Thinking About Biology

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Facts?

1.1 The problem with cannabis

In Amsterdam, they say, you can approach a policeman and ask the best place for buying cannabis. Very likely you will be courteously pointed to one of the city's 'coffee shops', where marijuana in a number of forms is on sale, to be enjoyed along with coffee and newspapers. The legalisation of cannabis in the Netherlands is 'The Dutch Experiment', and is a focus of interest for the interminable arguments about drug control in other countries. The liberal Dutch attitude contrasts with the stricter attitudes of the authorities in the UK, where until recently cannabis use was an arrestable offence, with 300 000 people street-searched each year and 80 000 arrested. The differing attitudes of the European countries to drug use is one reason for the constant newsworthiness of cannabis. Another reason is its widespread use. Some 50% of British 16–19 year olds have smoked cannabis; across Europe, there are 45 million regular users. The controversy takes various forms. Some argue that cannabis should be decriminalised. With this strategy, possession remains an offence, but leads to a fine or a warning, rather than to prosecution and a criminal record. Others go further and call for legalisation, so that cannabis is freely available, taxed and even supplied by the state. According to its advocates, legalisation of heroin and ecstasy, as well as of cannabis and amphetamines, will reduce the demand for drug dealers, and so reduce drug-related crime. Moreover, so the argument runs, when criminal suppliers are put out of business, the health problems associated with contaminated drugs will disappear too: government-controlled supplies will be quality assured.

In July 2002, the UK Labour Government confirmed that it was to reclassify cannabis, changing it from a Class B to a Class C drug, so that it will be in the company of mild amphetamines, tranquillisers and anabolic steroids rather than barbiturates, codeine and speed.[1] The change has a pragmatic element and was driven by a consideration of police priorities. Telling someone to stub out a joint takes 10 seconds; arresting and charging them takes 3 hours. No doubt establishment opinion is warming to the idea that cannabis is no more dangerous than alcohol or nicotine: politicians want to visit their undergraduate sons and daughters at college, not in jail. Changing views in the medical profession are also forcing a reappraisal. For example, in 1998 a committee of the House of Lords (the UK parliamentary upper house) recommended that doctors should be able to prescribe herbal cannabis to people with certain illnesses, such as multiple sclerosis. According to the committee's report, the possible benefits patients might get from cannabis meant that it was wrong to expose such patients to legal action simply because they decided themselves to use the drug to alleviate symptoms. Scientists too are involved in the debate over society's proper attitude to drugs. It might be, for example, that scientific research will establish more precisely when and how cannabis, or heroin, is dangerous. A government, facing calls for a change in the law, will ask the following questions: does cannabis use carry the risk of long-term personality change, does it reduce your aptitude to work, is it addictive? The experts called in to rule on the issue will be physiologists as well as the police, psychologists as well as head teachers.[2]

There have been many scientific trials trying to measure the short-term and long-term neurological effects of cannabis or its active ingredient, tetrahydrocannabinol (THC). In addition, scientists and psychologists have investigated whether and how cannabis is addictive. Finally, it should be possible for social scientists to confirm or refute rumours that cannabis is a gateway drug, steadily drawing its users towards a life of needles, addiction and social dysfunction. On the one hand, no one disputes

[1] Class A drugs include heroin, opium, crack, LSD and ecstasy.

[2] The British parliamentary Conservative party generated amusement during its 1999 conference when Anne Widdecombe, then the party's home affairs spokesperson, declared that once in power she would inaugurate a 'zero tolerance' policy towards cannabis. Under the new law, anyone found in possession of even the tiniest amount would automatically face a fine of £100. The policy was quickly dropped after five senior Conservative politicians revealed that they had smoked cannabis when they were students. Soon cannabis was to be reclassified, and it became common to hear police chiefs speculating about the positive effects of full legalisation. The magazine *New Scientist* has a useful archive on both the scientific and the political debates (http://newscientist.com/hottopics/marijuana/). See also the archive of articles on the topic maintained by the UK newspaper *The Guardian* (http://www.guardian.co.uk/).

the importance of the issue: if cannabis is dangerous, then people should be protected. On the other hand, if it is not harmful, or can even alleviate medical conditions, then people should not be jailed for growing it in the greenhouse. Yet, in spite of the science brought to bear on the issue, no final judgement on the safety of cannabis has yet emerged. Even the facts generated by the scientific research are disputed: there are plenty of research data, but no one can agree on what they mean.

Take the question of addiction. An American study at Baltimore's National Institute on Drug Abuse described caged squirrel monkeys becoming addicted to THC. The monkeys were given an injection of THC every time they touched a lever. Soon enough they were hitting the lever deliberately and giving themselves injections as often as 60 times an hour; the conclusion drawn is that cannabis is physically addictive. Meanwhile, the statistics from the Netherlands, where cannabis is decriminalised, are sometimes used to point to an opposite conclusion: that cannabis is not addictive. The percentage of Dutch people who use cannabis is lower than in many other European countries, including Britain. Moreover, the number of Dutch drug addicts has not increased; in fact their average age is rising, showing that young cannabis smokers in the Netherlands are not moving onto something harder. The problem for campaigners on both sides is that the statistics do not close the argument. Neither the data from the Netherlands (done by survey of people's behaviour), nor the data from the Baltimore experiment (done by laboratory work on monkeys), are conclusive. Instead of producing useful predictions for people's behaviour and physiology in a wide variety of situations, the Dutch and Baltimore studies may simply tell us something about people in Amsterdam, and monkeys in Baltimore.

