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Breeding by numbers: an ancient endeavour that still resonates in the exciting era of functional genomics

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Abstract. 'Breeding by numbers' is the term commonly used to deride the practical application of quantitative genetics. However, even the most subjective methods of assessment of breeding stock actually involve breeding by numbers: whenever a judge has to choose a winner and a runner-up from a line of animals, he/she evaluates each animal for each of several traits, then assesses the relative importance of each trait, and then ranks the animals on a weighted sum of the traits, where the weights reflect relative importance. And if the aim is to rank animals in terms of how good their offspring will be, then the mental gymnastics also involves unwittingly taking account of all the relevant genetic and phenotypic parameters (heritabilities and correlations) of each of the traits and combinations of traits. This has been the situation for as long as animals have been domesticated. The only thing that is different with the quantitative-genetics approach is that the guessing and mental gymnastics inherent in the traditional method of assessment have been replaced by use of a transparent set of numbers that reflect actual performance (or subjective assessment of certain traits) that is directly relevant to profitability, followed by a set of calculations using the best-available estimates of genetic and phenotypic parameters, ending up with the best-available prediction of how the offspring of each animal will perform. Having entered the genomics age, humans will still be breeding animals by numbers in the decades to come, but the numbers will be informed by knowledge of the action of thousands of individual genes.

I am deeply honoured to have been awarded the 2003 Helen Newton Turner Medal. I would like to start by thanking the anonymous donor whose generosity initiated and sustains the award. Anonymous donations are not much in vogue these days. But it is an honorable practice that still has much to commend it. If there is anyone attending this oration who is connected with the donor (or who maybe even is the donor!): to you I express heartfelt thanks. I also thank the Board of Trustees of the Helen Newton Turner Medal Trust. In particular, I wish to note the generosity of spirit inherent in the fact that some of the most-deserving recipients of this medal are trustees, and are thus excluded from consideration for the award. I sincerely hope that, one day, their time will come.

As one who is sufficiently old to be able to say that I knew Helen Turner, I can certainly confirm that she was an inspiration. She 'retired' in 1973 — the year before I commenced my present job. But of course she kept on doing what she enjoyed so much. And when age finally caused her to phase down her genetic activities, I was privileged to receive the collection of reprints of her own papers, which sit on a shelf in my office as a continual inspiration.

When talking to prospective university students or their parents, or to undergraduates uncertain of their future, I like to tell the story of the young female graduate in architecture who, unable to get a job in her profession, trained as a stenographer and got a job as secretary to the foundation Chief of the then CSIR's Division of Animal Health, Ian Clunies Ross, in the McMaster laboratory on the grounds of the University of Sydney; was spotted for her extraordinary talent by Clunies Ross, who (to his great credit) sent her to England to learn statistics by working with Sir Ronald Fisher; and who returned to Australia and went on to become the world's leading sheep geneticist. A truly inspirational story, providing a wonderful illustration of why there is no need to be constrained by what subjects one might have studied at school or at university. For those not privileged to have known her, or who would like to revisit her adventurous life, there is always her informative and entertaining autobiography (Newton Turner 1996).

There is somewhat of a tradition for medallists to provide a brief summary of their formative influences: in my case, the main one concerns an inherited disorder, namely colour-blindness. In chemistry practicals at school and university, titration end-points were always a complete mystery to me, as were stained cells on microscope slides. Any hopes I may have had for a career as a chemist or pathologist were soon cast aside. And my prospects as a farmer were no better: my father was once somewhat taken aback to discover that, when left with the simple job of drafting a mob of sheep according to their ear tag colour, I had managed to create 2 exceedingly random assemblages of ear tags! When I went to Edinburgh as an enthusiastic PhD student, my supervisor Alan Robertson was as surprised as my father had earlier been, to

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learn that I could not undertake the proposed project on mapping QTL in *Drosophila* because I could not distinguish the various eye-colour mutants that were then the standard markers. In the end, my inherited disorder led me to one of the few remaining career possibilities: writing textbooks. In the second edition of 'Introduction to Veterinary Genetics', I gained a somewhat perverse revenge on my colour-sighted brethren when, due to having not yet reached the stage where a publisher would sanction coloured illustrations, I was obliged to reproduce an image of the 4-coloured output from an ABI sequencer in black and white. For those not familiar with such output, the whole point is that the sequence of nucleotides is read by detecting the colour of each 'blip', with each colour corresponding to a different nucleotide. So, the black and white version completely fails to illustrate the point being made!

Apart from being congenitally defective, I am also not wired up like Helen Newton Turner or, in fact, like many of the audience in this theatre: I am not, in other words, mathematical. It was for this reason that I related so well to the response of Solly Zuckerman, who, when asked how he got through anything mathematical in papers, said that he hums his way through (Lewontin 1993). I would like to think that being mathematically challenged has made me a better teacher of quantitative genetics: I certainly understand what it is like NOT to understand!

Speaking of teachers brings me to the first of several important mentors in my life. It is a great pleasure to be able to pay a public tribute to Stuart Barker, a previous medallist, who introduced me to population and quantitative genetics, who supervised my very first research project (and yes, it did involve scoring what seemed like trillions of *Drosophila* bristles), and who, with great generosity of spirit, encouraged me to go to Edinburgh. There I was equally fortunate to be taken under the wings of Alan Robertson and Bill Hill. On returning to Sydney, I was once again privileged to be under the care of Stuart. I have never forgotten his generosity in giving almost all the lectures in my first year, providing me with ample and invaluable time to adjust to this challenging role. So intense was the new lecturer sitting in the front row of all of Stuart's lectures that year, that some of the undergraduates speculated that I was actually a ventriloquist! Given the high standard of Stuart's lectures, I took this as a great compliment.

