The rough and the smooth

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The Transforming Principle: Discovering that Genes are Made of DNA.
By Maclyn McCarty.
W. W. Norton: 1985. Pp.252. $14.95, £14.95.

FOR most young molecular biologists, the history of their subject is divided into two epochs: the last two years and everything else before that. The present and very recent past are perceived in sharp detail but the rest is swathed in a legendary mist where Crick, Watson, Mendel, Darwin — perhaps even Aristotle — coexist as uneasy contemporaries. It would not surprise me to find that most graduate students have not heard of Avery, MacLeod and McCarty or of their discovery that the transforming principle of the pneumococcus was DNA. The general ignorance of our times might easily consign this book, with the wonderful title *The Transforming Principle*, to the "Religion and Occult" section of a bookshop, as once I found Levi-Strauss's *The Raw and the Cooked* under "Recipes".

The book is Maclyn McCarty's account of his own life and, at the same time, the story, told from first-hand knowledge, of the discovery that genes are made of DNA (or, as it was seen then, that inherited characters could be introduced into bacteria by DNA). It is a story that is plainly and simply told, with none of the self-centred pomposity of so many autobiographies, and with an objectivity that increases its interest and fascination. McCarty came upon the scene quite late, and departed soon after the publication of the important paper; he seems to write about the work from the stance of a less involved observer but is nonetheless decisive and clear about his personal contribution. In addition, he has produced an interesting picture of the old Rockefeller Institute and an evocation of what it was like to be a scientist 50 years ago.

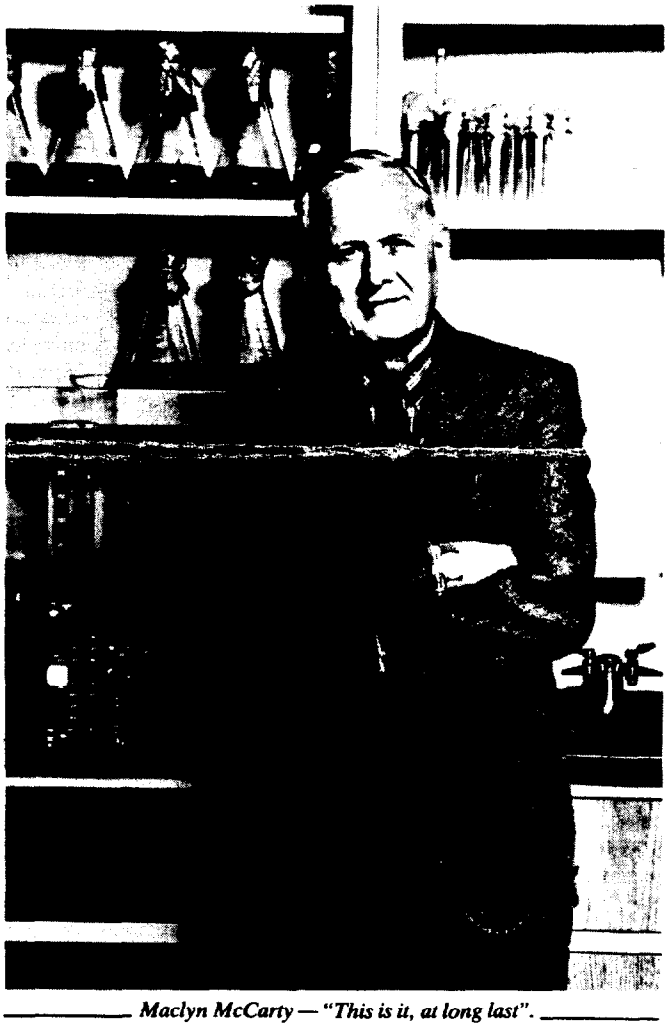
The sequence of events can be briefly recounted. Avery, like many of his contemporaries, had a lifelong interest in the pneumococcus, a great killer of pre-antibiotic days. In 1917, together with Dochez, he discovered that culture fluids of pneumococci contained a specific soluble substance (SSS) which could be typed with antisera. More or less concurrently it became clear that SSS was derived from the capsule of the bacterium and that virulence depended on the capsule. Cultures of pneumococci underwent "dissociation" to throw off avirulent strains; on agar plates these gave "rough" (R) colonies, as opposed to "smooth" (S) colonies of the virulent, encapsulated strains. In 1926, Heidelberger showed that SSS, and hence the capsule, was a polysaccharide, and, two years later, Dubos was able to enrich for a bacterium which produced an enzyme that degraded SSS type III which was to play a significant role later.

