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TO WHAT EXTENT HAS FISHER'S RESEARCH PROGRAM BEEN FULFILLED IN AUSTRALIA?

The Knibbs Lecture for 2002

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Summary

This paper reviews Fisher's research program, showing how it constituted a theoretical basis for Darwin's evolutionary, genetical and experimental work, and identifies those fields where Fisher, through his influence on colleagues and students, caused some of his aims to be carried through in Australia, particularly in experimental design and evolutionary genetics.

Key words: evolution of dominance; field experimentation; R.A. Fisher; self-incompatibility.

1. Introduction

When R.A. Fisher retired to Adelaide in 1959, one of his former students, Henry Bennett, had been Professor of Genetics for three years, and an old colleague, Alf Cornish, was both Professor of Statistics and Chief of the CSIRO Division of Mathematical Statistics. Although complications after surgery cut Fisher's life short only three years later, he had come to Adelaide because the intellectual and physical climates were congenial. It was a great privilege to have him around, even though the younger of us, such as myself, did not fully understand the extent of that privilege and therefore how best to take advantage of it.

Fisher communicated that he had a very clear research program in his head, even though he often solved problems for others as major activities for lengthy periods. And Fisher's research program came from Darwin's. Before making this comparison, however, I should state that I do not mean a Lakatosian research program, though a case could be made for such a one, in the sense of the hard core (evolution by natural selection, fiducial inference, etc.), the protective belt (applications to plant and animal breeding, etc.) and other requirements (see Mayo, 1996 for discussion).

It is also very clear that Fisher was not averse to proposing a 'programme of research'; he does so rather deprecatingly on p. 45 (and happily we can quote the page number of the first edition in 1930 or the variorum edition edited by Henry Bennett and published in 1999) of *The Genetical Theory of Natural Selection.* I write 'deprecatingly' because he is proposing an

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enormous body of integrated ecological research, to study the distribution and abundance of animals and plants in an ecosystem, how their physical and biological environment influences them, and how they are changing over time.

2. Darwin's and Fisher's programs

Fisher and Major Leonard Darwin, Charles Darwin's youngest son, conducted a lengthy correspondence on evolution, eugenics and statistics, Fisher learning much about Darwinian inheritance and the world from Darwin, and Darwin learning new science. These letters are published in one of Henry Bennett's very valuable compilations to which I refer further (Fisher, 1983). Several passages are relevant to this paper's theme.

Darwin to Fisher, 4 December 1929:

> My father only had one old and inefficient gardener for his 'staff' for many years, and I believe his work was in some ways all the better in consequence. It made it more original.

Fisher to Darwin, 6 December 1929:

> at about 50, your father had decided that there was little more to be done for the subject out of his own head, but that as a good theorist makes a good observer, so still more in experimentation, that there was a great need for well directed experimentation which should answer the problems, and consolidate the conclusions, at which he had arrived?
>
> If this is so, he was several generations in advance of his time . . .

Darwin to Fisher, 7 December 1929:

> My father wrote [*The Variation of Animals and Plants Under Domestication*] when he was 59 years of age. . . . he said he was physically incapable of attacking another big job, and he took to his botanical work as being much easier. Certainly, team work does a lot, and it wants a good man to shove it along. But I still think that the highest and most original work is done by the nearly unaided individual.

Ghiselin (1969) has demonstrated that Fisher was closer to the truth than Darwin's son. Darwin began his scientific career in 1839 with reports of the voyage of HMS *Beagle* on which he was unpaid resident naturalist, went on to specialist taxonomy, mainly of barnacles, became more innovative with his theory of coral reef formation, then revolutionary with his *Origin of Species* (1859) and *Descent of Man* (1871), and then filled in details on evolutionary mechanisms, adaptation and variation, from orchids in 1862 to earthworms in 1881. Thus, Darwin's scientific career has in retrospect a clear shape: some very specific and detailed works published while Darwin was getting his major ideas in order, followed by the monographs with the major arguments consisting of bold inductive generalizations and masses of supporting evidence, followed by detailed experimental studies of the topics that especially supported his major argument on evolution through the agency of natural selection.