Apart from the question of addictiveness, one of the particular concerns about cannabis is that it lowers mental performance. Once again, science finds it hard to rule one way or the other. There are claims that cannabis users do worse at school and college, and are more likely to become delinquent, but the evidence for this is disputed. For example, there are trials where heavy cannabis users are asked to refrain from smoking for some days, and then to undergo manual and intellectual tests. In a study at Harvard Medical School, individuals who had smoked more than 5000 joints agreed to abstain and then take part in some computer games. They were found to be more aggressive than a group of light smokers. This, however, does not prove long-term damage, but perhaps only the irritation caused by withdrawal symptoms. Moreover, people who become

aggressive in laboratory trials will not necessarily be violent in the real world. Even if it was shown that cannabis users underperform in class, this would not necessarily pin down the drug as to blame. Perhaps people who fail at school are also more likely to use cannabis. The old stereotyping of cannabis users as lazy, or underachieving at college, or unable to maintain relationships, are not likely to be judged true or false by simple scientific trials. The problem is distinguishing between cannabis as a cause, and cannabis as an irrelevance. One in ten road accidents involve drivers with cannabis in their bloodstream, but many of these drivers have alcohol in it as well, and the way individuals vary in their response to cannabis simply is not understood. As a result of these kinds of problems, neither the effects of cannabis, nor its dangers, are reducible to a neat series of undeniable statements. The scientific research is not producing general truths.

The fact that the science does not offer certainty allows another factor to make a strong impact. This is the world of social and political opinion. Many people are horrified by the idea of cannabis being decriminalised. For them, it is simply a fact that cannabis is dangerous, causes college dropout, and inevitably converts our finest youth into comatose junkies. They would much rather someone drinks half a bottle of whisky, than smokes a joint. The fact that others consider alcohol more dangerous, more addictive and more socially ruinous, is an irritation mostly ignored. Clearly, prejudice is at work here. Could prejudice affect the interpretation of scientific results, turning the data in a particular direction, or in none? Cannabis researchers may be looking for particular results. The availability of money may determine whether research is done in the first place, and who does it. Opinions affect whether research is carried out, how it is received, and even whether it is published. The conclusions of the House of Lords report, though based on sifting through the scientific evidence available, were sidelined by the UK Government, who announced that they would wait for more conclusive evidence to emerge. More dramatically, when the World Health Organization compiled a report comparing the dangers of cannabis with those of alcohol and tobacco, and this showed that cannabis is the least dangerous of the three, political pressure led to the report remaining unpublished.

Summary: the facts of cannabis

Cannabis contains a chemical that affects the body. Many claims are made about the dangers of cannabis – to individuals and to society. With so many people buying and smoking cannabis in defiance of a hostile

establishment, it is important to research the truth of these claims. The scientific tools for this research include neurophysiology, psychology and sociology, but we have seen that science is not able to close the argument: its data are disputed, and its interpretations vary. It is a common assumption that the particular merit of science is that it is one area of life where proof and certainty are guaranteed. The cannabis debate suggests something else: that science does not provide final answers and definitive proofs, but rather, that all science involves dispute, and that all science is fought over. This is true not only of the science of cannabis, but of every area of biology too.

1.2 The making of the cell theory

I started this chapter by discussing cannabis. I emphasised how hard it is to find clear evidence on the safety of cannabis. Clearly, social prejudice is a powerful force in determining the history of legal attitudes to cannabis. I discussed too the way that scientific research also finds it hard to avoid dispute and equivocation, and I suggested that this ambiguity, or at least lack of certainty, is a core feature of all of science, not only of admittedly complex physiological interactions. In this section, I take the argument further by looking at cell biology, a much more traditional and mainstream area of biological research than tests on cannabis addiction in monkeys. Cell theory, like evolutionary theory, is a well-established field that forms the basis of all biology courses, and of all biology. Surely this is a field so well understood that it has long since settled into a middle-aged complacency, with everything determined except for a few minor upsets here and there. I will suggest instead that here too, uncertainty and dispute are a central theme. My aim is to raise in your mind the idea that biology is more dynamic, and less fact oriented, than some of your textbooks, and your teachers, may suggest. In particular, I will look at the history of research into what we now call fertilisation – the fusion of sperm and egg – and try to show how a basic biological idea was itself the product of much confusion and disagreement. However, I do not want to imply that all the disputes took place a long time ago, and by using some examples from contemporary cell biology, I hope that you will see that uncertainty and lack of knowledge are fundamental aspects of the modern scientist's life.

Behind the daunting detail of a cell biology textbook lies something simple and fundamental. I refer, of course, to the cell theory itself: the profound concept that all living things are composed of cells, that all

cells come from earlier, pre-existing cells, and that all organic material in nature has been formed by cells. Yet this basic rule of biology was not established merely as a result of the invention of microscopy and the first observations of tissue fine structure. There is a gap of 174 years between the first description of box-like units in cork (1665), and the confident assertion of the cell theory (1839). The pioneer microscopist was Robert Hooke, who examined slices of cork, and was reminded of cells – the places where monks sleep and pray; but he did not immediately suggest that all tissue is made of cells, or comes from cells – why not? The answer is that cell theory had to be made, a net of ideas had to form. It was not simply a matter of looking down a microscope at plant material, finding square structures, and instantly realising that cells make up all tissue, divide, and have different parts. It was not just a blinding flash of inspiration. A great amount of thinking and arguing, as well as looking down microscopes, would be needed before cells, at least as we conceive them, could be seen. Microscopes were needed to make the structure visible; but to make sense of that structure, you need to think, and to have arguments. Those arguments in turn influence how the microscope is used, and what is observed. It is this mix of looking and thinking that makes doing biology a creative process, not simply a cataloguing of facts. It is in this sense that cell theory was created, not discovered.