Another of my very important teachers has been Chris Moran, who also happens to have been my immediate colleague for the last 25 years — ever since Stuart left for the University of New England. Together, Chris and I have shared the teaching of genetics to more than 2000 veterinarians and 400 animal scientists. And, of course, we have shared the supervision of about 45 postgraduate students from whom we have both learned so much. Even more importantly, we have shared the many intellectual adventures that have come our way over the years, and I have benefited greatly from Chris' insight into so many new developments. I am enormously indebted to Chris for being such a wonderful friend and colleague: I could not have asked for anyone better.

In the last decade, I have also had the marvellous good fortune to have Herman Raadsma as a colleague. Herman has added several new dimensions to my academic life, and is a continual source of intellectual stimulation. So too has been John James, the first Helen Newton Turner medallist, who, in the years since his retirement, has graced our laboratory for 2 days a week, providing in those 2 days more help, guidance and stimulation to me and many other staff and students in Reprogen, than most mortals could provide in a full week.

Finally, I wish to extend a very special thanks to my wife, Jan, who has been with me, and supporting me in many ways, since the very start of this adventure — ever since we were fellow undergraduates. Any equilibrium or balance that exists in my life is due to her.

I shall now move on to make what I feel is an important point about the area of science that is commemorated by the Helen Newton Turner Medal.

Helen Newton Turner was a pioneer in the application of quantitative genetics to sheep improvement — sometimes referred to (with more than a hint of derision) as 'breeding by numbers'. Criticism of this approach is usually in the context of comparison with the traditional approach to assessment [those associated with traditional judging at shows and (in the wool industry) with traditional wool and sheep classing] so well described by Darwin (1868) in the following quotation:

'In Saxony the importance of the principle of selection in regard to merino sheep is so fully recognised, that men follow it as a trade; the sheep are placed on a table and are studied, like a picture by a connoisseur; this is done 3 times at intervals of months, and the sheep are each time marked and classed, so that the very best may ultimately be selected for breeding.'

This captures the traditional method of assessment very well: it is very akin to judging pictures at an exhibition.

The really important point that I wish to make is that even the most subjective methods of assessment of breeding stock actually involve breeding by numbers: whenever a judge has to choose a winner and a runner-up from a line of sheep, he/she evaluates each animal for each of several traits, then assesses the relative importance of each trait, and then ranks the animals on a weighted sum of the traits, where the weights reflect relative importance. And if the aim is to rank animals not just in terms of their own appearance, but in terms of how good their offspring will be, then the mental gymnastics also involves taking account of all the relevant genetic and phenotypic parameters (heritabilities and correlations) of each of the traits and combinations of traits. And this has been the situation for as long as animals have

been domesticated: even prehistoric humans bred their animals by numbers, without realising it.

The only difference between what has been happening ever since animals were domesticated and the modern quantitative-genetics approach, is that the guessing and mental gymnastics inherent in the traditional method of assessment have been replaced by a transparent set of numbers that reflect actual performance (or subjective assessment of certain traits) that is directly relevant to profitability, followed by a set of calculations using the best-available estimates of genetic and phenotypic parameters, ending up with the best-available prediction of how the offspring of each animal will perform. And, as John James reminded me when commenting on an early draft of this paper, 'the formal mathematical approach forces us to state all of our assumptions, and this can help us to clarify our approach. It also helps us to identify those things which we ought to know but don't.' These are very important points.

We can conclude, therefore, that the issue is not whether there is any future in breeding by numbers; the important issue (worthy of much debate) concerns which traits are important and the extent to which (and the manner in which) particular traits should be changed by selection. Many people, of course, have realised this for a long time. But I suspect that it bears repeating from time to time. And what better time than a talk that honours the achievements of Helen Newton Turner?

Having acknowledged the importance of breeding by numbers, we can't escape the fact that this lecture is being presented in the middle of an international celebration of the 50th anniversary of the discovery of the structure of DNA — a discovery that heralded the commencement of the molecular era. In fact, Helen lived to see our New Zealand colleagues (Montgomery *et al*. 1993) map the *FecB* mutation — the gene to which she had devoted so much effort. She would have been thrilled with the recent discovery of the actual coding sequences involved in this and other forms of high fecundity in sheep (e.g. Galloway *et al*. 2000; Wilson *et al*. 2001; Souza *et al*. 2001; Mulsant *et al*. 2001), giving rise to simple DNA tests for high fecundity; and she would have been over the moon with even-more-recent molecular detective work (again led by our New Zealand colleagues) that has confirmed her suspicions that the high fecundity of the Booroola Merino can be traced back to Garole (Bengal) sheep (Davis *et al*. 2002).

These discoveries provide a hint of the amazing potential of the molecular era. There is much to be done. And it is very timely that MLA and AWI have joined forces with a national team of molecular and quantitative geneticists to embark upon a 5-year sheep genomics program. There are substantial challenges in getting this program up and running in such a way as to enable it to fulfil its true collaborative potential. But the potential benefits of a truly collaborative program are enormous.

In the decades to come, humans will still be breeding animals by numbers, but the numbers will be informed by knowledge of the action of thousands of individual genes. And this same knowledge will also lead to novel non-genetic means of enhancement of productivity. Very importantly, Helen Newton Turner would have been very excited by such prospects.

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