NATURE'S ASYMMETRIES: FROM ATOM TO BRAIN

Review of Chris McManus' *Right Hand, Left Hand: The Origins of Asymmetry in Brains, Bodies, Atoms and Cultures*. ISBN 0 297 64597 8, Weidenfeld & Nicolson, 2002. 412 pages, Price U.K. £ 20.00. U.S. $ 27,95. € 30,00

We live in an age of increasing specialisation. As scientific knowledge increases exponentially, most of us have difficulty keeping up with even a small corner of our chosen field. It is a rare person indeed who can span disciplines and write authoritatively about physics, chemistry, biology, psychology and social anthropology. In *Right Hand, Left Hand*, Chris McManus does just that, and furthermore does so in a lively and engaging style, without compromising scientific standards. This volume is the fruit of a prize scheme set up by the Wellcome Trust to provide funding for a scientist to write a popular book about some aspect of the life sciences. As McManus points out in his preface, writing popular science involves suppressing the academic's habit of peppering the text with references to sources. The largely effective solution adopted here is to provide references to points made in each chapter at the end of the book, supplemented by more detailed treatment of particular points in a website (http://www.rightandlefthand.com/main.htm).

As befits a popular text, a fair proportion of the book is devoted to good plain fun, dealing with what McManus terms "handedness trifles, trivia, and miscellanea". However, this more lightweight material is balanced by detailed coverage of two serious scientific themes that are of particular interest to neuroscientists: (a) why are there species-universal bodily asymmetries? and (b) how can we account for the minority of individuals whose laterality departs from the species-typical standard?

The topic of why organisms have asymmetric bodies has been a particular focus of interest to developmental biologists, and in 1991 Lewis Wolpert chaired a small meeting at the Ciba Foundation to examine this question. Although the title of the meeting was "Biological Asymmetry and Handedness", a great deal of the debate was about hearts rather than hands. In humans, with only a handful of rare exceptions, the heart is situated on the left. At the *individual* level, biological asymmetry is not too difficult to explain. As a body develops from an initial embryo, chemical gradients control growth and cell division to yield a symmetric body, but small chance events can slightly distort this process so that the right develops more than the left in some people, and the left more than the right in others. This is termed 'fluctuating asymmetry'. What perplexed the embryologists was not that the heart is situated asymmetrically in the body, but that in the overwhelming majority of cases the direction of asymmetry was the same. This indicated that there must be some biological landmark that tells the developing organism which direction is left and which is right. At the time of the Ciba meeting, nobody knew what the landmark was, but subsequent research using mice with reversed body organs (*situs inversus*) indicated that heart placement was determined by the direction of flow of a current in a cellular organelle concerned with molecule transportation. Normal leftward flow is influenced by cilia that always rotated in a clockwise direction. A range of biochemical abnormalities can disrupt the leftward flow, and atypical heart placement results.

However, finding cellular asymmetries simply pushes the question back one step further. Why do cilia rotate one way and not the other? McManus argues that this is a consequence of the asymmetric structure of the molecules from which bodies are built. Many molecules occur in two forms that are structurally mirror images of one another, a dextral (D-) form and a laevo (L-) form. In most living organisms, the D-form dominates for sugars and the L-form for amino-acids. So we can explain asymmetries in the behaviour of a biological system in terms of chemical asymmetries in the building blocks from which the system is constructed. But once again, we solve one question only to raise a new one – why is it the case that organic life-forms have such an asymmetric distribution of D- and L- forms of molecules? This could just be chance: if the first life forms on earth had a predominance of one form over the other, then this would be propagated throughout subsequent generations and seen in all organisms derived from the same origins. McManus, however, prefers a more principled account, in terms of greater stability of L-amino acids resulting from physical asymmetries at the level of sub-atomic particles, demonstrated in experiments on the spin of electrons emitted during radioactive decay of atoms. Scientists attempting to test this theory have been studying amino acids found in meteors – if the excess of L-amino acids is literally universal and not just terrestrial, this would support the view that these forms are intrinsically more stable. The jury is still out, but this account of the origins of asymmetry has considerable appeal because of its potential to follow a causal path all the way from physics, through chemistry to biology.

What does all this have to do with handedness and cerebral lateralisation? McManus is quick to point out that in humans there is no correlation between *situs inversus* and handedness, and so we cannot explain one in terms of the other. Nevertheless, the studies on *situs inversus* are important because they provide a model of how asymmetries at the cellular level can lead to asymmetries in developing organs. McManus adopts the traditional line that functional asymmetries in brain function could results from small differences in rate of development of the two hemispheres, with a common factor causing humans to be biased to right-handedness and left-brainedness.

