepts) to the sex organ of female plants. His findings were published in *The Anatomy of Plants* in 1682 (Grew, 1682). The possibility that plants possessed sexuality was offensive to many, especially the Bishop of Carlisle, the Reverend Samuel Goodenough (1743–1827). Goodenough was one of a number of prudish botanists who vehemently rejected the entire concept, carrying considerable public opinion with him (Pearn, 1997). It took great courage for Grew to stand by his anatomical observations.

## Erasmus Darwin (1731–1802)

In one sense, Erasmus Darwin was another founder of modern genetic theory, including what today is accepted as evolution, mutation and the implications of the fossil record (Pearn, 2004).

Erasmus Darwin wrote in 1794, courageously for his time and place, that sudden changes in species were brought about by 'monstrosities' or 'enormities of shape' (Darwin, 1794) — 'mutations' in the current terminology of contemporary genetics. Erasmus Darwin wrote of sexual selection through the competitive advantage of the fittest and strongest: 'the strongest and most active animals should propagate the species, which … thence become improved'. Erasmus Darwin knew that dramatic changes had been produced in domestic animals over the relatively few millennia of recorded history; and extrapolated this to affirm the concept of evolution. Sixty-five years later, his grandson, Charles Darwin, elaborated these principles in *The Origin of Species* (Darwin, 1794). The point here is that Erasmus Darwin was a man of dominant personality and fearless resolve. He was personally courageous, no more so than in his wooing of the wife (Elizabeth Pole) of a fierce, retired Major General who had been wounded three times in battle and who lived at Litchfield, nearby (Darwin, 2008).

His grandson, Charles Darwin, was much troubled by the potential consequences of his theory of evolution by natural selection. It is said that he was: '... a man without arrogance who overturned our view of how all living things came to be as they are … suffered fear, doubt and frequent tummy aches' (Ince, 2011).

Charles Darwin lacked the initial courage to publish his work for two decades, finally manifesting resolve when he learnt of Wallace's impending publication.

## Emeritus Professor Raymond Dart (1893–1988)

Another 'genetic' example of the courage needed to maintain scientific integrity in the face of enormous resistance is



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that of Raymond Dart, the discoverer of *Australopithecus* (Dart, 1925).

Raymond Dart was born in Toowong, on the banks of the Brisbane River at the height of the devastating Brisbane flood of 1893. His family home was flooded. The newborn infant (in a box) and his mother were floated to safety through an upper window to a rescue boat (Tobias 1984). After graduation from the University of Queensland with an Honours Bachelor of Science Degree (in 1913) and a Master of Science (1915), he graduated in Medicine in 1917. As a young Professor of Anatomy at the University of Witwatersrand in Johannesburg, Dart was given fossil bones from the Buxton Quarry, near Taung in November 1924.

One of the specimens contained fragments of a skull, with an endocast of the brain cavity. He immediately realized that the skull was neither human, nor that of any living ape, but possessed intermediate anatomical features of both. He 'delivered the fossil from its stone matrix… and with incisive neuroanatomical and evolutionary acumen, and not a little courage… recognized that this creature was relevant to the study of hominid emergence and evolution' (Tobias, 1985). Dart was subjected to enormous scientific and social vilification following his initial publication in *Nature*. Of resolute and determined *persona*, Dart nevertheless withstood the attacks, and within 20 years his work was the foundation of an understanding of perhaps 4 million years of hominid evolution, and much of our genetic ancestry.

## Professor John Kerr and Apoptosis

Apoptosis was discovered by the Brisbane pathologist, Professor John Kerr. In a milestone paper in the *British Journal of Cancer*, published in 1972, apoptosis was formally described and named (Kerr et al., 1972). Over the ensuing decade in Brisbane, Professor Kerr and his students (especially Professor Jeff Searle, and Dr Michael Harrison and the microscopists David Collins and Brian Harmon) published the definitive papers that established apoptosis as an ubiquitous kinetic process in all vertebrate tissues (Kerr & Searle, 1972a; 1972b; 1973; Kerr et al., 1974; Wyllie et al., 1973).

Apoptosis is sometimes described as programmed cell death. The phenomenon is under genetic control. Apoptosis is distinct from cell death due to necrosis. Unlike necrosis, apoptosis does not engender any inflammatory response. Apoptosis is the manner in which the embryo is sculpted, some areas growing by mitosis and other areas being 'sculpted' or reduced by apoptosis. Apoptosis occurs spontaneously in tissues and organs and is the process by which tissues are remoulded during regeneration and scar formation. It is widespread in neoplastic tissue.

Professor Kerr first observed the peculiar and distinctive changes in cell nuclei, in 1965. He studied the phenomenon extensively, appreciating at that time, that this was an entirely new and distinctive type of cell death. Initially, he called the process 'shrinkage necrosis' (Kerr, 1965). Ubiquitous in many tissues, it required considerable resolve to point out its presence, obvious in retrospect to every microscopist ever since Virchow's first microscopic studies of the cell a hundred years earlier.

Over the last decade, from 2001, apoptosis is the most discussed and mentioned topic in biology and medicine. Of the 6.3 million refereed papers in the international medical literature in the last decade, some 145,000 papers discuss apoptosis (compared with 126,000 papers in HIV-AIDS and 101,000 on breast cancer).

As the process is determined by genetic control, and as disordered apoptotic mechanisms underlie all dysmorphology and congenital genetic syndromes, the theme will increasingly be a feature in the work of geneticists into the unknowable future.

## Conclusion

These examples show that two *desiderata* are needed for scientific advance. The first is that in the observation and interpretation of data, a 'free spirit' of contemplative speculation is needed to create new paradigms. The English philosopher, Stephen Law, in a recent book described the analogy of the power of one's conservative peers and environment, in astronomical terms:

> Intellectual black holes are belief systems that draw people in and hold them captive as they become willing slaves of claptrap. Belief in homeopathy, psychic powers, alien abductions — these are examples of intellectual black holes.' (Law, 2011)

The second quality is resolve, sometimes courage, that new concepts may be exposed to the timely audit of one's peers.

Such resolve is always needed to propose concepts which will break the old mould, however threatening such change might be. Scientific progress depends upon it.

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