In order to develop further the creativity of making science, I will now concentrate on one type of cell, and its intellectual history: the reproductive cell – gametes, or sperm and eggs. As with cell theory in general, there was a huge gap in time between the first observation of sperm under the microscope, and their conceptualisation as partners in fertilisation. Sperm were first observed under the microscope in 1670. Yet the idea of fertilisation as a process that puts together inherited material from two parents, dates only from 1870 – a 200-year interval. This delay in reaching the modern understanding was not simply a matter of waiting for better microscopes: a great deal of thinking had to happen too.[3] Some of that thinking we now find strange: one nineteenth-century biologist, von Baer, thought that spermatozoa were parasitic worms swimming in the semen.

[3] Historians of science strongly dislike accounts of science that see the work of previous centuries as slowly clearing mists of ignorance. It is easy to characterise past scientific knowledge as simply a catalogue of mistakes. Historians point out that it is too simplistic to use the 'spectacles' of our modern understanding as a technique for judging the work of earlier scientists. This discredited historiographical method is known as 'Whiggish history'. Such accounts of the past are distorted by being filled out with recognisable ancestors to our intellectual world. Ideas that we now make no use of are simply stripped out, or condemned as absurd. As a result, the history becomes an unreliable account of the debates and intellectual battles that were actually taking place.

However surprising this idea seems to us now, it does remind us that the observation of small motile objects in semen does not in itself amount to a discovery that these wriggling things were needed for reproduction. It was obvious that sexual intercourse is needed to make babies, and that ejaculated semen is the vital male component; but what exactly was this thing that the male supplied – nutrition, or heat, or a mysterious force, perhaps electrical? The basic function of the male semen had been perfectly captured in the Old Testament story of Onan in the book of Genesis. There, Judah orders Onan to have sexual intercourse with (and make pregnant) his brother's widow Tamar (Judah's daughter), in accordance with levirate law. Reluctant to help out his brother in this way, Onan attempted subterfuge by practising coitus interruptus, or to put it in the words of Genesis: 'Then Judah said to Onan, "Go in to your brother's wife, and perform the duty of a brother-in-law to her, and raise up offspring for your brother." But Onan knew the issue would not be his; so when he went in to his brother's wife he spilled the seed on the ground, lest he should give offspring to his brother. And what he did was displeasing in the eye of the Lord, and he slew him.' Onan's sad end is marked by the word 'onanism', a simile for masturbation – but in this case it was Onan's disobedience of God's law, not the act of masturbation, that proved the fatal mistake.

Human semen is a much more obvious thing than human eggs, and so there was early speculation on what and where might be the corresponding 'seed-stuff' within the woman. The ancient Greek philosopher Aristotle was interested in the question and declared that the role of semen was to act upon the menstrual blood, fashioning it into a baby. These and other ideas floated up through the centuries; a more modern scrutiny followed the development of the microscope and the discovery by Antony von Leeuwenhoek of 'spermatic animalcules'.

Antony van Leeuwenhoek is the most famous, though not the first, of the early microscopists. His interest in microscopy was provoked when he saw the illustrations of a completely new microscopical world, as revealed in a revelatory book, *Micrographia* (1665). It was in this book, alongside drawings of magnified full stops and pin heads, that the English physicist Robert Hooke had described the monkish compartments – cells – that he saw inside cork. For Hooke, the cell was empty and inactive: far from the boiling turbulence that is evoked for modern biologists by the word 'cell'. Leeuwenhoek dramatically improved the magnifications available by simplifying the optics, choosing to build microscopes with only one lens instead of two. Leeuwenhoek was so miraculously expert that with

one expertly ground lens, and his own presumably superb eyesight, he could achieve working magnifications of ×200. The cells he saw were more dynamic than Hooke's, more recognisably alive. He was a fine letter writer, and the reports he sent over to the Royal Society of London (founded in 1660) are a reminder of how vivid technical writing can be. Here, for example, is a description of the green alga *Spirogyra*, found in a local lake: 'Passing just lately over this lake ... and examining this water next day, I found floating therein divers earthy particles, and some green streaks, spirally wound serpent-wise, and orderly arranged after the manner of the copper or tin worms, which distillers use to cool their liquors as they distil over'. Thus, in the liveliest of prose, Leeuwenhoek introduced to the reading public such things as blood cells, microscopic nematodes, and, during the 1670s, the 'spermatic animalcules'. These were what we now call spermatozoa.

