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Article

Birmingham and Beyond

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Abstract

Nick Martin was a doctoral student of mine at the University of Birmingham in the mid 1970s. In this review, I discuss two of Nick's earliest and most seminal contributions to the field of behavior genetics. First, Martin and Eaves' (1977) extension of the model-fitting approach to multivariate data, which laid the theoretical groundwork for a generation of multivariate behavior genetic studies. Second, the Martin et al.'s (1978) manuscript on the power of the classical twin design, which showed that thousands of twin pairs would be required in order to reliably estimate components of variance, and has served as impetus for the formation of large-scale twin registries across the world. I discuss these contributions against the historical backdrop of a time when we and others were struggling with the challenge of figuring out how to incorporate gene-by-environment interaction, gene–environment correlation, mate selection and cultural transmission into more complex genetic models of human behavior.

Keywords: Twins; power; multivariate; gene–environment correlation; assortative mating; cultural transmission

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The destinies of mentors and students are closely intertwined. I am blessed by and envious of the accomplishments of both over the last half-century. It is a great privilege to pay tribute to Nick. He is hard to keep up with. He walks faster than me. He has far greater insight about the worldly twists of academic lives and influence; he is more knowledgeable, more energetic, more up to date, more generous and more passionate about science than most people I have known. I remember walking quickly with him through the streets of Rome during a Twin Congress, commenting on the significance of the ancient designation 'S.P.Q.R.' on the metal drain covers in the sidewalks. 'Senatus Populusque Romano', I said. 'No', said Nick, 'SenatU Populoque Romano. Ablative not nominative'.

Nick taught me much more than science. A few hours between talks at my first Twin Congress (Washington, D.C., 1977) found me following him breathlessly around the museums and galleries on the Mall, culminating in a visit to the Air and Space Museum that left me in awe of such a cathedral to courage and ingenuity. As a poor British postdoc, I could never have afforded the trip to America had Nick not dictated the letter he insisted I send to the organizers begging for a paid invitation. This led to a sabbatical a year later and, ultimately, to emigration from Oxford to Richmond with my wife, two children and the family cat. Nick's wedding to Georgia in Richmond a few years later was the occasion of my becoming licensed to perform weddings in the Commonwealth of Virginia so that I could assist.

In the early 1970s, I was a keen new postdoc with the Medical Research Council research program in Psychogenetics at Birmingham. The program was directed jointly by John Jinks, F.R.S., Chair of Genetics, and Peter Broadhurst, Chair of Psychology. In collaboration with Sir Kenneth Mather, F.R.S., the previous chair, Jinks had established Birmingham as an international center for 'Biometrical Genetics' in the study of polygenic effects on continuous variation across a range of model systems in flowering plants, micoorganisms, fruit flies, rodents and, most recently, humans. The program in psychogenetics had its roots in earlier previous collaboration between Jinks and Broadhurst on behavioral development in the laboratory rat. In the late 60s, David Fulker pioneered early classical papers on the biometrical genetic analysis of behavior in *Drosophila*, rats and humans.

I had read some of this early work in 1966 as an undergraduate in Genetics. Two years later, John Jinks generously agreed to become my predoctoral mentor in his department after my detour through seminary ended in autumn, 1968. Early in 1968 I had met with Jinks and Broadhurst to discuss possibilities of graduate research in human behavioral genetics. They presented me with a preprint of the Jinks and Fulker landmark, 'A Comparison of the Biometrical Genetical, MAVA and Classical Approaches to the Analysis of Human Behavior' (Jinks & Fulker, 1970). This paper still represents one of the intellectual landmarks in our field for its introduction of human behavioral geneticists to the power of a model-fitting approach to guide the process of choosing among multiple conceptions of the underlying causes of human variation and assigning numerical estimates to unknown parameter values.

I was leafing through my daily pile of line-printer output one morning in the early 70s when the phone rang. 'G'day', I heard. 'Nick Martin here.' 'Uh?' I thought. 'Did you read that paper I sent you?' he asked, referring to a preprint of a paper on the inheritance of scholastic abilities in a sample of Australian twins coauthored with his father, P.G. Martin (Martin & Martin, 1975). 'D[ur]n!' I thought, not having read it. 'Ahem!' I coughed, trying to hide my embarrassment. 'Where are you?' I asked, changing the subject.

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'Oxford', he replied. 'Can I come and see you?' So Nick came to Birmingham, becoming my first graduate student, lifetime friend, colleague, eminent scholar and inspiration.

The next decade was a time of energetic transformation and clarification. Most of the basic ideas were already there in the publications of distinguished colleagues around the world, but the pieces needed gathering together and sharpening. Three problems emerged as most pressing in the next decade.