2.1. What was missing from Darwin's program?

We can list the following topics that are missing from Darwin's program:

Geological time
Links between continents
Theory of variability (statistics)
Experimental design (statistics, modes of inference)
Theory of inheritance (Mendelian genetics)
Theory linking genetics and selection.

Fisher's research program is largely set out in the titles of his seven books:

Statistical Methods for Research Workers, 1925
The Genetical Theory of Natural Selection, 1930
The Design of Experiments, 1935
Statistical Tables (with Frank Yates), 1938
Theory of Inbreeding, 1949
Contributions to Mathematical Statistics, 1950
Statistical Methods and Scientific Inference, 1956.

It can be seen that Fisher very consciously sought to supply topics missing from Darwin's program: he took from mathematical physics and his own extraordinarily profound insight to provide the mathematics that linked Mendelism and natural selection; he refined and invented methods for analysing experimental and observational data; and for the first time, with the introduction of new concepts such as randomization, he provided a sound basis for the planning, design, conduct and analysis of the sorts of experiments that Darwin himself had done in his greenhouse and in the field.

If one reads Fisher's early papers (and again we are indebted to Henry Bennett for their availability: see http://www.library.adelaide.edu.au/digitised/fisher), one can see that he had many of his great ideas early. He was so busy throughout his life, not having the luxury of private wealth to support him as did Darwin, that many major ideas, such as the invention of kin selection, he had to leave for others to develop.

Fisher himself made major contributions to many specific areas of genetics: mimicry, breeding mechanisms, polymorphism, dominance, mouse genetics, human blood groups. However, many of these were the result of consultations by colleagues and students. Accordingly he frequently made a contribution to a topic and never returned to it. Most remarkable, in this respect, is his anticipation (Fisher, 1914 p. 315) of what is now called Hamilton's (1964) rule:

> Suppose, for example, that a group of distinguished families possess potential or actual versatility to the extent of being able successfully to fill the role, either of a landed gentleman administering his estates, or of a soldier. A is the eldest son, and stays at home; his brother B goes to the wars; then so long as A has some eight children, it does not matter, genetically, if B gets killed, or dies childless, there will be nephews to fill his place.

Fisher would, one feels, have loved the general flowering of the social biology of insects (e.g. Crozier & Pamilo, 1996; Gadagkar, 2001), where indeed Ross Crozier is one of the world leaders.

3. Where is Fisher's program today?

3.1. Achievements

First, consider Fisher's achievements:

Statistics	Genetics
Design of experiments	Reconciliation of Mendel and Darwin
Randomization	Theory of selection
Sampling distributions	Breeding systems
Maximum likelihood	Human, animal and plant methods

It is beyond the scope of this paper to discuss all of these topics. Some useful references

evaluating his work are: Fienberg & Hinkley (1980), Mayo (1990), Edwards (1994), Efron (1998) and Healy (2003).

3.2. Failures?

Fisher did not succeed in establishing a complete framework for scientific inference. Had fiducial inference lived up to his expectations, he might have done it. Probably the major attempt to revive it was that of Wilkinson (1977) and that has not met general acceptance. Similarly, the likelihood approach is generally seen to be part of Bayesian inference, not a thing in itself. Nevertheless, his ideas permeate the whole of statistics today, and also genetics.

Perhaps in only one area did Fisher go outside Darwin's program: Man in Society. Darwin, for all sorts of reasons that have been over-analysed, showed very clearly in his books on man's place in nature that man was, in Fisher's (1930) words, 'an old world monkey, most closely allied to the tailless apes'. However, he did not touch social evolution in any great detail. Fisher did just that. The human chapters of *The Genetical Theory of Natural Selection* read in a rather archaic, even grotesque, way today at some levels, especially the concern with underpopulation and the proposal for positive eugenics, but are nevertheless very important in highlighting the issues that we need to address as we learn more how biology and society interact.