Thinking about sperm and eggs

The function of sperm was as unclear as their interior. Though the sperm had been described, no one as yet had seen a mammalian egg. However, supplementing the few (and varying) microscopical descriptions there came a rich mix of expectations, both scientific and social. Leeuwenhoek was vigorously opposed to the idea of spontaneous generation – the belief that the decay of plants and animals produced new life in the form of worms and insects. He mobilised all his microscopical discoveries to show that life could be very small indeed, even though invisible to the eye, and argued that the tiny intricate components he saw inside worms and insects could come only from life, not from putrefaction. Leeuwenhoeks's discovery of spermatozoa was important to the campaign. Though the mechanism was unknown, a reproductive role was suggested by the fact that, with care, spermatozoa could be found in the semen of any mammal. Leeuwenhoek favoured 'preformationism', the belief that the embryonic animal contains, in miniaturised form, all the adult organs, which gradually enlarge and become visible as the embryo develops. The concept was applied also to eggs (ova), and to sperm: they too could be a tiny storehouse of preformed parts. However, there was disagreement on whether the miniaturised organism would be in the sperm or in the ovum. Social factors may have contributed to a temporary dominance of the sperm as the home of the embryo. It is men who make sperm, and generally, it is men and not women who inherit titles and fortunes. 'Animalculist preformationsim', the embryo-in-the-sperm, was the biological manifestation

of one of society's most rigid prejudices, that power and influence pass down the male line. With such a view, the female contribution to making babies can only be in providing a nourishing home for the little baby, whether folded up inside the sperm, the womb, or the cot. The sperm, in other words, contained a preformed person, which would be able to grow as soon as implanted in a woman. The female role in such an account does not include inheritance, but does include nurturing. This is an example of science echoing society. All this is dramatically illustrated by Hartsoeker's 1694 drawing of a perfectly formed man or 'homunculus', arms and legs folded, miniaturised but recognisably human, sitting inside the spermatic animalcules.

However, there was opposition to Hartsoeker's homunculus. If every sperm carries a little man, then there must be millions of them, but even the most active father would be hard-pressed to manage more than a dozen offspring. This certainly represented a waste of valuable male heritage. Meanwhile, by the beginning of the eighteenth century, dissection established that mammals develop from an egg. Preformationists therefore began to favour the idea that it was the egg which must contain the perfect, preformed person. This idea, ovism, became the dominant model for preformationists. The theory still fitted well with contemporary ideas of the universe. The seventeenth century physicist Isaac Newton, famous today for his three laws of mechanics, had described a clockwork universe, made by God but understood – and celebrated – by scientists. Newton demonstrated that the physics of terrestrial mechanics and celestial movements were the same. In this view, both God and science have a role. God makes and fits the minute cogs together and sets them running; science locates the cogs and describes their movement. The idea supported preformationism. Perhaps the egg, like the solar system, is a kind of machine, whose pre-squeezed components unfold and grow as the individual develops.

The freshwater polyp hydra was an important element in the eventual demise of preformationism. In 1741, Abraham Trembley watched hydra, described its cartwheeling walk and contractibility, and so showed it to be an animal, not a plant. Then, on further investigation, he found something really sensational: cut a hydra in two and two new animals regenerate. This did not fit well with ideas about preformation. If everything is preformed inside eggs, how can you have whole new organisms being created simply out of ordinary chopped-up animal tissue? Here was reproduction that involved neither egg nor sperm. It had been a central feature

of ovism that eggs are the only tissues able to generate descendents. Trembley's descriptions were hard blows to the theory of preformationism, but did not destroy it completely, for as is well known, one can always ignore bad news. According to Trembley, the scientists of the Royal Society were themselves slow to see the significance. He remarked: 'The singular facts that are contained in the history of these small animals are the admiration of a great many people: but several people have been hesitant to admit them. There are those who have even said that they will not believe it when they see them. Apparently these men have some cherished system that they are afraid of upsetting.' Yet the 'cherished system' of preformationism was indeed opposed by another belief about embryology: epigenesis. This is the belief, emerging in the eighteenth century, that tissues and organs form gradually from an initially undifferentiated mass. During development primitive jelly-like material simply begins to acquire structure: an eye forms, a heart appears, a wing bud emerges. Under the microscope, as time goes by, the detail emerges. According to the epigeneticists, the details become visible slowly because they are forming from translucent living matter, initially devoid of structure. According to the preformationists, the detail becomes visible because the tiny invisible structures finally get large enough to be seen.

We do not need to go into the details of the argument between these two camps, but two points are worth noting, because they are relevant to many other scientific debates. Firstly, there is the question of evidence: what observations might definitely sway the argument in one direction, for example from epigenesis to preformationism? The two theories fitted the observations equally well. Those who believed in epigenesis argued that there was no evidence of preformed parts existing in the early embryo: nothing could be seen. Those who believed in preformation argued that there was no evidence that form was derived simply from jelly: though not visible, the preformed parts were surely there. Secondly, in this dispute, the lack of what we would call scientific evidence was amply compensated for by the robust intervention of belief and expectation. The preformationist saw the hand of God in the formation of all embryos, all at once at the Creation; once made, the mechanical unfolding of embryonic forms simply revealed God's divine purpose. The epigeneticists, in contrast, saw in the coagulation of jelly into tissues a greater triumph for the laws of nature: that such laws can create living matter, not just keep the cogs of the universe turning. Not that the epigeneticists were atheist: they believed in God, but did not see him as having to set everything off right at the

beginning of the world. Epigenesis revealed how God was present in every Law of Nature, and had no need to make a special creation of every embryo: embryos formed naturally from undifferentiated matter.

