P J Morrison (–)

President of the Ulster Medical Society 2016–17

Presidential Opening Address
Ulster Medical Society
6th October 2016

MEDICAL MYTHS AND LEGENDS[1]

'I daresay you haven't had much practice', said the Queen. 'When I was your age, I always did it for half-an-hour a day. Why, sometimes I've dispelled as many as six medical myths before breakfast. There goes the shawl again!'

– abridged from, and with apologies, to Lewis Carroll.

I have chosen six myths that have been dispelled over my career in genetics during the last 30 years, with six legends to accompany them—all of which I've been involved in.

1. ISN'T GENETICS THAT DNA STUFF THAT STARTED IN THE 1990'S?

In the late 1890's a department of sanitary science was set up by Queen's University. It developed into the university department of Social and Preventative Medicine and out of this grew a series of services including Public Health Medicine, Medical Statistics, General Practice and Medical Genetics. The first proper genetics service was started in Northern Ireland in 1948 by Professor Alan C Stevenson, the Professor of Social and Preventative Medicine at Queens University Belfast (Figure 1). Genetics arose out of the department of Social and Preventative medicine, a natural home for studies of risk and prevention, most members of the department having epidemiological as well as medical training. Having been appointed as Professor and also honorary physician to the Royal Victoria Hospital and the Royal Belfast Hospital for Sick Children in 1948, Stevenson carried out a series of population studies in genetic disorders.

Stevenson started his clinics in 1948, a year before JA Fraser Roberts started the first formal genetics counselling clinics at Great Ormond Street. The Belfast clinics started when Stevenson saw patients primarily for his genetic epidemiology studies and were the first attempts to see 'genetic' cases in the UK.

He produced the best ascertainment studies of the time on genetic conditions in Northern Ireland, including the prevalence of achondroplasia, myotonic dystrophy and Marfan syndrome, in a series of seminal papers published between 1953-1958. He later moved to Oxford to set up the MRC Population genetics unit in 1958 and published the major clinical textbook on genetics at that time. Several students fondly remember him tinkering with the carburettor in his car engine trying regularly to get it to start so he could return to the Royal Victoria Hospital for his clinics, after giving morning lectures at the university main campus.

His successor at Queens was Dr (later Professor Sir) Peter Froggatt. Froggatt was appointed as a Professor of Epidemiology in 1968 and later became

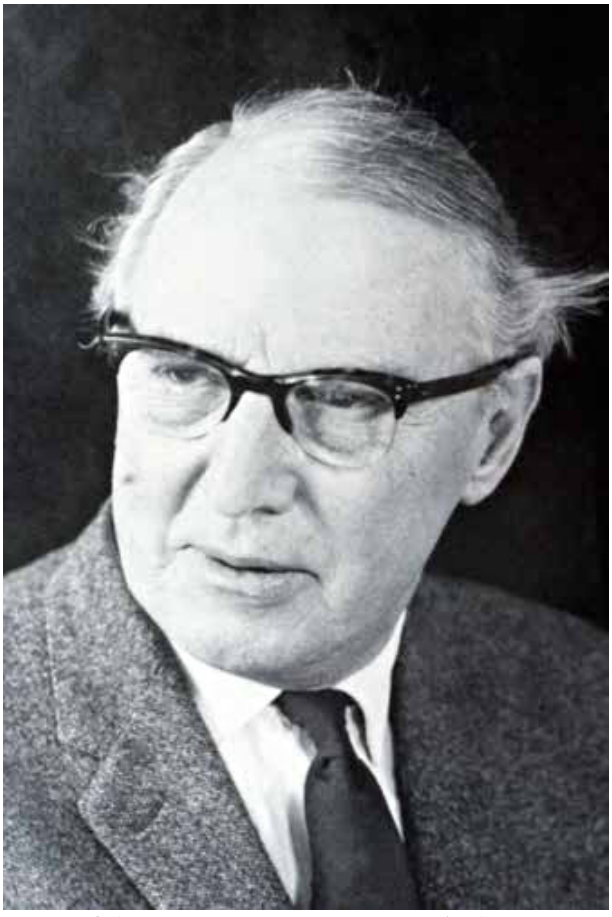

Fig 1. Prof Alan Stevenson, 27.1.1909 -18.9.1995. (Photo courtesy of Prof Alun Evans).

