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The Birth of the Biotechnology Era: Penicillin in Australia, 1943–80[1]

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Abstract *As Australia and other countries seek to establish biotechnology industries, it is timely to review successes and failures in this field. One of the most notable stories is the development of penicillin, as a wartime project, to which Australians made major contributions. Australians during and immediately after the war contributed much to the scientific identification and purification of penicillin, and to the industrial scaling up in its production at the Commonwealth Serum Laboratories in Melbourne. This was a classic instance of war accelerating innovations in public administration. Yet the nascent antibiotic industry was never allowed to gain international competitiveness, and was allowed to run down and eventually disappeared by the end of the 1970s. This article is concerned to tease out the puzzle posed by this contrast in aspirations, between the highest levels of scientific and technical achievement in bringing penicillin into widespread use (Australia being the first country in the world to provide penicillin to the civilian population in 1944) and shockingly poor performance in sustaining and developing a national antibiotics industry. As the stirrings of a biotechnology industry may be observed in the first decade of the twenty-first century, it would be unfortunate to ignore the lessons of this earlier experience at the birth of the biotechnology era.*

Keywords: penicillin; antibiotics; Commonwealth Serum Laboratories; national industry nurturing; biotechnology

Introduction

Australia has always had to wrestle with a sense of its own identity, finding it difficult to escape both its own British colonial heritage and the current US influence mediated via globalization. In such a setting of cultural ambivalence, it is hard to establish genuinely new industries. Despite the current success of the resources export boom, there have been some notable failures in industry development in Australia. One of these involves penicillin, the twentieth century's first antibiotic, where Australia was in at the ground floor of a new scientific development and the creation of a new industry. Overseas the antibiotics sector flourished,

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but in Australia it was never allowed to develop beyond its spectacular wartime achievements. By 1980 Australia's penicillin and antibiotic industry was dead. This paper is an investigation of this spectacular achievement followed by spectacular failure.

In a context of raised expectations for biotechnology, in Australia and around the world, it is timely to recall how Australia was actually a major player at the very birth of the biotech industry half a century ago. Penicillin was in every sense of the word the 'first' biotechnology. It was a completely novel solution to the problem of fighting bacterial infection, utilizing a highly selective toxin produced naturally by the mould *Penicillium notatum*. After the discovery itself (for which the Australian scientist Sir Howard Florey was awarded the Nobel Prize in 1945, along with Ernst Chain and Alexander Fleming) there had to be developed novel methods of extraction of the active ingredient, purification and concentration, a safe delivery method for the active ingredient to be introduced into the body, and a supportive industry infrastructure. The 'old' biotechnologies of fermentation and dairy separation were to some extent harnessed in developing the new, but it was essentially a case of innovation of the most extraordinary character.

From a perspective of national identity, the striking thing is that Australians were present at the very birth and at every stage of the biotechnology revolution. It was an Australian who did all the vital scientific work of identifying penicillin as the biologically active ingredient in the mould, and demonstrated its effectiveness in treating wounds that would otherwise be sentences of death—all under intensely trying conditions in wartime Britain. Sir Howard Florey's scientific tenacity was of the highest order, and his Nobel Prize justly awarded—although he is still barely celebrated in his native country.[2] Moreover Australian wartime officials moved so quickly to industrialize the production of penicillin that Australia was the first country to provide it to the civilian population, even before the war ended.

This was a remarkable achievement, typically ignored or under-celebrated in Australia. It meant that a viable industrial scale production and distribution system was built, based on fermentation technology transferred across from brewing. All this was achieved at the state-owned Commonwealth Serum Laboratories (CSL) under the wartime leadership of a charismatic officer, Captain Percival (Val) Bazeley. Men and women in wartime Australia worked day and night, under the most dangerous conditions, to find the optimal chemical and biological processes that would extract, concentrate and deliver safe (i.e. non-toxic and sterile) doses of the antibiotic wonder drug, penicillin.