I do not mean to suggest that developments in science are simply a result of wider changes in attitude. Indeed, just as the epigeneticists won the argument, a whole series of changes took place in the capabilities of scientists. One major change was in the microscope, now capable of finer resolutions and greater magnifications. However, a key factor in the adjustment of scientific minds to the plausibility of epigenesis was change in the wider intellectual context. Towards the end of the eighteenth century, the Romantic Movement in Europe reacted against the idea of a mechanical universe. In England, the great romantic poets included Samuel Taylor Coleridge and Percy Bysshe Shelley. However, in Germany, the movement was represented most strongly by philosophers such as Herder, Schelling and Hegel. Their descriptions of a progressive, living, universe clashed with the cold and automatic mechanics of Newton. In science the influence would be strongest where Newtonian mechanisms had made the smallest headway: biology. The influence was felt particularly in the debate between the preformationists and the epigeneticists. The great German philosopher Immanuel Kant, himself interested in science, stated in his *Critique of Judgement* (1790) 'Absolutely no human reason can hope to understand the production of even a blade of grass by mere mechanical causes'. Instead, according to Kant, one should simply take it for granted that life is self-organising and self-regulating. Epigenesis, descriptive of organic matter becoming more organised, fitted this philosophy well.

Political and social forces would also support epigenesis. The Enlightenment, a wave of ideas in Europe at around the end of the eighteenth century, saw hope in the power of human reason and doubted the value of religion and tradition. Human thought – an exemplar is science – would transform the world from backwardness and lawlessness to a place of justice and progress. Clearly, this resonates more completely with epigenesis than with preformationism. The former evokes images of jelly-like masses transforming themselves into ordered cells: progress. Preformationism, in contrast, suggests that we are in the grip of fate, with life unfolding itself remorselessly without any possibility of improvement or even real change. In this intellectual climate, scientists who supported epigenesis no longer had to defend themselves: the self-organising abilities of life were now taken for granted. The task now was to use better optics to improve descriptions of development, from the earliest stages. A new way

of working had been inaugurated, with a new set of preconceptions, and if the early stages of life no longer consisted of a miniaturised adult, then the real role of sperm and egg could be given new scrutiny.

If you consider your own understanding of fertilisation, you very likely regard it a matter not simply of the fusion of two nuclei but, more crucially, as the bringing together of two sets of chromosomes. For a modern biologist, it is simply impossible to think of a sperm fusing with an egg without at the same time seeing a rearrangement of chromosomes, but in the eighteenth century, not only were there no ideas about chromosomes, there was also no stable scientific sense about cells or inheritance. You can easily understand, therefore, that when questions began to be asked about the function of sperm and eggs, the answers given would depend not solely on the improvement of microscopes, but also on the changing views of cells, cell division and inheritance.[4]

When chromosomes were first seen, it was their involvement in cell division that was so obvious, not their role in inheritance. This is not so surprising. What was starkly visible was simply that chromosomes go through a complicated series of movements during division; perhaps that was their job – some kind of mechanism for getting cells to split into two. Yet for many biologists, a theory of inheritance ought to be based on what was known about cells. Cell contents should give clues about inheritance. Moreover, common-sense observations of children, who look a bit like both their parents, suggested an equal investment from sperm and egg. The nineteenth-century cell biologist Nageli asked himself the simple question: with the sperm so tiny, and the egg so big, how could the two of them ensure an equal contribution of the 'inherited material'? Nageli suggested that there must be a fraction of the egg which is important in inheritance; he proposed calling this fraction the 'ideoplasm'. He thought that the ideoplasm could only be a fraction because the egg is 1000 times bigger than a sperm, and yet makes an equal contribution to the offspring. The part of the egg contributing to the offspring cannot

[4] I am emphasising here a fundamental aspect of the history of science – that scientific discovery is not simply a matter of improvements in technique and of new observations. There is always a context to scientific work, influences that extend far beyond what is usually called 'the world of science'. It is in this sense that scientific theories can be seen as created rather than discovered. The unpicking of the many factors that make up a scientific change is highly complex, and my description of seventeenth- and eighteenth-century biology is necessarily brief and selective. For a more in-depth account of the historical events outlined in this chapter, try Ernst Mayr's *The Growth of Biological Thought* (Cambridge, Mass.: Harvard University Press, 1982) and Shirley Roe's *Matter, Life and Generation* (Cambridge: Cambridge University Press, 1981).

therefore be any larger than the sperm. This excellent idea, a 'thought-experiment really', did not lead Nageli to make the apparently obvious connection: that the ideoplasm might be the nucleus.

The whole point about inheritance is that something passes down through the generations – but what? Perhaps at this time – around 1880 – ideas were beginning to link up. Microscopists could now watch fertilisation, and knew it to be some kind of interaction between the sperm and the egg. With Nageli's idea of the ideoplasm so influential, and the nucleus coming under closer scrutiny by an ever-growing community of cell biologists, some details began to emerge. The nucleus was patterned, not simply a blob of jelly. There were those large structures inside, which had proved so thought provoking: the chromosomes. Stains allowed their regular movement to be charted, and wondered at. Earlier in the nineteenth century, biologists liked to think of electrical excitation as the most important aspect of fertilisation. In this, they were simply being fashionable: the physicists of the time were revered for their laws of electromagnetism, and for their impressive, useful machines. Yet if fertilisation was simply a matter of a sperm electrically exciting an egg (as some physics-loving biologists had suggested) then why was cell division, and especially the movement of the chromosomes, so complicated? Alternatively, if the nucleus was merely a chemical storehouse, full of some kind of glutinous ideoplasm, why not simply divide it into two rather as you divide a bottle of wine? If equality of amount is the important thing, then you would expect a rather simple splitting, not this remarkable chromosomal dance. A theory was needed to put together all that was known about inheritance, cells and development.