[1] *Ulster Medical Journal*, 2018, v87(2), p102.

Fig 2. Prof Sir Peter Froggatt b.1928. (Photo courtesy of Queens University Belfast).

Vice-Chancellor of Queens University from 1976-1986 (figure 2). He submitted his doctor of Medicine thesis on albinism in Northern Ireland in 1957, establishing how common it was in the province, and was appointed a lecturer in community medicine in 1959. He worked with the famous Dutch ophthalmologist and Professor of genetics, Petrus Waardenburg. (Waardenburg suggested that Down's syndrome might be a chromosomal disorder as early as 1932, and the syndrome named after him, in 1951, includes the association of deafness, iris hetero-chromia and a white forelock).

Froggatt appointed Norman C Nevin to a lectureship in Human Genetics in 1967. Dr Nevin spent 1965-1966 as an MRC fellow in the Oxford MRC genetics unit and did genetic research on the condition tuberous sclerosis under the supervision of Alan Stevenson. Norman later became a Senior lecturer and honorary Consultant in Human Genetics based in the Royal Victoria hospital in 1968. He was appointed to a personal chair in Medical genetics in 1975 and then as the first full Professor of Medical Genetics in 1978 at Queens University when the university established a series of departmental chairs, one of which was a new department of Medical Genetics (figure 3). Genetic clinics were still provided in the Royal Belfast Hospital for Sick Children and also

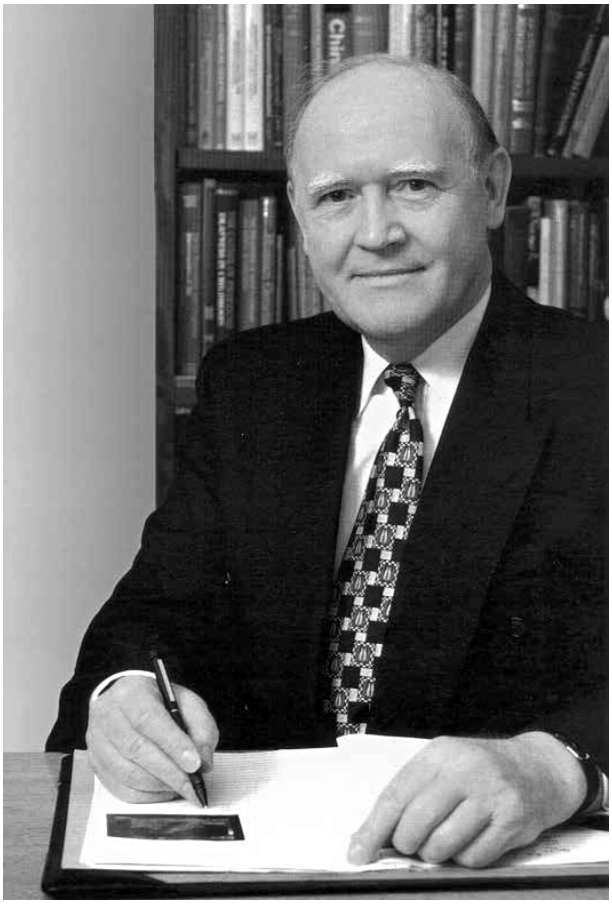

Fig 3. Prof Norman Nevin, 10.6.1935 - 28.6.2014.

in the Mulhouse building in the Royal where the department of medical genetics was based until 1987. With the building of the new City Hospital tower block, services transferred to Belfast City Hospital when the tower block opened in 1987. The Regional Medical Genetics Centre has been located on A floor on the 'West podium extension' ever since (figure 4). Norman's wife Jean ran the prenatal genetics laboratory until 2001 when they both retired. Norman was awarded the OBE in the Queen's birthday honours in June 2003 for services to gene therapy research having chaired the Gene Therapy Advisory Committee in London for a time. Norman was a gifted teacher and his lectures to medical students were fascinating for their apparent simplicity, and he inspired a generation of doctors, several of whom went on to gain an MD or PhD in genetic aspects of their own subject. He had a great warmth and kindness when dealing with patients with difficult genetic disorders. He would often draw out the complex genetics in a diagram on a page for them and could write upside down—several patients marvelled at this skill, often only surpassed when mothers of

Fig 4. The completion of the West Podium Extension in 1984 (bottom right of picture just visible behind the black pipework).

children with Down syndrome found out he too had bilateral simian creases on both palms (as had Tony Blair and some other prominent people) and some remarked that their child might too grow up to be a Professor. He always encouraged hope in difficult cases and dealt with a wide remit of cases from early pregnancy, paediatrics and complex late onset adult genetic diseases.