It was in the course of study of the smooth and rough variation that Griffith discovered transformation. In a 46-page paper published in 1928, he reported that mice injected with an avirulent, rough strain, derived from one type, together with a heat-killed smooth strain of a different type, succumbed to infection; remarkably, the virulent organism isolated was of the type of the dead smooth strain. Thus, type I rough strains could be "transformed" into type II or III, and type II into type I or III by using the appropriate heat-killed strains. Griffith tried to get transformation *in vitro*, but failed. His interpretation of the results can be judged from the following remark in his paper:

> When the R form of either type is furnished under suitable experimental conditions with a mass of the S form of the other type, it appears to use that antigen as a pabulum to build up a similar antigen and thus develop into an S strain of that type.

There was no genetics involved here, and his idea was very much that the antigen acted as a "primer" and itself determined what antigen was subsequently made.

The *in vivo* research was quickly confirmed by other workers, in particular by Dawson who was working in Avery's laboratory on S–R interconversion. His 1930 paper also reported the failure to produce transformation *in vitro*, but, together with Sia, he was able to announce success a year later, after he had left the Rockefeller Institute. Alloway continued the experiments in Avery's laboratory and by 1933 had found a way of making extracts with consistent transforming activity. None of these papers had Avery's name on them but there is evidence that he followed the work closely.



Maclyn McCarty — "This is it, at long last".

The hero of the tale is, without doubt, Colin MacLeod, who entered Avery's laboratory in 1934 to work on transformation. He selected a stable rough strain, R36, which showed no reversion and was efficiently transformed. He used Dubos's enzyme to prove that transformation by type III could not be due to the polysaccharide; this method of using specific enzymes to assay the chemical nature of the transforming principle was to be applied over and over again, and indeed was important to the final proof that it was DNA. MacLeod aroused Avery's interest in the work again, and research proceeded for three years when it was dropped, and MacLeod went to work on other aspects of the pneumococcus. It seems that he needed to push out publications so as to ensure his future career. Times have not changed very much so far as this familiar problem is concerned, but what has changed is that nobody else entered the field during the three-year hiatus.

In 1940 the research was taken up once more, but MacLeod left the Rockefeller Institute in 1941. Nearly all the subsequent work was done by McCarty, who joined Avery's laboratory in the same year, and in the book he

gives a first-hand account of all the experiments which led to the conclusion "that a nucleic acid of the deoxyribose type is the fundamental unit of the transforming principle of Pneumococcus Type III". The famous paper appeared on 4 February 1944 in the *Journal of Experimental Medicine*; on the reprint he sent to his mother, McCarty wrote "This is it, at long last".

Gunther Stent has tried to explain why this result had so little impact on contemporary genetics by arguing that it was a "premature" discovery. McCarty does not accept this. He believes that it made possible the development of molecular genetics but that "it required further biological, chemical, and structural development before it could be manipulated by geneticists". Bacteriology developed quite separately from the rest of biology and was connected strongly with medicine. All of the participants were trained in medicine and were interested in infectious disease; they did not believe for quite some time that they were in fact doing genetical research, although they were clearly conscious of the importance of the result once they got on the right track. I think Stent is right in saying that the field was not ready to assimilate this result. There was no way at that time that anybody could have conceived how to go from DNA to polysaccharide. The role of proteins was not understood, the one-gene-one-enzyme hypothesis had not been formulated, and haploid genetics in organisms with no visible chromosomes had yet to be invented. Indeed there were many people who believed that bacteria did not have genes because Mendelian experiments could not be performed with them, and it would have been an impossible leap for geneticists to view the transformation experiments as a kind of genetic cross. In 1952, Hershey and Chase showed that when a bacterial virus infects a bacterium only the DNA enters the cell while most of the protein is left on the outside. Although this experiment was not as "clean" as the transformation experiments, it had a greater impact precisely because of the intervening conceptual developments that had taken place in fields such as biochemical genetics.