It is salutary to read Hogben (1931) and to see how one of the few people who could understand Fisher's novel and difficult results could at the same time draw such different conclusions from Fisher's own discoveries. Indeed, Hogben's book, though untouched by the insight provided by Fisher's fundamental theorem of natural selection, is a respectful attempted refutation of most of Fisher's social biology. (And the theorem was perhaps misunderstood by Hogben; not an unusual occurrence, as Edwards (1994) has shown.) Hogben wrote (p. 143):

> Those who are most vocal in proclaiming a genetic interpretation of the rise and fall of civilizations are most insistent in asserting that civilization has failed to devise a method of encouraging the fertility of individuals specially adapted to its requirements. We do not know sufficient about the nature of the genetic factors which determine differences of social behaviour in individuals of the same race and different races to justify the confident acceptance of such a view. Conversely, there are not sufficient grounds for denying that there may be an element of truth in it.

Have we those sufficient grounds today? I think not, but it is a part of Fisher's program that is currently under renewed investigation.

Fisher advocated a particular social policy — family allowances to encourage the more intelligent to have more children — that sounds and indeed is inegalitarian: 'middle class welfare'. In his own words (Fisher, 1983 p. 234), it sounds more innocuous:

> If you take family allowances in their fullest sense as meaning allowances sufficient in magnitude to give an equal standard of living to parents and non-parents doing equivalent work, then the family allowances offer no bribe for parenthood; they merely annul the existing economic bonus for refraining from parenthood.

It could be argued, since the middle class is in a better position to benefit from supposedly egalitarian measures like heavily subsidized tertiary education for all, that much of what Fisher sought is in place, as part of what remains of the welfare state. In one of Fisher's last comments to have been published on the area (Fisher, 1983 p. 272), he wrote in 1950 to a colleague:

> I do not see ground for pessimism in the genetical situation presented by Man, but I think it is quite inconceivable that any existing national state should have the courage to treat it as it requires.

Cronin (1992) summarized thinking in the year of Fisher's centenary. She and others have spearheaded a revival in the application of the genetical theory of natural selection to human society. Sociobiology and evolutionary psychology have been developed on the basis of the application of the theory to human behaviour in small and large groups. What is disheartening to some Fisherians, such as myself, is the certainty with which the implications of some of the new research is presented. Is human nature fixed, and if so, how should we respond?

To a Fisherian, variation is the key: there will almost always be non-deleterious genetical variation influencing any trait in any population. There is no reason to suppose that every man has the genetical potential to rape, for example. Even if it were accepted that one could have such an innate tendency, as advocated by Thornhill & Palmer (2000), for example, that is not to say that there is no genetic variance in the trait. Furthermore, society can overcome this particular propensity, if it is solely a sexual drive, by castration; this is not to advocate such a course of action, simply to recognize that some of what is innate can be changed. We also need to recognize that Hogben's caution applies, *mutatis mutandis*, to statements like:

> Men's psychological adaptation for preferring young adult females evolved because of the positive relationship between fertility and young adulthood in females in the human evolutionary lineage. (Thornhill & Palmer, *loc. cit.*, p.41)

3.3. Life in the mainstream

Most of Fisher's program is part of the mainstream, apart from fiducial inference, though even there some recognize its promise and work towards its full implementation (Albert, 2002). I deal simply with a few developments in a few fields, those with which I have been involved.

Before doing so, however, I address the question of what it means to be part of the mainstream. It does not mean merely that some concept or method is widely used, sometimes without acknowledgement, or that old ideas can lead to new insights. For example, Fisher information, widely used for its original purpose (see Mayo, 1991), is still fresh and has recently contributed to what may be, if correct, a new, and partly Australian in origin, understanding of quantum uncertainty (Hall & Reginatto, 2002).