Clinical Geneticists

Dr Fiona J Stewart MBE was appointed as a second consultant in medical genetics in 1995. She has special interests in paediatric genetics and lysosomal storage disorders and has established clinics and treatment for patients with enzyme defects in the province. I was appointed as a consultant in clinical genetics with a special interest in cancer families on 1 st January 2000. I was awarded honorary professorial chairs of Human genetics from the University of Ulster (2002), Nottingham Trent (2005) and Queens Belfast (2007). These helped partially replace the academic void left by Norman

Fig 5. Genetic Medicine team 2016 (left to right: V McConnell, D Donnelly, P Morrison, A Magee, T Dabir, F Stewart, S McKee).

Nevin's retirement and then subsuming of his academic post and funding into other areas of the university. My main task on appointment was to set up the cancer genetics section of the Regional Genetics Service, and I extended cancer genetics clinics to the cancer centre and cancer units in Northern Ireland, establishing clinics in Antrim, Altnagelvin, Craigavon, Erne and Ulster hospitals, to supplement the general genetics clinics already taking place in those hospitals. Start-up funding for my post and laboratory staff was obtained from the charity Action Cancer led at the time by Peter Quigley—a man with great foresight who could see that genetic screening could be a key part of cancer prevention and diagnosis. Cancer genetics referrals quickly became a large part of the service accounting for over two-thirds of referrals in 2001 and soon further expansion was needed with more genetic counsellor appointments and a series of consultants with a special interest in cancer genetics were appointed in the same decade. Funding was secured for these after a series of business cases which allowed the appointment of new consultants now called clinical geneticists, having changed the name from medical geneticists in 1999. The appointments included Alex C Magee (2002), Shane A McKee (2005), Vivienne PM McConnell (2007), Tabib A Dabir (2009) and Deirdre E Donnelly (2014). Dr Gillian Rea was appointed in 2016 replacing Alex Magee following her retirement earlier that year—figure 5).

The future.

Genetics as a specialty has had a rapid development. The next step may be its demise as a separate specialty as genetics integrates into the mainstream of medicine. Most disorders appear to have some genetic component—if not a physical or

familial genetic diagnosis, then often a laboratory assisted one. In the next few years, most medical professionals will be looking at personalised genome testing in their patients and will need to interpret the results and target therapies accordingly. The cost of genetic testing has started to decrease with tests that once were expensive and time consuming, now costing much less with more rapid turnaround times. In the next couple of years, the cost of analysing the entire genome of each patient will drop to less than £500. This will allow personalised genome testing and tailored treatments. Medical geneticists having changed their name to clinical geneticists in 1999 more recently changed again and became consultants in genetic medicine. Further expansion will depend on whether geneticists are needed to assess patients in a separate specialty or whether 'mainstreaming' of the specialty integrates it directly into medicine as a whole. The specialty of clinical genetics has gone from a single-handed consultant to pervading all areas of medicine.

2. MAMMOGRAMS ARE A WASTE OF TIME.

In 1995 I wrote to the editor of the Lancet suggesting routine mammograms were probably a waste of time and suggested that women with a family history should be targeted instead (figure 6). At that time there was considerable debate on the utility of mammography, and cancer genetics was just in its early stages. I had returned from Nottingham, UK and had started to set up cancer genetic clinics as pilots for hereditary breast cancer. BRCA1 testing started in 1997 and figure 7 shows the early referral pattern with a predominance of breast cancer cases followed by ovarian and bowel, and then rare cancer syndromes. Clinics were set up following the Calman-Hine model with a 'hub and spoke' pattern

An approach to breast cancer screening (perhaps better called surveillance) would be to restrict the screening group in the cancer prevention strategy. It is difficult to estimate what proportion of detected breast cancer cases have a familial basis, but gene-targeted screening would allow increased detection of cases in a higher-risk group; thus the predictive value should increase and the false-positive rate should decrease. Women with a family history of cancer are often doubly anxious (because of their history as well as concerns over the screening procedures). They may have most to gain with both reassurance and early detection. Over 60% of women offered a *BRCA1* test will accept.[3] Positive results will soon identify a large cohort of women at very high risk of developing cancer during their lifetime.