But this achievement is overshadowed by another. For while CSL built a world-class penicillin plant, and remained at the forefront of developments in antibiotics generally and new varieties of penicillin in particular, nevertheless the penicillin industry in Australia never became a vital national industry seeding new companies, exports or related activities in antibiotics. CSL was never allowed to spin off new, dynamic companies involved in antibiotics or vaccines. A combination of factors meant that by the 1960s Australia's industrial lead in penicillin was being frittered away. There had been no effort made to diffuse the industrial processes of antibiotic production to the private sector, in order to build up a national antibiotic industry. There was no effort made to build a supportive cluster of fermenter technology suppliers, either in terms of equipment and pump technology or in terms of specialist chemicals. Foreign multinational pharmaceutical companies were allowed to set up plants in Australia to produce cheap penicillin and other antibiotics, without any requirement being imposed on these companies to localize their supplies or in

any other way contribute to the creation of a new national industry in Australia. Meanwhile CSL itself continued to produce the highest grade, safe and reliable product, but in increasingly difficult competitive conditions, and with ageing process technology.

The upshot was that by the 1970s there was a call to run down the small, 'uncompetitive' Australian-owned penicillin production industry, in favor of branch plant production by pharmaceutical multinationals. The Industries Assistance Commission (IAC), established by the 1972–75 Whitlam Labor government to take over from the former Tariff Board, held hearings on the 'antibiotic and veterinary products' industry in 1974–76. In its typically myopic fashion, the IAC discussed the issues purely in terms of current activities as seen from a consumer standpoint, rather than from a perspective of national industrial development. It was accordingly recommended eventually that penicillin production at CSL be wound down, in favor of a single foreign pharmaceutical corporation, Abbott Laboratories, operating a small branch plant in Sydney's Kurnell peninsula—which was itself closed shortly after the decision. So by the end of the 1970s Australia had no penicillin industry at all, and hardly any wider antibiotic industry. What a sorry end after such a brilliant beginning.

This is a puzzle of major proportions that lies at the heart of Australia's quest to seek a national identity. In the story of penicillin, Australia has a combination of the highest possible intellectual and scientific achievement, followed by the highest possible technical attainments, succeeded by the most miserable failure in sustaining industrial performance. We have the contrast between Australia's greatest scientist, Howard Florey, and his brilliant capture of the miracle drug, combined with unparalleled dedication and innovation in establishing a national production facility for penicillin under wartime conditions—and the indecisiveness and 'cultural cringe' that allowed the nascent industry to be run down and handed over to foreign interests which were themselves entirely indifferent to the industry's fate.

This article is an exploration of this puzzle. It is not a finger-pointing exercise. No attempt is made to allocate blame, or to claim that some were right and others wrong. Instead, the puzzle is explored from the perspective of the national institutional framework within which Australia's eminence in antibiotics was established in the 1940s and 1950s and how this framework perversely created pathological industrial dynamics that led to the demise of the industry by the end of the 1970s. The contrast with the institutional framework developed for national R&D in other more successful sectors, such as the wine industry, is striking.[3]

The major producer in Australia, from the first efforts at biotech industrialization in the war years of the 1940s, to the late 1970s, was the public sector body, CSL. This made Australia most unusual amongst antibiotic producers in the postwar years. Few countries maintained such a sophisticated and commercially oriented public sector producer of ethical human and veterinary products, with a special brief to protect the public interest (exhibited in the CSL focus on producing specialized Australian products such as anti-venoms for the rare but deadly cases of spider and snake bite in Australia).[4] Rigid efforts were made to 'fence off' CSL from private sector competitors, with the result that obvious commercial possibilities, like spinning off an antibiotic business from CSL and allowing it to export and compete with other multinationals, were simply not entertained. As an entity under the control of the Commonwealth Department of Health, CSL was given no encouragement to expand internationally or to develop its own portfolio of intellectual property governing its own innovations.

By the 1970s, indeed, CSL had been divorced from commercial realities for too long, and it had become a series of warring fiefdoms, each under the control of a scientific-cum-medical overlord. A new Director, brought in from outside the Australian industry in the early 1970s, took it upon himself to refocus the organization on its primary markets and its value-adding processes. This long overdue and well merited focus had the unfortunate side-effect of further marginalizing penicillin production, which was seen as being hopelessly 'uneconomic'. Thus the new competitive focus at CSL saw off penicillin at a time when a broader conception of industry development and nurturing, properly overseen from Canberra, might have managed to save the accumulated capabilities and spun them off into a viable antibiotic business. This in turn might then have further seeded a flourishing domestic pharmaceutical industry. But this did not happen.