Being part of the mainstream also means that a person's work goes unread, quoted by hearsay, misinterpreted, in the cases where it is identified with the person at all. Where it is absorbed into technology, it is probably correctly absorbed, even if not correctly used.

Consider a single, simple example: Fisher's (1918) great establishment of the principles of analysis of variance and reconciliation of biometrical and Mendelian heredity, a work used, but not cited, in his 1930 classic, *The Genetical Theory of Natural Selection.* Bradshaw *et al.* (1998) have recently written:

> QTL [quantitative trait locus] mapping has been suggested as an experimental method to distinguish between Fisher's infinitesimal model, in which quantitative traits are controlled by a very large number of loci, each with a very small phenotypic effect (Fisher, 1930), and the oligogenic model, which postulates that continuous phenotypic variation may be because of a few loci with very large effects (reviewed in Tanksley 1993).

They investigated reproductive isolation in two *Mimulus* species, and found that 12 floral traits that contribute to such isolation had at least 64 QTL influencing them. As several of the traits had only 1–3 QTL influencing them, Bradshaw *et al.* concluded that their results strongly supported their oligogenic hypothesis. Sixty genes are evidently very few on their scale. They were following Orr & Coyne (1992), who claimed to have refuted 'Fisher's (1930) assertion

that major mutations almost always suffer severe, deleterious side effects'. The grand old man of US evolutionary research, Ernst Mayr (1998), in the course of explaining 'How I became a Darwinian', referred to 'Fisher's genetic [sic] theory of natural selection, with its emphasis on the fitness of individual genes' as something that 'simply did not speak to the taxonomist'. But then, in the same article he said he had not read Fisher (1930). What did Fisher think? Here he is in 1940:

> In studying the selective response in lint-length of cultivated cottons Panse [1940], for example, has recently exhibited parallel models, some using few (only three) factors, and others an infinite series. The number of factors involved is in fact one of the least influential features of the systems investigated.'

Sometimes, as my colleagues have found for resistance to parasitic worms in sheep, major genes simply cannot be detected in a particular population, even when heritability of the trait is as high as 40% (Beh *et al.*, 2002). This does not mean there are no such major genes; rather, they are not segregating in the cross in question.

We can take Mayr's analysis of Fisher's role further. In a 1991 book, Mayr tabulated the modification of Darwinism, and identified 1918–1933 as the period of 'Fisherism' when 'evolution [was] considered to be a matter of gene frequencies and the force of even small selective pressures'. However, Mayr went on to identify 1969–1980 as the period of 'rediscovery of sexual selection', when the 'importance of reproductive success for selection' was identified.

Since 10% of Fisher (1930) is on sexual selection and over 25% on reproductive performance, one requires only a brief glance at the book to see how contradictory travesties of what he wrote have been set up as straw people by scientists who have not read the book; the variorum edition already cited is particularly instructive.

3.4. Unfinished business: examples

Experimental design

Experimental design, as developed by Fisher and Frank Yates, is now the norm for research where randomization, replication and local control can have a benefit, which is most biological work. We are 'all' Bayesians now, but even so we still use randomization. Some of us think, with Fisher and his descendants, such as Graham Wilkinson, that it is the only valid basis for inference; others just know that it works in practice.

As Yates & Mather (1963) pointed out in their obituary of Fisher, his work is littered with old controversies. One was between him and 'Student' (reviewed in Wilkinson & Mayo, 1982; see also Wilkinson *et al.*, 1983), and it was over the place of randomization as against system in experimental design. In brief, Student contended that systematic designs were more efficient, Fisher that this was largely an illusion when it was not actually wrong. It was unfortunate that they had an altercation just before Student's death, for otherwise they might both have moved to synthesize the two approaches. Fisher (1926) had earlier noticed approvingly that Student had shown an otherwise unacceptable 'sandwich' design (ABBAABBA) could be analysed by treating its parts as units, and with Student alive, Fisher or Yates might have noticed Papadakis (1937). (No doubt they had seen Bartlett (1938).)