Since all cancer is genetically determined, public money may be better used in targeted screening programmes only, abandoning general population screening. Genetic advances allow for increased refinement of high-risk groups.

*P J Morrison, J A Raeburn

Fig 6. Letter to The Lancet 1995

Cancer referrals to the Northern Ireland regional genetics service for 1997

Type of cancer	Number of referrals
Breast	86 (60%)
Breast and Ovarian	20 (15%)
HNPCC	15 (10%)
Multiple endocrine (MEN 1, 2A, 2B, FMTC)	6 (5%)
FAP	5 (1%)
Li-Fraumeni	3 (1%)
Others	6 (5%)*
Total	141

* Includes VHL RB, NF2, WT, Ataxia telangiectasia, Cowden syndrome, juvenile polyposis, Peutz-Jeghers syndrome and other rare dominant cancer syndromes.

Fig 7. Early Referrals to the cancer genetics service in 1997

aligned with the cancer centre and cancer units, and a consultant led service. I managed to get funding from various research sources including a large EU BiomedII grant, and this allowed clinical and laboratory staff to be appointed and kick-start service developments. A rapid rise in referrals meant that by 2001, over 70% of referrals were cancer-related, and eventually genetic counsellors took over the main referral triage. The rapid number of referrals and our careful system of evidence gathering meant that we were major UK contributors to the evidence base in this area with over 200 papers on cancer genetics, new genes and genetic counselling processes produced. Some major clinical evidence included the recognition of the inability of mammograms to detect BRCA1-related cancers, and this lead to the national screening programme in the UK adopting a combined digital mammographic and Magnetic resonance imaging approach in 2012 and within 6 months we had the largest number of patients enrolled in a screening programme in the UK. The benefits of preventative surgery and careful counselling and teamwork with psychology, breast surgery and oncology teams has paid dividends. The 'Angela Jolie effect' when Angelina Jolie and her then husband Brad Pitt went public with risk reducing breast cancer surgery caused a huge increase in referrals to our service and a further surge in referrals to the breast surgeons. In 2017, a Cambridge group published a risk stratification of mammographic screening groups based on family history—largely what I suggested might be good to happen in 1995, so it is great that technology and progress have been able to allow this to happen in my lifetime.

3. FINN MCCOOL WAS A MYTHICAL GIANT.

In 2007, Professor Brew Atkinson in the Royal Victoria hospital in Belfast sent me two cases of early onset acromegaly. Family studies confirmed probable autosomal dominant inheritance and further families

Fig 9. Genetic field trip to Tesco Dungannon 2013. Patrick Morrison (second right) and Marta Korbonits (Right) were the field team co-ordinators. Brendan Holland, a local giant and relation of Charles Byrne, can be seen very clearly in the very back row.

were identified. We were able to show that a large number of Northern Ireland families had a common mutation, R304X in a recently isolated gene called AIP. All the families were from west Tyrone and in a series of collaborative studies, the families were shown not only to be related to each other, but also to the famous Irish giant Charles Byrne whose skeleton is in the Hunterian museum in Lincoln's Inn Fields in London (figure 8). DNA from two of Byrne's teeth confirmed he also had the mutation, and more recently the mutation was traced back to the iron age—clearly Northern Ireland is the land of giants with various notable giants having been documented some of whom may well have had Acromegaly. Finn McCool is likely to have existed and there are some links to his Scottish cousins—hence the legend of the Giant's Causeway extending up to Staffa and the home of Scottish giants. We also showed that Giants in biblical times also were likely to be a form of hereditary acromegaly. To take the giant research further, and to see how common they were in the population, we obtained funding for a population study. We carried out population testing using saliva samples taken from the general public who were visiting Tesco super markets in Dungannon in two consecutive weekends (figure 9). Results showed around 1 in 156 people in West Tyrone may carry the 'giant' gene and our work now allows early detection and prevention of gigantism—a fairly unpleasant disorder with multiple complications and early death. Our motto is 'no more giants'. The work was shortlisted for the Times Higher Education award in 2013 and we just lost out to the work identifying Richard III buried in a car park in Leicester. Both