1. **Extension of the 'model-fitting' approach of Jinks and Fulker to the multivariate case.** The power of biometrical genetics tended to focus on specific single model variables such as final height and time of first flowering in *Nicotiana rustica*, the number of sternopleural chaetae in *Drosophila* and growth rate in *Aspergillus* sp. The study of human behavior, by contrast, was often inherently multivariate, building upon the early psychometric studies of the structure of multiple abilities and personality. Several pioneers (e.g., Loehlin & Vandenberg, 1968) attempted to answer the question of how genes and environment imparted structure to the pattern of covariation between multiple variables, especially human abilities. Most of these early attempts were modifications of existing methods for multivariate analysis, such as factor analysis of estimated components of variance and covariance, or attempts to squeeze twin data into the multivariate analysis of variance. Was it possible to extend the heuristic power of Jinks and Fulker's model-fitting approach to the multivariate case? On a visit to our collaborator Hans Eysenck at the Institute of Psychiatry in London, the problem was outlined to the late Owen White, codeveloper of the Promax algorithm for oblique factor rotation. 'Sounds like you need to look at Joreskog (1978) on the analysis of covariance structures. Maybe look at LISREL'. Owen was the unheralded inspiration for the next step. Unfortunately, the initial versions of LISREL could not quite handle the multiple group problem inherent in kinship analyses, but we were able to figure out how to write our own crude FORTRAN IV program and apply it to a small set of multivariate twin data on primary mental abilities generously supplied by John Loehlin and Steven Vandenberg (Martin & Eaves, 1977). Plant and fruit fly colleagues, used to the fine dissection of genetic effects in complex breeding experiments, were skeptical of these crude attempts. One 'drosophilist' colleague remarked over lunch one day: 'Hm! I have enough problems doing the genetics of one variable let alone spending time trying to analyze five'.

The program, laboriously coded on punched cards, took all night to run on the Birmingham University 240K, KDF-9 mainframe computer, but seemed to work and give sensible answers. These days, a similar analysis in Mx probably runs in one second on a $500 laptop. In the 40 years since, the computer revolution has made it possible for other investigators to extend, teach and apply this basic approach to human quantitative data. Others will write of the twin 'workshops', taught initially in Leuven using updated more flexible versions of LISREL in the presence of Karl Joreskog, and of Mike Neale's persistent work on the development of Mx to allow the unprecedented flexibility of models implying nonlinear parameter constraints.

Like me, Nick experienced the Birmingham course in biometrical genetics. It combined magisterial lectures with exhausting daylong, hands-on analytical sessions where we had to compute generation means and variances as a prelude to weighted least-squares estimation of biometrical model parameters. The nadir was the requirement of inverting by hand the 4×4 information matrix of additive, dominant and environmental components of means and variances on an electromechanical calculator. But everyone who had to do it learned to look at and think about the raw numbers. Every single plant or fruit fly mattered. For Nick, as for many who sat through those long days, the classes were a never-forgotten model of teaching.

In the conference lobby at another Twin meeting, after a depressing series of papers with little common conceptual or analytical thread, Nick energetically urged the possibility of using the Birmingham approach to teach new generations of researchers. Thus were born the first Leuven NATO workshops, under the hospitable eye of Bob Vlietinck and Robert Derom. Later the Leuven workshops evolved, with National Institute of Mental Health support, into the current series of Boulder workshops hosted by John DeFries, John Hewitt and their colleagues at the Institute for Behavioral Genetics. On many occasions, informal gatherings of faculty at the back of the room were the treasured occasion for exploring and discussing new problems.

2. **Toward better models for genes and environment in human behavior.** The early models for genetic effects were embarrassingly simple and due largely to the genius of Ronald Fisher. Our fungal, fly and fruit fly colleagues knew that the effects of genes were far more subtle than Fisher's basic additive and dominant components of variance. Our colleagues in psychology were skeptical of the simple partition of the environment into effects shared and not shared by family members. The elements of more subtle models were already recognized in plant and animal studies with the recognition that different genes may be expressed in different environments and that part of the environmental variation between individuals is a function of the genotypes of their relatives, spouses and peers (the 'genetic environment').

The issue of how best to integrate a biometrical–genetic approach to genetic effects, modeled basically on the pioneering work of Fisher (1918) and Mather (1949) with a mathematical formulation that allowed for the nongenetic interaction among family members was a source of much controversy, even acrimony at times. Different groups applied different numerical approaches to data. They disagreed about the relevance of different theoretical assumptions about genes, environment and mate selection, and even differing traditions of notation for genetic variation. At times, the academic dialogue was even described in terms of 'schools' holding fast to different views of what is worth doing. Controversy about genes and environment in that climate was further compounded by disagreement about the social and political implications of behavioral genetics and the role of single gene models derived from medical genetics to the complexities of quantitative human traits. The biometrical genetic heuristic was articulated clearly in discussion of a conference paper in Eaves (1977). When a senior skeptic questioned why John Jinks' group were not trying to look for the individual genes of large effect, Jinks responded testily (and presciently) on the basis of his life's work so far: 'The number of genes is directly proportional to the industry of the investigator'.