This might, once computers were readily available in the late 1950s, have led rather earlier to the Papadakis–Bartlett–Wilkinson succession that has now given us greatly increased efficiency in field trials, especially variety trials. Of course, this is not the only valid approach, but it works. In Australia, most cereal trials are now laid out with some degree of neighbour

balance; that is, the randomization is constrained so that no genotype has the same neighbours too often within blocks, whether complete or incomplete, and there is a definite gain in precision from the use of these designs. Graham Wilkinson calls them 'moving block' designs, in contrast to Fisher–Yates fixed block designs, and this is certainly how he thought of the improvement over Papadakis that has spurred much of the last two decades' work in the area.

In Australia, we have gone over to a standardized approach, summarized by Gilmour, Cullis & Verbyla (1997). They conclude that there are three major components of spatial variation in plot errors: non-stationary global variation across the field, stationary variation within the field, whether local or trend, and extraneous variation largely introduced by the experimental procedures and therefore usually associated with rows or columns. These can be identified by a sequential procedure and so require a strategy starting with the design of the trial, as should be the custom in any case.

While this approach, which is now used for 500 national variety trials a year, has been criticized by Besag & Higdon (1999) as possibly leading to error through over-complexity and separation from the data, it retains the merits identified by Bartlett (1999, in discussion to Besag & Higdon):

> the practical simplicity of Fisher's scheme of design and analysis of agricultural field trials was quickly appreciated worldwide . . . [of importance was] Fisher's identification of the analysis with the design. Such an association seems less compelling for a Bayesian; and Bayesian design is not particularly considered by [Besag & Higdon].

Nor was randomization. In fact, what was remarkable about this excellent discussion paper was that most parties agreed that Bayesian analysis would rescue bad designs, but design itself was left to Fisher–Yates principles.

Now that these tools are in routine use on a large scale as in Australia, we can no longer show what the gains in efficiency are in the actual trials themselves. What we can say is that they are meeting the needs of the users. This is the Fisherian program in practice.

Evolution of dominance

Dominance was one of Mendel's new concepts, though breeders had been aware of 'prepotency' for quite some time, so that Darwin also considered it. However, only Mendel had the clarity of thought and penetrating insight to demonstrate how it had to be defined in order to make sense of particulate inheritance. Neither Mendel nor Darwin considered whence it came. In 1920, favourably reviewing a book on inbreeding and outbreeding, Fisher quoted the authors (East & Jones, 1919): 'may not the tendency to produce dominant unfavourable mutations have been reduced to a minimum by natural selection?' His answer was a short demonstration that direct selection of this kind could not be effective.

In 1922, he wrote:

> Recent work in genetics (East & Jones, 1920) leads unavoidably to the conclusion that inbreeding is not harmful in itself, but is liable to appear harmful only through the emergence of harmful recessive characters. This raises the question as to why *recessive factors should tend to be harmful, or why harmful factors should tend to be recessive: unless this association exist we should expect to obtain great improvements by inbreeding ordinarily crossbred species, as often as great deterioration.* (OM's italics.)

So when Fisher (1928) initially proposed his theory of the evolution of dominance, which in a sense was just as much the evolution of recessiveness, he was seeking to put Mendel's great insight into a Darwinian framework and to explain inbreeding depression, as well as to explain dominance itself. If you reread his early papers on the subject, you see that he

considered that his theory would encompass simultaneous selection for developmental stability of many genes, an idea on which others have worked only recently, as discussed below. The correspondence edited by Bennett (Fisher, 1983) is also important (e.g. p. 235). What he wrote was quite straightforward: deleterious mutations that manifested themselves in the heterozygote would be selected against mainly in heterozygotes because of the rarity of the mutant homozygote. Hence, genes that modified the manifestation in the heterozygote would be favoured. This selection, though weak, would accelerate over time, and in the end ensure that the mutant form became recessive.