Today we do not use the word ideoplasm. We say instead that the inherited material consists of particles called genes, arranged on the chromosomes, but in 1880, though Mendel had done his work and had indeed discussed inherited particles (he called them 'factors') his paper was languishing, unappreciated, and nothing was known of genes or DNA. So when a biologist called Roux, working at exactly the same time as Nageli, and thinking about the nature of the ideoplasm, worked out from first principles that the material must be particulate, the insight was crucial. Roux thought: if inheritance is by the passing on of particles, how do you make sure each of the daughter cells gets a full set? If each particle represents (today we would probably say 'codes for') a particular aspect of the living form, it is no good giving half the particles to one daughter cell,

the other half to the second daughter cell; the result of this straight split would be to give each of the daughter cells a completely different set of particles, yet in mitosis the daughter cells are identical. Roux realised that for particulate inheritance to work each particle would have to double and the resulting pairs be split away from each other into two new cells. The best way to do this would be to have the particles lined up, like beads, and for the string to split longitudinally. Roux wrote: 'The essential process in nuclear division is the halving of each of the maternal corpuscles; all other processes serve the object to transfer one of the daughter corpuscles to the centre of one of the daughter cells, and the other to the centre of the other daughter cell.' Meanwhile, improving techniques in microscopy meant that the chromosomes could be studied not just during cell division, but also during fertilisation. A Belgian scientist, van Beneden, did the crucial experiment in 1883. Working on the nematode *Ascaris bivalens*, he showed that at fertilisation the two chromosomes of the male gamete join but do not fuse with the chromosomes of the female gamete, so that the zygote has four chromosomes.

So you can see that in the 1880s a whole series of ideas, new techniques and observations were coming together quite quickly to form an understanding that is recognisably modern. It must have been an exciting time. Theories about inheritance and about development had met with theories about cells. There was better microscopy and there were better conditions for scientific research. Each of these factors worked its influence, and a stable agreement amongst biologists became possible. The cycles of experiment and theory seemed to be leading to a coherent view of cells, chromosomes, and cell division and fertilisation: one that would last. As biology moved into the twentieth century, the foundations of cell biology had been laid: the nucleus is the carrier of inheritance; fertilisation is the fusion of two cells, but not the fusion of the chromosomes; there is a continuity of nuclei, from one generation to the next; there can be no break in this cellular continuity, and no possibility that a cell can form from anything other than another cell.

Summary: the making of cell biology

With few exceptions, cells are too small to be visible to the naked eye. In order to investigate cells, intervention with a microscope is required. The refinement of microscopes over 300 years has profoundly influenced biology, but it would be a gross simplification to imagine that the development of cell biology has simply been a matter of improving optics. A cell

biologist works not only with cells and instruments, but also, as I have described above, with ideas.

Scientists, being human, speculate. They have imaginations, and see their work as creative. Therefore, however excellent the microscope, there will always be the need, and the desire, to interpret the shadows of a dimly seen image. The scientist's own preconceptions shape the interpretation. The scientist does not just read data passively; the information is sculpted and given meaning. It is this active searching – sculpting – that makes science a creative activity where social and intellectual contexts, personal whim and ambition, technique, skill and luck are each important. Together they make up 'the mangle of science'. To sum up, science is a complex social phenomenon, not just a technical activity. We expect to find in its discussions and its published papers plenty of facts and theories, but the production of these ideas is not simply a matter of accurate observations being carefully recorded. It is neither a list of discoveries made by modest workers, nor an expression of ambition, prejudice and academic manoeuvring; instead it is a mix of all these, and the mix is as creative in the twenty-first century as it was in the eighteenth century.

1.3 The edge of the amoeba

You might imagine that as the technique of microscopy improves, the possibility diminishes that scientists can argue about the meaning of observations, but you would be wrong. When electron microscopes were invented in the 1940s, magnifications of $\times 40\,000$ became possible. Ultrastructure, for example the detail of mitochondrial architecture, became visible. How can we be sure though, that those lines and dots and circles represent real biological structure, rather than lumps of precipitated stain or tears and folds in the specimen? Bear in mind the extremes of manipulation a biological specimen undergoes prior to being slid into an electron microscope's holding bay. Cells must be killed, dehydrated, fixed, stained, and sliced, before being positioned in a vacuum chamber and bombarded by a beam of electrons. Along the way, you can imagine, something might be added that fools the microscopist. Such changes, produced by a procedure rather than by nature, are called artefacts. Artefacts worry biologists, who want to take for granted that their complex techniques generate reliable data about cells. Thus, though it is true that biologists may be aware that they are active in giving shape to their data, they certainly do not want that active involvement to extend to the generation of false data, either

deliberately or by accident. So biologists have to work hard to feel confident that the things they see do indeed exist.[5]