This, however, brings us to the thorny question of individual differences. The genetic account presented by McManus is essentially the theory he published in 1984, which postulates one genetic locus with two alleles to explain both handedness and brainedness. The D (dextral) allele boosts left hemisphere development, and virtually everyone with this allele will be right-handed and have left hemisphere speech. The C (chance) allele causes no bias to either right or left, so handedness and speech lateralisation are (independently) determined by random factors. Heterozygous individuals (with the DC genotype) have a 75% chance of being left-handed. Although McManus argues that the model can account for patterns of handedness in families, and for associations between handedness and cerebral lateralisation, it faces a number of difficulties. The first is that, as he notes, family data on their own are ambiguous – family members share environmental and cultural as well as genetic influences on development. Twin studies allow some disentangling of these effects, by comparison of monozygotic (MZ) twins, who are genetically identical, with dizygotic (DZ) twins, who share on average 50% of their segregating genes. A model such as that proposed by McManus does not predict that MZ twins will have identical handedness, because of probabilistic influences on hand preference in those with CC or DC genotypes. Nevertheless, concordance for hand preference is expected to be greater in MZ than DZ pairs. Twin studies that have looked at this question have typically yielded highly ambiguous data that are as compatible with non-genetic as genetic explanations for individual differences in handedness (Neale, 1988; Carlier et al., 1996; Orlebeke et al., 1996). In my own recent study, family resemblance in twins and their parents was best accounted for by a model that included cultural rather than genetic effects (Bishop, 2001). McManus bases his arguments for genes less on model-fitting than on the lack of evidence for specific environmental explanations, such as one that attributes left-handedness to perinatal stress. However, he does not take into consideration fairly banal reasons for parent-child similarity in family studies, such as biased reportage when one family member reports on handedness of parents, spouse or children. Yet he notes that left-handers are much more sensitive to the presence of left-handedness in other people than are right-handers.

A second problem encountered by a genetic model of individual differences in handedness is that one has to explain why the different handedness alleles persist in the population. Like most writers before him, McManus assumes that a lateralised brain evolved because it was functionally more efficient than a non-lateralised brain. But if this is so, then one would expect those people carrying the D allele to have a survival advantage over those with the C allele, in which case the C allele would gradually disappear from the population. In order to rescue his genetic model from this difficulty, McManus undergoes a pretty serious intellectual contortion. Yes, he argues, the D allele did become universal in humans, but then there was a *new* mutation, back to something like the original C gene. However, this new C gene is not the same as the original C gene (now termed the ancestral C* gene), because it somehow allowed the person carrying it to retain all the advantages of the D gene in terms of rapid cerebral processing, without forcing language and manual dexterity into the left hemisphere. Nevertheless, as McManus himself notes, even if the new C allele did not have the same disadvantages as the original C* allele, it is still difficult to explain its persistence in evolutionary terms. McManus proposes the ‘theory of random cerebral variation’, which maintains that whereas DD individuals have brains that fit the ‘standard textbook’ account of lateralisation, and CC individuals have ‘brain functions flying at random into right and left hemispheres’ DC individuals have most of their functional modules organised normally, with just a few atypically located. This, suggests McManus, could convey functional advantages. Essentially, the claim is that heterozygotes (with DC genotype) are fitter than either DD or CC individuals. The problem is that while it is plausible that certain patterns of cerebral organisation may work better than others, direct evidence is lacking, the situation being complicated by the fact that we can only infer cerebral lateralisation indirectly and imprecisely from handedness (see also McManus et al., 1993). Although McManus is usually careful to check sources and evenly weigh all the evidence, on this topic he was somewhat cavalier, confidently citing dyslexia and stuttering as conditions involving anomalies of handedness and brain lateralisation, in the teeth of much conflicting data (cf. Bishop, 1990).