Wright (1929a) immediately criticized the theory on the ground that selection of the intensity suggested (of the order of the mutation rate) would be ineffective because of other factors influencing gene frequency: sampling, and primary selection on the modifier gene.

Over the years, the battle rolled back and forth, most of the population genetics discussion ignoring Fisher's original model. Many of the participants have been Australian (e.g. Ewens, 1966; Sved & Mayo, 1970). The consensus today, for those who have kept up with the subject, is roughly as follows (from Mayo & Bürger, 1997). Most of the analytical work has been carried out on an engagingly simple model that Wright (1929b), introducing it, claimed was particularly favourable to Fisher's theory:

	AA	Aa	aa
MM	1	1	$1-s$
Mm	1	$1-sk$	$1-s$
mm	1	$1-sh$	$1-s$.

Here the gene whose dominance is being modified is A with alleles A, a, the intensity of selection against aa is $s > 0$ and $1 \geq h \geq k \geq 0$. The rate of mutation from A to a is μ. The rate of recombination between A and M, the modifier gene, is r. If $r = 0$, the case is that of competition among alleles of one gene. Most of the analyses in the literature assume that changes in frequency of the modifying allele M and the alleles at the primary locus can be described simply in terms of allelic frequencies at the two loci. This is wrong.

The appropriate nonlinear analysis of Bürger (summarized in Mayo & Bürger, 1997) yields a range of results that differ substantially from those derived by Wright and Fisher and their successors, except for the general point that the selective advantage of M depends on the frequency of A. For example, there are cases in which the frequency of the modifier allele can decrease, as can mean fitness of the population. The case of modification of the heterozygote, where it is at an advantage to both homozygotes, has also been shown to be favourable to dominance modification, and this matches observation. Overall, however, there is no certainty that dominance will evolve in an indefinitely large population. In other words, evolution by natural selection cannot be the general explanation for the pattern of dominance of all genes.

But this is only half the story. Wright and, later, Kacser, produced biochemically more detailed theories to explain that dominance would be an inherent property of any metabolic network, and therefore need not be explained separately. The reason for this result is that most catalysed steps in a metabolic network are not rate-limiting, so each step's control over flux through the pathway must be small, even a 50% reduction in enzyme availability (as from a null mutation) having little effect. This theory, like Fisher's, has a number of correct predictions to its credit, e.g. the generally modest effects of increased gene dosage (Wilkie,

1994). To many, therefore, the theory of the evolution of dominance through selective modification of the heterozygote is irrelevant, perhaps dead, particularly because of doubts about some of the experimental evidence, doubts now popularly published (Hooper, 2002; though the particular case she discusses, industrial melanism, had been a matter of controversy before the rediscovery of Mendelism: Smith, 1897).

Unfortunately, the Kacser–Rapoport–Wright theory has no predictive power as regards ecological genetics and the demonstrated cases of modified dominance in traits subject to strong selection, especially mimicry (see e.g. Sheppard *et al.*, 1985). Furthermore, Omholt *et al.* (2000) have presented an argument to the effect that a different class of biochemical–genetic model provides a better explanation for

> 'why recessive mutants are so common'; genetic dominance through intralocus interaction; 'the appearance of dominant mutations'; and 'the existence of functional recessive homologues'.

Data to test between the theories need to be obtained, and may well come through post-genomic studies of large numbers of genes and their products simultaneously, as briefly discussed below.

In summary, the origin of dominance through natural selection is not a closed book, and Fisher's original suggestion is part, possibly only a small part, of the story to whose incomplete elucidation it has been a major spur.

Self-incompatibility

This was a topic dear to Darwin's heart. Having identified the extraordinary adaptations in plants that led to specialized cross-pollination by specialized agents such as insects, and the strength of inbreeding depression, he devoted years to the identification and investigation of some of the mechanisms by which plants ensured genetically that close inbreeding would be avoided.