Did this work deserve a Nobel Prize? Of course it did, and probably more so than many of the ones given since. But as McCarty suggests, the Committee was more careful than wise and let it go by. Thus the story ends on a somewhat sad note, and leads the reader to contemplate the ruthlessness of the process of scientific research, and why, as one grows older, one comes to value books such as this, not so much for their scholarship, but for the memories of men and the humanity they bring with them. □

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Homage to Patagonia from the hard-nosed palaeontologist

Leonard Krishtalka

Bone Hunters in Patagonia: Narrative of the Expeditions. By J. B. Hatcher. *Ox Bow Press, PO Box 4045, Woodbridge, Connecticut 06525, USA: 1985. Pp.209. Hbk $24; pbk $12.95.*

FEW FIELD journals are classic, slow-paced thrillers. Darwin's *Voyage of the Beagle* is one. John Bell Hatcher's *Bone Hunters in Patagonia* is another. From March 1896 to September 1899, Hatcher, a renowned American palaeontologist and collector, led three year-long scientific expeditions to Patagonia on behalf of Princeton University. Like Humboldt and Darwin before him, Hatcher was one of a succession of illustrious naturalists lured to South America by its strange faunas, living and fossil. What drew Hatcher in particular were the exotic, extinct marsupial and placental mammals preserved in Patagonia's basaltic badlands and towering sea cliffs. The results of his work — the seven-volume *Reports of the Princeton University Expeditions to Patagonia* — appeared in 1903; four of the volumes described Hatcher's huge palaeontological collections and three equally massive ones the extant mammals, birds and plants. Buried in the first volume of the *Reports*, and rarely read, is Hatcher's fascinating "Narrative of the Expeditions", of which *Bone Hunters in Patagonia* is a facsimile reprint. As such, it is a rhapsodic yet blood-and-guts overture to an early scientific masterpiece and ranks with the South American sections of Darwin's *Voyage* in its mix of adventure, adversity and natural history.

Nine chapters of *Bone Hunters in Patagonia* describe the first expedition (March 1896 to July 1897), two deal with the second (November 1897 to November 1898) and one covers the third (December 1898 to September 1899). Throughout, Hatcher is a study in dualism. His travails with equipment, horses, food, disease, injury and Patagonian winters and terrain are, in gentlemanly fashion, understated. Twice he came close to death, once from a severe head wound, and again from a violent recurrence of inflammatory rheumatism, a lifelong disease. From between his lines emerges a "wild-west" loner and hard-nosed perfectionist of unshakable determination and courage who felt driven "beyond the limits of civilisation [to study nature] in her true form" (p. 169).

Hatcher bitterly resented the "fireside naturalist, who seldom goes beyond his private study" (p. 37), especially those "parasites" who gained palaeontological repute by describing his collections. Rural Argentina too evoked his ethnocentric ire, from the cold, filthy villages to the overrated talents of the gauchos. But his view of Patagonia's natural history and geography is almost elegiac. Here, Hatcher's "love of nature" brought a focused eye and sensitive pen to the appearance, ecology and behaviour of myriad species of mammals, birds and lizards, and made him rue his "brutal" killing of these animals, whether for food or science. He was awed, almost seduced, by the grand contours of Patagonia's coastal, interior and Andean terrain, much of which Hatcher was the first to explore and map. His geographical discoveries included new mountains and rivers, and helped settle the Argentinian–Chilean boundary question.

Hatcher makes only passing reference to the geology and palaeontology of Patagonia, subjects he reserved for the scientific volumes but never completed. He does exult (deservedly so) over the wealth of Santacrucian (Miocene) fossil mammals he and his sole assistant, O. A. Peterson, collected at Killik Aike (1.5 tons) and Corriguen Aike (4.5 tons) and correctly challenges Florentino Ameghino's erroneous association of dinosaurs (Cretaceous) with the mammalian fauna from the *Pyrotherium* beds (Oligocene). He was unable to find these beds, however, and as this was the goal of the second and third expeditions, it was Hatcher's only failure, and one he constantly lamented. Nevertheless, his geological work helped refine the stratigraphy of Patagonia, and his voluminous collections of Patagonia's extant and fossil animals and plants — many of them new species — allowed an unprecedented comparison of faunal composition and evolution in the Americas. Curiously, Hatcher does not mention his notion of a single southern landmass, an idea he hoped to explore during a fourth expedition in 1903 while employed at the Carnegie Museum, Pittsburgh.

This Patagonian narrative should stoke the spirits of all palaeontologists, geologists and field biologists, and will coax the "fireside naturalist" away from the fire. Its appearance now as *Bone Hunters in Patagonia* is especially timely, as it can be read alongside G. G. Simpson's recent (and excellent) history of palaeontological explorations in South America (*Discoverers of the Lost World*; Yale University Press, 1984). There are two epilogues to the narrative; both are sad and ironic. Five years after surviving the rigours of the expeditions, Hatcher died of typhoid fever contracted from Pittsburgh's untreated drinking water. And in 1985, Princeton University gave away its palaeontological collections, including Hatcher's hard-won lode of Patagonian fossils. □

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