McManus's focus on genetic rather than cultural explanations of familial trends in handedness leads him to dramatic conclusions about gene frequencies in different populations. First he uses familiality of handedness in different cultures to argue that there are fewer C genes in Asian and African populations than in Western ones: this in itself is not such an outlandish idea, given other polymorphisms that have different frequencies in different races. But he then goes on to argue that a similar pattern of results is seen when one compares data from Western samples at the start of the 20^{th} century (where rates of left-handedness are relatively low but familiality is relatively high) with findings from the end of the 20^{th} century (where left-handedness is more common but familiality rather lower). He concludes that Western populations at the end of the 20^{th} century have more than twice as many C genes as they did at the start of the century. This is hard to believe, given that significant shifts in gene frequency usually take many generations to occur, even under clear selection pressure. The family data can be readily explained without invoking any genes, if we make the simple assumption that sinistral parents are more tolerant of left-handedness in offspring than dextral parents. McManus argues that a genetic account is supported by evidence for reduced reproductive fitness (i.e. fewer offspring) in left-handers at the start but not the end of the 20^{th} century. However, he falls into a statistical trap similar to one he describes much later in the book, when rebutting claims of differential mortality for left- and right-handers. Left-handers have become increasingly tolerated with the passage of time. Suppose that before 1900, most children were forced to be right-handed, whereas after 1900 the pressure eased. This would mean that in 1920, people in their 20s and 30s would be more likely to be overt left-handers than those in their 40s and 50s. Thus on average, we would predict that at a given point in time in the first half of the 20^{th} century, left-handed parents will have been younger (and hence had less opportunity to have a large family) than right-handed parents.

Belief in a genetic basis for handedness is so widespread that it is seldom questioned. The model proposed by McManus is ingenious in postulating a phenotype of dextral vs. chance, rather than right- vs. left-handedness. However, I would argue that this model, like other genetic models, runs into serious difficulties when confronted with empirical data and evolutionary arguments. The alternative is not to assume that handedness is simply a learned behaviour, but rather to recognise that there can be genetic influence on handedness as a species universal, with departures from the normal right-handed bias being due to environmental factors rather than allelic variation. In effect, one accepts that there is a gene that biases toward dextrality, but there is no polymorphism – every normal human has the same (D) form of the gene. Left-handedness is accounted for by assuming that proportion of those with the D gene who are right-handed (and left-brained) is closer to 78% than 100%, and will depend on both random and systematic environmental pressures. Laland et al. (1995) showed that just such a model could adequately account for family patterns of handedness if one postulated some cultural influence to account for transgenerational effects. These could include greater tolerance of, and awareness of, left-handedness in others by left-handers, as well as effects of imitation and positioning of the infant. Such a model can be used to make many of the same predictions about relationships between cerebral lateralisation and handedness, but does not lead one into the thickets of confusion that arise when evolutionary factors are taken into consideration.

I have taken time to lay out my reasons for disagreement with McManus's genetic account because I think the arguments he puts forward so cogently need a counterweight, especially in an age when genetic explanations are often accepted uncritically. However, despite my disagreements with some of the conclusions, I must stress that I regard this volume as a *tour de force* that is quite outstanding in its scope, scholarship and clarity. Readers already familiar with the field of laterality will find a great deal of new material and food for thought. Those coming fresh to the area will see just why laterality continues to fascinates neuroscientists. There is still a great deal we do not understand about the origins and functions of human asymmetry: McManus's enthusiasm for his subject will undoubtedly inspire more scientists to use new technologies in both functional neuroimaging and genetics to tackle these questions.

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BOOK AND NEW MEDIA REVIEWS

EVEN-HENDED

Reply to Dorothy Bishop review of *Right Hand, Left Hand: The Origins of Asymmetry in Brains, Bodies, Atoms and Cultures*. Weidenfeld & Nicolson, 2002.

Authors really shouldn't reply to reviewers. And they usually shouldn't reply to kind, generous, even-handed reviews of the type provided by Dorothy Bishop. If after several hundred pages an author has failed to convince or clarify then the failure has to be in the author's presentation and not the reviewer's understanding. If there is a slight excuse for violating that principle, it can only be that *Right Hand, Left Hand* was written for the general reader, with all the inevitable limitations that imposes, rather than for a reader as knowledgeable as Professor Bishop. Short-cuts were inevitably taken and simplifications were sometimes made, perhaps justifying a few brief clarifications and background comments. If at times I was 'somewhat cavalier', I think I may to some extent prefer, as it was put in *1066 and all that*, to be "Wromantic but Wrong", rather than to be like the Roundheads who were "Right but Repulsive".

The core of the book is the genetic model of handedness and cerebral lateralisation on which I first started working in the late 1970s (McManus, 1979). Like any interesting model it is simple and yet continues to surprise. It provides a reasonable fit to the great mass of family data in the literature, and also, as Bishop comments, readily explains why monozygotic twins do not show identical handedness. It also, incidentally, predicts that dizygotic twins show a slightly lesser concordance than monozygotic twins, as has been found in a meta-analysis (Sicotte et al., 1999). Perhaps most gratifying was that in 2001 the model predicted surprisingly accurately the rates of right-sided language dominance that Stephan Knecht and his colleagues found in right- and left-handers using functional transcranial Doppler ultrasonography (Knecht et al., 2000a, b).

