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EDITORIAL

LIFE, CELLS, HETERODOXY AND SURVIVAL: PROBLEMS OF THE EXCLUSION PRINCIPLE

We pick up the essence of an idea and confabulate some appropriate model that adds a suitable amount of flesh to the raw bone. Usually a 'leading light' expounds the new idea—who else gets a hearing? This immediately gives it gravitas and authority before it has been put under the dissecting microscope, or on the scales to weigh the evidence for and against it. Disciples cluster around, offering their bright-eyed comments, pleasing their mentor further, and adding even more substance to the new idea. After all, he who dares to challenge the master might be cast into the scientific wilderness. Before long, the elaborate construct has totally swamped the original idea and a new 'model' is unveiled. Further evidence is accreted at a phenomenal rate during these early days, observations or bits of evidence that are difficult to explain being sidelined (if not flatly ignored).

Very soon, people from another school get news that there has been a sudden advance or breakthrough. Either they fall in line with the model, or pour scorn on it when it shakes their own precious received beliefs and persuasions. Usually it is the latter, and the rival school can be so incensed that their own model has to be revamped and corners tidied up, so that the whole edifice becomes even more impregnable to the possibility of challenge from the other camp's hastily dressed-up creation. Competition at this stage can become extremely heated, and the new and old schools vie for limited funds to uphold their cherished beliefs, in order to carry out work—entirely contrary to the best Popperian principle—that blatantly seeks to secure further unassailable evidence in favour of their hypothesis, hoping to gain themselves further credibility and at the same time expunge the fancies and fantasies of the rival school. These schools were spawned by big fish, who themselves are part and parcel of the funding mechanisms, adding to the charade. The game can get increasingly vindictive, and the sides increasingly polarised. It continually gains momentum, and the rivals continue seemingly oblivious of two things. First, that all available funds directed towards this sector of research will soon be exhausted between them in pursuing their own ends; and second, that any of perhaps many further alternative possibilities have by now been prevented from entering the game and/or are simply ruled out of order. Before long, one school gains the ascendancy and for a generation, maybe more, we are overwhelmed with a 'fact', an unproven theory that we seldom remember is but a hypothesis, and one which pervades the scene by becoming promulgated and entrenched in textbooks.

We stumble along until someone one day calls 'Halt! Enough!' Brave of anyone to do this against the establishment. But we are still in the dawn of scientific thought today, not so much in the way we think, but in the way in which we seem to handle options as alternatives that are *exclusive*. Options are more often than not available, and depending on the circumstances we take one or another, but in changed circumstances just a few moments later we might need to make a completely different choice.

Eventually some heterodox idea might be fired across the bows of rival schools, but momentum means that they generally plough on regardless. However, sometimes as Max Planck's said, 'new ideas do not necessarily prevail, but can persist when old ones fall by the wayside'. Slowly, some of the heterodox thoughts percolate into the general daily thinking of scientists; some begin to make sense of the bigger picture and they slowly replace ideas of the old schools. Occasionally the old school guards come out in gleaming new colours, switching suddenly to support the 'heterodoxy', claiming that a bit of new evidence that recently came to light has meant that their old idea can be quickly restyled in a better form, and that really it had been more-or-less like this all the time, without them fully appreciating it. They take advantage of the heterodoxy they spurned *when* it suits them or there is nowhere else to run. The warlords of science fight another day under a shiningly new and different banner, like politicians crossing the floor of the house when their survival in the party of first choice is seriously threatened. These scenarios are not allegory; they are potted version of how we professional scientists, like politicians, often go about our lives.

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This introduction leads to two points.

(1) *Heterodox ideas* need to be given a fair hearing and a chance to justify themselves as much as the received wisdom needs to be worked on and supported, on the assumption that the former not uncommonly turn out to be true. To dismiss heterodox ideas out of hand is unscientific, especially when we proceed according to Popper and try to demolish rather than vindicate our currently cherished orthodox model. Many great discoveries have come from an isolated individual who has not gone with the crowd, but 'has seen something that everyone else has seen, but thought something that no one else has thought'. Today's heterodoxy can be tomorrow's orthodoxy, and examples are numerous since Galileo and his heliocentric theory.