We can get a sense of the importance of artefacts in biology by looking at that great classic of cell science, the movement of amoeba. There was a time when every A level and High School biologist studied the internal motions of the amoeba's cytoplasm. These movements are so familiar that you might imagine that little remains to be found out about the way cytoplasm squeezes and pushes. The basic ideas were worked out at the start of the twentieth century. As a subject for investigation, cell movement has some obvious difficulties. How do you study the movement of cells if you cannot stain them, for fear of killing them? This was of particular relevance for scientists in 1970, who asked themselves the simple question: how does the amoeba grip? Strangely, when biologists worked to understand amoeboid movement, they only considered what was happening inside the cell. But whatever the internal wanderings of the cytoplasm, an amoeba is going nowhere if it cannot grip onto a surface. In other words, if an amoeba is to move, it must have traction. In the laboratory (though not in real life) amoebae move along cover slips or glass slides, suggesting that the friction – the traction – must be occurring in the zone between the amoeba membrane and the cover slip. This is an extremely thin zone; it is transparent, and any 'contact' between membrane and glass is going to be well below the theoretical resolution of light microscopy. Assuming that there is something interesting happening, how are you going to make it visible without killing the amoeba, and if you do find a technique for making it visible, how will you ensure against artefact?

The optical problems are huge. Although some amoebae are amongst the biggest cells in existence, they are transparent. Therefore, not much detail is seen using ordinary bright-field optics. The problem has long been solved by various breeds of interference microscopy, optical techniques that provide contrast by emphasising those tiny differences in density existing inside transparent cells, but not perceived by our eyes. Phase contrast microscopy is the most familiar of this stable of techniques, but there are many more, all exploiting the fact that if two wave fronts of light

[5] Philosophers have a name for most beliefs: 'realism' is the term used for the way most scientists believe their observations and theories describe real structures in the world, rather than (useful) figments of the imagination. Doubting realism is not the same as doubting the existence of the world, nor even that scientists discover truths. The philosophical debates over realism have been prompted by terms like 'electron' and 'quark'. These entities are not observable, yet they are important parts of physical theory, and are modelled successfully by mathematics. It is quite common in science and philosophy to find someone committed to the usefulness and even the truth of a scientific theory, but hesitant to declare the described entity (such as a quark) 'real'.

interfere after passing through a cell, destructive and constructive interference will provide a pattern of light and dark, a pattern that corresponds to real differences of density within the cell.

Having got the contrast, other tricks can be applied. Detail not picked up by the eye might be better served by highly sensitive cameras. Video can allow analysis of images at leisure, and such images can be analysed with computers. Every observation system creates 'noise' ranging from mess and scum smeared on lenses to the tough-to-eradicate problems like variations in background illumination, or small optical faults. A computer can store an image where there is only background illumination and no specimen, and compare it with a image where there is both background and specimen. Any detail in the specimen that also turns up in the specimenless background image can be removed by the computer, cleaning up the image.

For a microscope to be useful it must not simply magnify, it must resolve, that is, see as distinct objects that truly are distinct. A good example can be taken from something studied earlier in this chapter: chromosomes. These structures are quite small, inside the nucleus, and the number depends on the species of organism. To see chromosomes it is no good simply magnifying them: you must be able to distinguish one chromosome from another. If all the chromosomes appear as one single blur, the simple magnification of that blur will not help at all. It is the resolution of tiny things – telling them apart – that is the aim of microscopists. There is a limit to a microscope's performance. When two objects cannot be told apart, the 'limit of resolution' has been reached. In light microscopes the limit of resolution is about 0.2 μm – half the wavelength of blue light. A typical cell might be 10 μm in diameter, and so can be easily resolved from its neighbour. A nucleus might be 1 μm across, and a vacuole 0.8 μm; with practice, and the right stain, these organelles can be seen with a light microscope at high magnification. Bacteria too, sized around 1 μm, are visible, but organelles such as mitochondria or the Golgi body stand at the edge of the invisible. The inner structure of these organelles, for example, the membrane convolutions so commonly seen in mitochondria, resist the light microscope completely. The description of this ultrastructural detail awaited the development of the electron microscope: the wavelength of an electron beam is far smaller than that of light and this is the most important reason for the exceptional resolving power of these remarkable machines – 0.1 nm.

For those wanting to discover how the amoeba got its grip, the key technology was another form of interference microscopy, reflected light interference microscopy (RIM). Complex in detail, the technique nonetheless relies on a simple principle. Light bounced off two or more partly reflective surfaces will show interference if the surfaces are very close together. Imagine an amoeba crawling along a cover slip. There are several surfaces: the surface of the amoeba and the two surfaces of the cover slip. The closeness of these surfaces, and the fact they are partly reflective, allows interference patterns to develop. To get the effect, light is shone up through the cover slip and into the amoeba. Most of the light shines straight through the glass and the amoeba and out the other side; this light is lost and plays no part in the experiment. Some light, however, shines through the glass but is reflected back by the underside of the amoeba. Other light is reflected straight away by the glass cover slip. It is these two wave fronts, one reflected from the amoeba, the other from the cover slip, which can be made to interfere and produce a pattern. The type of interference pattern depends on the distance between the membrane and the cover slip: a wide gap will give a certain level of brightness, a narrow gap another. In short, all the conditions for resolving tiny objects have been met and indeed RIM has the ability to distinguish between a gap of 20 nm and one of 100 nm, simply because different gap sizes produce different patterns. A big gap can be resolved from a small gap. The prediction of course is that the amoeba gets its traction by making close contact in some way with the substratum: by tiny feet perhaps, or by larger blocks of membrane? RIM will show where the contacts are, and give an idea of their shape.