The model began as a *genetic* model, invoking only genetic factors (and measurement error). However, as Bishop rightly says, family data inevitably confound environmental and genetic influences on behaviour. As a result it has always been possible for critics to postulate "some cultural influence", however vague and ill-defined, which might, under the right circumstances explain some part of the family data. This can be seen in a piece of data which, in the absence of decent adoption studies, is fairly strong evidence that handedness is inherited – the children of two right-handed parents are more likely to be left-handed if a grand-parent is also left-handed (Klar 1996; see also http://www.righthandlefthand.com/html/NOTES7.htm, Note7:21). Of course this finding *could* be explained by social learning, but only if the grandparents are alive during the child's early childhood, and only if they have extended contact with them; or it *could* reflect a greater tolerance of sinistrality by the children of left-handers; or a dozen other arm-waving explanations. All those speculations *could* be tested by data, but the proponents of cultural influences rarely attempt to do so, the possibility of truth often being seen as sufficient to reject the genetic model in favour of the all-pervasive SSSM (Standard Social Science Model; Tooby and Cosmides, 1992).

In the mid-1990s the late Phil Bryden and I realised that such an impasse could be circumvented by modelling not only genes but also cultural pressures (Bryden et al., 1997). There is an inherent asymmetry between the precision of genetic theories, and the rather vague, unparameterised and largely *ad hoc* cultural models. When we modelled both genetics and cultural pressure we found they made opposite predictions of how handedness would run in families in countries such as India and Canada which respectively had low and high rates of left-handedness. The findings, subsequently also found in the Middle East, Japan, and Africa, strongly supported a genetic rather than a social explanation for the national differences.

Subsequently I realised that this model could also be applied to Western historical data. There was a strong suggestion that the increased rate of left-handedness between 1900 and 2000 was mainly due to an increase in the number of *C* alleles – of genes for left-handedness, to put it in shorthand. That surprises people, because it is commonly believed, as Bishop suggests, "that significant shifts in gene frequency usually take many generations to occur, even under clear selection pressure". That though is not the case. With natural selection, there can be dramatic shifts in traits over relatively short time periods (Laland and Brown, 2002; Malhotra and Thorpe, 1991; Turelli and Hoffmann, 1991; Vartanyan et al., 1993). Charles Darwin recognised that artificial selection can act even more quickly:

"The great power of this principle of selection is not hypothetical. It is certain that several of our eminent breeders have, even within a single lifetime, modified to a large extent some breeds of cattle and sheep. ... The most skilful [pigeon] breeder, Sir John Sebright, used to say ... that 'he would produce any given feather in three years, but it would take him six years to obtain head and beak'". Charles Darwin, *The Origin of Species*, chapter 1.

Social pressure acting upon left-handers to have fewer children would also be artificial selection, albeit acting on humans rather than other species. Consider a hypothetical story about people with blue eyes. A tyrannical caeruloöphthalmophobic regime takes power in the year 2100, the blue-eyed are decreed to be enemies of state, and the 10% of the population with blue eyes are not allowed to have children. In the year 2100 therefore only 5.8% of the new-born children have blue eyes, and result entirely from matings between brown-eyed but heterozygous parents. A generation later in 2125 the brown-eyed children of the 2100 cohort themselves have children, of whom only 3.8% are blue-eyed. A generation further on in 2150, only 2.6% of children are blue-eyed, and after a further generation in 2175 only 1.9% of the offspring are blue-eyed. Within a human life-time the rate of blue-eyedness drops from 10% to 1.9% – a factor of five. Even if a half of the blue-eyed children in each cohort had surreptitiously managed to breed, still by 2175 only 4.2% of children would be blue-eyed. Artificial selection by cultural pressure can result in large and rapid genetic changes. Whether such a mechanism can entirely account for the change in the rate of left-handedness in the twentieth century is not clear (and the rate of change is indeed extremely fast), but it is clear that any simple model of cultural pressure cannot account for the patterns found in the family data.

Bishop raises many interesting and important questions in her review, all of which could be the subject of several pages of discussion. I cannot however finish without responding to the suggestion that I might myself have fallen into a statistical trap in suggesting that left-handers at the turn of the 20th century had fewer children. Bishop is correct that at most times in the 20th century, left-handers will have been younger than right-handers, and therefore will have had fewer child-bearing years, and hence it might look as if they had fewer children. That explanation however cannot apply to studies such as Chamberlain (1928) in which the propositi were undergraduates and families would have been completed in most cases.

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