(2) Theory is theory, and received wisdom is not necessarily fact; it remains hypothesis until it is replaced by something better. Two main schools of thought on a topic of central importance, often with one the more predominant, are usually highly polarised and antagonistic. The idea is usually to prove one is 'correct' and the other false, rather than test both to destruction. But my chief concern is that such ideas are seen as *exclusive*; indeed, they are exclusive in two ways. First, one idea is thought to preclude or exclude the other—we are right, therefore you must be wrong. And second, as already argued, they exclude further possibilities. A good detective novel often leads you to see two key suspects with evidence mounting for each, but equally it is clear that only one was the criminal. As the tale unfolds, a new piece of evidence—often of little apparent consequence at the start—crops up again and is noticed with increasing frequency. In the end, we find that the author has played one character off against another whilst all along a third party was guilty, one who might previously have been the least likely suspect. I suggest that this happens in science and we should be aware that heterodox ideas are akin often to the third party, but I would not even restrict this to three.

When we are considering something like a living cell, as is our business and livelihood, we think too infrequently of viable alternatives operating simultaneously. When a ship gets into difficulties, it has to alter its activity (behaviour), its engines have to work harder, its bilge pumps must pump faster, etc., in order to recover the situation. If the engine fails, a vessel might at be able to turn to sail to get it out of difficulty (or *vice versa* on a modern yacht). And when this fails, then there are small rafts or boats in which to scramble. In these, there may be an engine, and if that engine fails, there are oars. No mechanism has been excluded. The crew of a well-equipped ship will survive best *by not adopting an exclusion principle when it sets sail*. The same is probably true of a cell. If the membrane theory is not totally adequate, then perhaps some other mechanism exists which *together* allows the 'milieu interieur' to maintain its balance and allow the cell to survive.

I am reminded here of my own field in which cell cycle behaviour must be carefully regulated so that cells do not continue to cycle when conditions simply would put such activity and the life of the cell in danger. A major checkpoint, a checkpoint that is the central controller, the decision mechanism for the above yes/no activity, has long been postulated. But let us analogise this situation with Metabolic Control Analysis (Fell, 1997). This states that in metabolic pathways, any enzyme might be rate-limiting, depending on the prevailing conditions. In the growing and dividing cell, there are innumerable checkpoints that have been known about for many years and new ones being decribed. Depending on the prevailing conditions, any one of them can become rate-limiting. Why is it, then, that we are obsessed with a kind of exclusion principle, when as survival machines, cells adopt different strategies, use different mechanisms and undertake a plethora of alternative pathways to circumvent difficulties arising from prevailing conditions that might be threatening their very existence? Why do Sonneschein and Sato (1999) appear to go against the received wisdom when they indicate that growth factors if anything are there to slow-down, not speed-up growth, based on the premise that the cell is normally in a positive-drive mode as far as its proliferation goes. The problem is not to drive it harder but to restrain it from unnecessary further division cycles when it has completed enough or conditions are unfavourable.

In this issue, we will be discussing the need for a broader thinking about the cell, the nature of cytoplasm and protoplasm, the strategies cells adopt to stay alive, to subvert or counteract the more destructive vicissitudes of nature. The first commentary will be by Professor Vladimir Matveev of the Institute of Cell Biology, St Petersburg, Russia, and will be directed at the underlying thesis put forward in Pollack's new book, *Cells, Gels and the Engines of Life* (Pollack,

2001). In the present issue, we can also read an alternative impression of the same book from an American, Professor Ivan Cameron.

Your own comments are very welcome, and should be sent directly to me. In the next few issues, we will be reviewing and discussing two further books that take a broad view of life and the cell. The first will be that of Professor Franklin Harold (Harold, 2001), and the second that of Dr Gilbert Ling (Ling, 2001). The latter seeks to restate the need to examine the theory that has probably been more explicitly dealt with in an earlier book (Ling, 1984). It provided the basis on which Pollack's book was produced. All three books seek to portray the *fundamental* basis of life, and imply we either take too narrow a perspective of it (the first mentioned), or we have the wrong physical premise (the latter two). My reason for opening up these books for commentaries is that the issues at stake are indeed too fundamental to be ignored, and more open dialogue would be healthy.

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(Editor)

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