The principal conflict of the 1970s arose between those who had learned the ways of Birmingham which followed the intellectual descendants of Fisher in emphasizing the richness of genetic variation and gene action and those, following Newton Morton and his colleagues (e.g., Rao et al., 1976), who had rediscovered the

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potential of path analysis to recover some of the major sources of nongenetic inheritance and spousal resemblance. It was a minefield of strongly held loyalties that led to some caustic exchanges. I still remember Jinks' withering skepticism when he came into the lab and saw me drawing a path model on a piece of computer paper. Also, I recall a passing conversation with Mather in the corridor when he noted his surprise that a paper I had published referred to the additive genetic variation as Douglas Falconer's 'V_A' rather than his '$^1/_2D_R$'. These were all first fumblings of people who were trying to do their best and 'get it right' in doing justice to the special problems associated with family resemblance in human behavior. It is almost embarrassing to look back at a summary published by a group of us, including Nick (Eaves et al., 1978). There is almost no mention of assortative mating because biometrical genetics had little to say about it. Indeed, most of what had been said by others using path analysis made untested assumptions about the underlying process of mate selection. How we wished for more IQ points! In the same year, John Rice and his colleagues (Rice et al., 1978) published a landmark attempt to integrate Fisher's (1918) model for polygenic inheritance and assortative mating with the insight of Cavalli-Sforza and Feldman (1973) that cultural transmission implied direct transmission from parental to child phenotypes. There were still a few more steps. It was a privilege to spend 2 years in Oxford as Andrew Heath's doctoral advisor. One of our burning questions was how to extend the model of Rice et al. to include both phenotypic assortment and social homogamy. I certainly didn't have a clue. I remember making a few comments to Andrew about my frustration during a tea break (see 'Importance of Tea Break' in the following) in the Psychology common-area. Next morning, I arrived at the office to find Andrew had figured it all out beautifully and attempted patiently to explain it to my flagging comprehension. This would not be the last time.

3. **Design, sample size and data.** By the end of the 70s, it seemed that many important statistical and numerical questions about how to develop and test quite complex models for human behavior had been resolved. These developments allowed a lot for the enormous growth in computer power and development of efficient software for numerical optimization embodied, for example, in that developed by the Numerical Algorithms Group from which we readily borrowed. What we lacked were the data. What kinds of data? How much data? Who was going to collect it? Who was going to pay for it? As long as the focus of behavior genetics lay in estimating heritability or testing for the nongenetic correlation between relatives, family studies before the 1970s were typically small, perhaps 10s or a few 100 relative pairs. Sampling errors, when they were computed were large, and the questions very simple. The influence of our colleagues in biometrical genetics, including Mike Kearsey and Brian Barnes, introduced us to the value of computer simulation of sample size and experimental design to resolve different components of the biometrical–genetic model. Human application of this was exemplified in the paper by Martin et al. (1978) on the power of the classical twin study. These early simulations heightened our awareness that samples in the 1000s or larger were a prerequisite for reliable inference.

During the early 80s, after Nick and Andrew moved to Virginia, this basic approach was extended to the more complex designs that had been generated by the extension of the classical twin paradigm to include the children of monozygotic and dizygotic twins (Nance & Corey, 1976) to explore the effects of the maternal genotype on child development (see also Haley et al., 1981). We were also absorbed by the information that the spouses of twins might yield about the social and phenotypic effects of mate selection (Heath & Eaves, 1985). The arrival of Ken Kendler at the Department of Psychiatry was also an important stimulus to implementing a dream about resolving the possible correlation and interaction of genes and environment by incorporating intensive individual environmental measures in a large psychiatric twin study. Among other studies spawned in this period were Dr Kendler's long-standing series of adult twin studies, the Virginia 30,000 study of the extended kinships of twins and the Virginia Twin Study of Adolescent Behavior Development. Elements of these studies have been transformed into further major studies pioneered by Nick and Andrew after their departure to prestigious appointments in Brisbane and St. Louis, respectively.

4. **The importance of tea break**. Effective science thrives in the crucible of collegiality. All of us who worked in Birmingham at that time remember the twice-daily rumble of the tea trolley pushed from the departmental kitchen to the genetics library where the faculty and students gathered, surrounded by racks of periodicals. In those days, genetics crossed many disciplines, from statistics to cytogenetics and biochemical genetics. Molecular genetics was nascent. It is impossible to do justice to those tea breaks. The range of characters, social and political values, and scientific depth was astonishing and moving. Exchanges were sometimes caustic. Many were the times when questions would arise that led to follow-up side bars where we got to pick the brains of colleagues who knew more than we did. After our arrival in Richmond, space was limited, so we occupied an unused wet lab that soon became littered with piles of paper. Largely under Nick's influence, we continued the tradition of tea break, often gathered round the blackboard, sometimes adjourning for a sandwich lunch at the 'Skull and Bones', a darkly named restaurant associated with the University Hospital. There, ballpoint and napkin took the place of blackboard and chalk.

The expansion of molecular genetics eventually led to our eviction from the wet lab and the removal of our piles of line-printer output, reprints and so on to a more appropriate setting for family-based research. But it turned out we would not be forgotten quite so easily. When the space was remodeled, it was discovered that the drain from the sink had been blocked by a lasting accumulation of lapsang souchong leaves. Nick's special tea.

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