In practice, to see the amoebae grip, they have to be made to crawl along in distilled water, which is difficult, as only some amoebae (for example *Naegleria*) can survive such conditions. If the water is saline, the image is grey and unpromising. As soon as the molarity of the saline solution is reduced enough, something extraordinary happens: black spots emerge vividly from the background, perhaps 15 to the cell. As the cell streams by, the spots stay in the same place: then, certainly, they must be attached to the substratum. The mathematics of the interference confirms the spots to be 'zones of extremely close contact' between the amoeba and glass. The cell uses these focal contacts as fixed points through which to gain purchase on the surface; the front of the organism puts down a few contacts onto the cover slip, and then flows past. Eventually, the focal contacts are at the back of the animal and are taken up into the cell. It is all very impressive, but how can we know that these observations of focal contacts

represent the real actions of amoeba, and are not merely artefacts resulting from extremely complex microscopy?

Even if focal contacts are shown to be real for laboratory amoebae crawling over cover slips, biologists will want to be sure that they also exist for 'wild' amoebae living on a bumpy, uneven substrate.[6] In the traction experiments, cells moved through controlled aqueous solutions, and when the salinity was reduced to zero, the focal points suddenly snapped into focus; but amoebae do not inhabit distilled water – could the focal contacts have formed simply as a result of the malign effect of the unfamiliar distilled water, or did they become visible only at that point, as a result of the type of optics? If the former is true then the focal contacts are simply an artefact of the experiment; if the latter is true then there is no problem.

The best way of reassuring yourself about the problem of artefacts is to use other sources of evidence. Suppose, for example, that you are observing cell structure using stains and the ordinary light microscope. Something apparently new appears; might it be an artefact? It will not be if it can be seen using other types of microscopy, for example, low power transmission electron microscopy, nor if it appears, day after day, in different preparations. Most people's first experience of science is at school. Here, they are repeatedly told that experiments must be 'repeatable'.

In the case of the focal contacts of amoebae, independent lines of evidence for their existence come from the fact that they have shown up in transmission and scanning electron microscopy. A vital, further, line of evidence involves biochemistry. Cytochalasin B is a drug with a well-understood ability to interfere with the polymerisation of actin, the molecule known to be the main component of the cytoskeleton. Focal contacts, if they are to act as anchor lines by which the amoeba pulls itself along, must not only be firmly attached to the substratum; they must also be integrated into the cytoskeleton. The hypothesis that focal contacts are part of normal life for amoebae – are how they get about – is supported by the following observation. Amoebae stop moving when they are

[6] This material is drawn from the work of Terry Preston (University College London), and from his book *The Cytoskeleton and Cell Motility* (T.M. Preston, C.A. King and J.S. Hyams, Glasgow: Blackie, 1990). The field of cell motility is an excellent example of research that embraces both molecular techniques and an interest in the life of the whole organism. The issue of how cells grip and move is of obvious medical importance, for example, in understanding the spread of cancer, and molecular techniques are necessary for the investigation. Preston's question 'how does this organism get around in its world', is an important influence in determining the design of the chemical and microscopical investigations. There is more on the virtues of thinking about the lives of organisms in the next chapter.

in the presence of cytochalasin B. Internally the cytoplasm keeps flowing, but is unable to move the organism along. What has happened is that the turnover of focal contacts, and their integration into the bulk of the cell, have been disrupted, and so they can no longer assist in locomotion. This piece of evidence, along with the observations from interference microscopy and electron microscopy, makes it extremely unlikely that focal contacts are artefacts.

1.4 How cells evolved

My next dispute over the meaning of evidence concerns mutualism and the origin of the eukaryotic cell: a cell containing a nucleus, cytoskeleton and cellular organelles. Mutualism is the beneficial living-together of organisms. The general phenomenon of evolved relations between different species now has the umbrella term 'symbiosis', and includes both parasitism (where one organism is harmed) and commensalism (where neither harm nor benefit seems to occur to either species). A common example of a mutualist relation is the one formed between the shark and the pilot fish that clears the shark's gills of parasites. The shark protects its guests from predators and in return gains relative freedom from parasites. A more intimate example is the lichen, which is a long-term association between algae and fungi. In the case of the lichen, and of the shark, the association is not itself inherited, but there are examples where a mutualist relation is passed on to the next generation. The plant *Psychotria bacteriophia* has an association with nitrogen-fixing bacteria. These bacteria are not only in the roots of the plant, they are deposited in the seeds before reproduction. Thus, the new generation is launched not only with a complement of parental DNA, but also with some helpful bacteria. Mutualist relations can be very complex, involving more than two partners. Termites, which cannot on their own digest their woody diet, rely on other organisms living in their guts to provide the proper enzymes. One of these guests is the protoctist *Myxotricha*. The protoctist benefits from shelter and a good supply of food, and digests enough wood to provide a good source of nutrition to the termite. In this case, however, even the protoctist is an association: it harbours on its outer coat colonies of motile, whip-like bacteria called spirochaetes, whose energetic undulations propel the protoctist forwards. This seems like an extraordinarily intimate cohabitation, and is greatly celebrated by biologists interested in mutualism. It was these enthusiasts who in the 1970s put forward and defended a theory claiming