Fisher worked particularly on some complex cases that Darwin and his granddaughter had investigated. One of these was tristyly; that is, a system whereby three different forms of perfect hermaphrodite flowers existed in a species: one with long styles and short and medium length anthers, one with medium length styles and short and long anthers, and one with short styles and medium and long anthers. Then, as Darwin and Hildebrand showed, no plant can pollinate itself successfully, but each can be pollinated with pollen from plants having a different style length.

Darwin and Hildebrand showed, further, that pollen from anthers at the wrong height on the right plants was as unsuccessful as that from anthers from the wrong plants, which (of course) would also be the wrong height. Darwin's (1876) results from *Lythrum salicaria* demonstrate this clearly, from pollinations and records of seed set from about 250 flowers. He published these results fully, and one can consequently analyse them to evaluate Darwin's qualitative conclusions.

This experiment, which is one of scores performed by Darwin and his 'old and inefficient gardener' on heterostyly, illustrates the scale of Darwin's endeavours, as well as a phenomenon that awaits explanation, and data that only the Fisherian approach allowed to be analysed fully. The results with Long and Short as female parents show no difference between selfing and illegitimate cross-pollination, whereas with Mid as the female parent selfing is significantly less effective than illegitimate cross-pollination. However, overall it is clear that genotypic legitimacy and phenotypic legitimacy are different.

Darwin was a great experimenter, something Fisher never had time to become.

Fisher and his colleagues provided the final evidence that the two-gene hypothesis advanced earlier was correct. They further showed that *L. salicaria* manifested tetrasomic inheritance, and Fisher produced the formal expectations for such systems. However, they did not begin to consider the epigenetics inherent in the results just presented; how was it that crosses that were genotypically compatible were phenotypically ineffective, as if they were incompatible?

My colleagues have shown that three- or even four-gene models are needed for some species of *Oxalis*, and their elucidation is only just beginning (Bennett, Leach & Goodwins, 1986).

4. What was missing from Fisher's research program, and what does the future hold?

Taxonomy was almost absent, and Fisher's dislike of that sort of science is anecdotally established (Box, 1978 p. 17); yet Ghiselin (1969 pp. 78–102) has made a case for the importance of Darwin's taxonomic work in the development of Darwin's thought and in his ability to reason and to defend his reasons. Fisher could not do everything, and his eyesight perhaps precluded much interest in the splendour of the diversity of nature.

One particular contribution that was in Fisher's program, or rather that he suggested for the future, has perhaps not been taken up to the extent that one would have hoped. I refer to the development of a marsupial laboratory animal, the fat-tailed dunnart (*Sminthopsis crassicaudata*). Actually, it is not always the most suitable marsupial to study. In my colleagues' work on the wool follicle there was a need to study the development of follicles of early embryos if possible. Many marsupials develop follicles in the pouch, so are a better object of study than the sheep, which develops them mostly in the first half of gestation. However, the dunnart, unusually among marsupials, has its follicles mostly laid down before birth.

What was missing? The most striking gap is molecular genetics. While Fisher was interested in this area, it neither fitted Darwin's program nor was practicable given what else Fisher was doing, which was mainly mathematically based. In recent years, genetics has become much more focused on DNA (one sometimes thinks to the exclusion of almost all else), and it is of great interest to see the methods that Fisher and others developed to deal with linkage being applied to data inconceivably more extensive than when the methods were developed. Junctions, as a tool, have provided an essential step in using DNA markers in livestock breeding (e.g. Franklin, 1999).