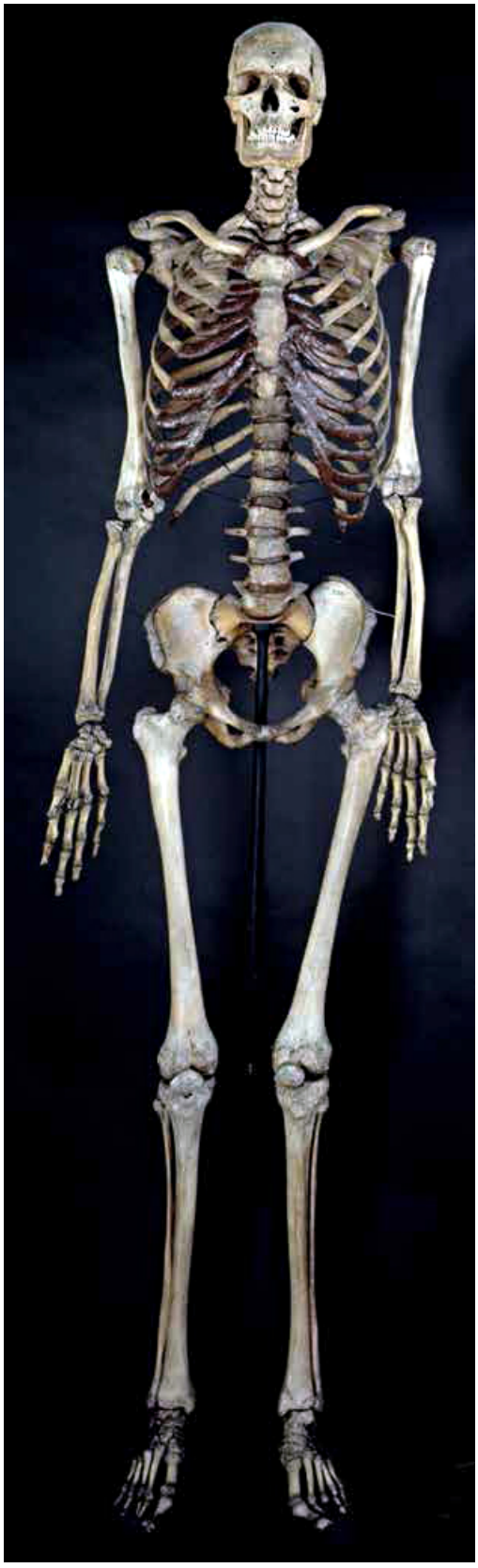

Fig 8. The skeleton of Charles Byrne.

projects put the study of ancient DNA to the forefront and such studies are now routine.

4. PARKINSON'S DISEASE ISN'T FAMILIAL.

I identified a three-generation family with Parkinson's disease (PD) in 1995 and published this, suggesting that 10% of PD cases probably had a genetic component and devised a genetic classification of the common suspected likely PD types. At the time few people thought a genetic basis was likely, but the latest genetic testing panel now includes 96 genes for PD and the genetic classification is widely used. Motor neurone disease and a series of other neurological disorders previously thought to be sporadic have now also been shown to have a genetic basis.

5. IS IT A BOY OR A GIRL?

Geneticists have long recognised gender identity, gender expression, biological sex and sexual orientation to be on a continuum. More recently we have recognised that male sexual orientation has a strong genetic basis. My genetics colleague Cecile Janssens in Rotterdam estimates that 30% of homosexuality is heritable. My own experience in clinics over the last three decades is that around 10% of cases have a strong genetic basis. Male homosexuality is a bit like where PD and breast cancer were in the early 1990's—with no clear recognition of a genetic basis and few studies to back up the science. Recent studies confirm male gender genes on the X-chromosome and on chromosome 8q. More studies are needed and are already in progress in areas of the world where homosexuality has acceptance and no stigma or is not still illegal. There may be several genetic advantages to carrying an X-linked gay gene, as there may be increased reproductive fitness and attractiveness in female gene carriers and gene carriers for either of the identified high penetrance genes may have increased stamina and increased achievement. My feeling is that like PD and also Huntington disease (HD) the genetic component will be increasingly recognised and the stigma steadily decrease so that the attitude of society to homosexuality will change as it has for HD, slavery and other taboos that have been generated out of lack of understanding. Also like breast cancer, lots of low penetrance genes will give an additive effect and lower penetrance genes are more susceptible to environmental interactions, factors that now explain lifestyle interactions and genetics in the contributions to breast cancer. I have shown how 20 years ago there was virtually no genetic interest in breast cancer or Parkinson disease and this is now completely changed. Recently I was tossing some dying petunia plants into my compost heap and noticed that the stems looked and smelt like potato and tomato plants. On looking into the genetics of their origins I found that recent DNA analysis has shown how the same genes in the same species—*Solanaceae*—can produce tomato, pepper, aubergine, tobacco and petunia plants—all completely different shapes but from the same genome, whereas at the other end of the genetic spectrum, a recent paper has shown that there are four Giraffe species rather than one, all with different DNA but a similar external appearance. This is a clear demonstration on why we need to be careful about ignoring genetic effects or having perceived bias about phenotypes and conditions until the evidence can show how wrong we were!

6. HUMANS STOPPED EVOLVING SEVERAL MILLENNIA AGO.

Figure 10 shows a typical group of 'intellectuals' the person on the left has the biggest skull and the person on the right, the least hair. These are markers of recent evolutionary advantage. A (fictional) DNA analysis might find that the person on the left might have 3.1% (above normal) Neanderthal DNA and the person on the right might have 2.7% (normal) Neanderthal DNA. Neanderthal DNA incorporated into human DNA in recent millennia, has allowed development of a bigger skull size and prominent nose and larger nasal chambers. This has allowed the evolution of a bigger brain within the larger skull vault with a better breathing control in colder climates—clearly advantageous adaptations welcome in the job of a Chief Medical Officer. What about the person on the right? Even with 'normal' Neanderthal DNA there are adaptations—modern humans have evolved a higher brow and narrower shoulders and

Fig 10. Three GAIN annual meeting delegates, 2008, including Dr Michael McBride (left), Dr Tom Trinnick (centre) and Prof Patrick Morrison (right).

that person has a thinner amount of hair on his forehead—thus increasing the amount of vitamin D that he can metabolise, thus the erect posture and better bone structure confer recent evolutionary advantage. A recent study has confirmed an association between intracranial volume and intelligence, so we can conclude humans are also continually evolving and a small amount of Neanderthal DNA and adaptations to reduce sunlight have both allowed us to flourish in more northerly climates.

CONCLUSION.

I acknowledge six legends to complement the myths, whose personalities were clearly deserving of note and who have influenced me in various positive ways in various stages of my career. In order of myths, these include Norman Nevin (every taxi-driver reminisces about him fondly when they find out I'm a geneticist); Angelina Jolie (she made risk reducing breast surgery an acceptable choice for patients); Charles Byrne (technically the oldest patient whose DNA I've helped test); Dr Richard Godwin-Austin (changed the menu from beef to duck at the last moment at the 1996 association of British neurologists annual dinner so that the pre-dinner speaker just after my presentation on hereditary Parkinson disease—Dr Bob Will—with his breaking science on a new disorder human Bovine Spongiform encephalopathy—wouldn't cause a dietary scene); Elton John (gay, talented, amazing stamina); Dr Michael McBride—a man with many talents and a colossal work-ethic.

The author has no conflict of interest to declare.

DEDICATION

To the memory of Professor Liam J Murray (9th January 1963–12th January 2018), clinical epidemiologist, true gentleman, and medical school ward round partner (figure 11).

Fig 11. Liam Murray deciding not to be a surgeon, ENT student attachment, autumn semester 1984.