Finally, Fisher's approach to the study of the phenomenon of interaction should be clarified. History is written by the winners, and so the general impression in the dominant part of the genetical world today, that is the United States, is that Fisher neglected interactions and Sewall Wright understood them. Nothing could be further from the truth. Indeed, Fisher, inspired by Mendel, invented the methods by which we study a few interactions at a time, and in a celebrated passage he set out the argument over 75 years ago (Fisher, 1926 p. 511):

> No aphorism is more frequently repeated in connection with field trials, than that we must ask Nature few questions, or, ideally, one question, at a time. The writer is convinced that this view is wholly mistaken. Nature, he suggests, will best respond to a logical and carefully thought out questionnaire; indeed, if we ask her a single question, she will often refuse to answer until some other topic has been discussed.

When we consider the current approaches based on Fisher's conception, e.g. that in Lewis & Dean (2001), we can see that they simply do not work for the patterns of variation that we find in practice. This excellent work considers problems where factors can be categorized as

'design' or 'noise', and variation between categories can be used for error assessment. Such an approach is not appropriate when one deals with several hundred genes that can be deleted one by one and the effects on the whole system assessed, gene by gene. In fact, the results obtained so far from such analyses (e.g. Featherstone & Broadie, 2002) are of great interest as they relate back to dominance modification and other interactions and how these may arise in networks. Featherstone and Broadie showed, among other results, that over 95% of induced deleterious mutations in yeast significantly altered the expression of one or more other genes.

All Fisher's work on breeding mechanisms, on blood groups, and on some other topics such as the evolution of dominance, related to the importance of interactions. How he would have enjoyed the opportunity to invent new methods that we need now to study not just a few interactions but scores, hundreds or even thousands simultaneously. It is one of the biggest challenges to the young mathematically literate geneticists of today.

5. Conclusion

Did Fisher have a research program, and has it been fulfilled? The answer to both questions is yes and no.

Yes, he wanted to provide the theoretical underpinning, mostly mathematical in nature, to Darwin's great and correct theory, and he and all his successors have provided that framework. Indeed, we are still filling in gaps, but the framework stands.

And yes, he did seek to provide an integrated theory and methodology for experimentation in biological research, broadly conceived.

But no, many of his major hopes, especially those related to social biology, remain merely hopes, and are widely regarded as false. This is not, however, to agree with Ruse (1999) that Fisher was driven by the urge to 'justify God's ways to man'. Ruse (1999 p. 84) wrote:

> Fisher's passions were eugenics and Christianity (Box 1978). He believed that God created the world in a progressive fashion ...
>
> Biological degeneration ... can be prevented only through wholesale eugenic practices .... Not to act in this way is to turn from our Christian duty.
>
> One cannot overemphasize the extent to which these views informed Fisher's thinking about the evolutionary process.

In a letter to me, Box (2002) wrote:

> I cannot think of RAF's Christian faith as prime motivation, nor, I am sure, did my book give justification for such a view. ...
>
> No, he was not motivated by Christian faith. I do not know what he believed. But I know that he loved thinking, pursuing lines of thought, enjoying the manipulation of ideas, delighting himself and his hearers when the ideas hung together beautifully in coherent patterns that proclaimed the truth — a truth about earth, of course, we have no evidence beyond. Is that motivation enough?

Letting one's fancy roam, note how Fisher worked, after his early years of struggle for recognition, during which he produced most of his major insights. He was always busy, always responding and often producing his best work in response to what others sought from him, just like Samuel Johnson. Add poor eyesight, worse temper, extraordinary knowledge, head full of worked-out but unwritten material. As Boswell (1791, of 17 April 1778) recorded Johnson as saying: 'Tom Tyers described me the best: "Sir, (said he,) you are like a ghost: you never speak till you are spoken to."' If we conduct careful experiments with numerical results, if we work in evolution, breeding, human genetics, Fisher is the resident ghost in many of our research programs today.

Has there been something special about Fisher's contribution to Australian scientific progress, and Australia's response? Yes: much of the direction of research, from experimental design to plant population genetics to human family studies to evolutionary theory has followed the lines he set down, rather than those of manifold other contenders. Further, some of the major achievements, such as plant variety trial methodology and answers to important theoretical evolutionary problems, have been resolutions of problems Fisher left unsolved.

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