Now, amidst the stirrings of another great biotechnological revolution, the lessons of this first involvement, initially in a position of leadership which was then squandered for want of adequate follow-up from Canberra, must not be lost. The lesson is certainly not to try to do it all within the public sector, as CSL found itself battling to do in the absence of a domestic industry. The lesson is not to try to hide behind tariff barriers, which was the only policy ever discussed and implemented in Australia in those long, bleak years of the Tariff Board and the IAC. The lesson is to ensure that the ingredients of a national industry are put in place. This means creating a viable mix of biotech firms with complementarities and export orientation, forming a cluster that can become self-sustaining, and supported by complementary chemical, biological engineering and manufacturing equipment suppliers forming a wider industrial cluster.[5] It means promoting the scientific knowledge base of the industry within various kinds of public institutions, from university laboratories to dedicated public sector labs devoted to the vast range of issues that come under the heading of 'biotechnology'—from human genome issues to plant genetics and the application of biosynthesis principles to every conceivable kind of technology.

More fundamentally, a country needs to celebrate its achievements in scientific and technical fields, and take pride in the formation of new world-class companies doing world-class research and acquiring portfolios of world-class intellectual property.[6] These cultural traits seem to be evident where industries have been nurtured to success.

The Development of Penicillin: An Australian Success Story

The story of Florey's brilliant hunting down of the bactericidal properties of penicillin is well known, and the details need not be repeated here. He and his coworker, Ernst Chain, a German biochemist he had recruited from Cambridge to work with him at Oxford, shared the Nobel Prize for Medicine in 1945 for their brilliant work, along with Alexander Fleming, the man who gave the name penicillin to a mysterious mould secretion that he discovered. Florey is undoubtedly the greatest scientist Australia ever produced, and his development of penicillin was undoubtedly the greatest achievement of a remarkable career.[7]

What distinguished Florey's development of penicillin as a therapeutic agent from Fleming's chance discovery of its bactericidal properties was a relentless capacity for strategically directed, multidisciplinary research informed by the deepest intuition as to what is important and what is feasible. Florey was first of all determined to find an important and effective means of combating bacterial

infection utilizing substances produced for that purpose by nature. In this most fundamental of strategic directions he differed from his contemporaries such as the Germans who were pursuing the chemical route (pioneered by Salvarsan and the sulphonamide drugs).[8] Florey directed his staff to scour the world literature produced over decades for any hint of naturally occurring bactericidal activity, associated with plants, flowers, insects, other bacteria, yeasts, or moulds. It was through this directed search that the Fleming paper reporting the bacteria-killing secretion of a mould, *Penicillium notatum*, came to light.[9] Florey then directed his multidisciplinary team to identify the most promising of these leads, and to reproduce the effects reported in their Oxford laboratory. This is how the work on the Penicillium mould came to be carried out, as an effort to reproduce the findings reported by Fleming. Having established that this mould does indeed produce a bactericidal secretion, Florey then asked his multidisciplinary team to isolate and chemically identify the agent responsible, and capture its effects in a purified form—something that was way beyond the capabilities of a bacteriologist working on his own, like Fleming, and only within the capabilities of a multidisciplinary laboratory equipped with long-term funding and guided by long-term vision. Once Florey had penicillin in his sights, it was inevitable that it would yield up its secrets to him, rather than to some chance discoverer; he had assembled the scientific equivalent of a tank brigade to crack the mystery of this naturally produced infection-fighting compound.[10]

Florey and his team, led by Ernst Chain, had their moment of ecstasy when they conducted their now-famous mouse experiment, on 25 May 1940. Of the eight mice inoculated by Florey with lethal doses of *Streptococcus pyogenes*, all the control group of four were dead within 24 hours, while those injected with penicillin survived, some for as long as weeks after the event. Gazing at the living mice amongst their dead companions, protected by the hitherto unobtainable penicillin, Florey was moved to exclaim that this had to be counted as a miracle.[11] Penicillin turned out to exceed even his expectations, as well as those of everyone else, by orders of magnitude. It was indeed a wonder drug. Its development was by far the greatest medical advance of the century, a stunning achievement—and it was the work of an Australian scientist.[12]

Florey and his Oxford group published their findings in a paper entitled 'Penicillin as a chemotherapeutic agent', in *The Lancet*, on 24 August 1940.[13] This paper created a sensation around the world. Florey was catapulted to a public importance he had never anticipated; but not in Britain. There, he continued to come up against stubborn refusal to grant funding on the scale needed to develop the penicillin work, perhaps understandable given the fact that Britain was locked into a fight for its very existence with the German airforce at the time, in the 'Battle for Britain'. But the United States was not yet at war, and scientists and public officials there immediately comprehended the strategic significance of the penicillin findings. Funding to continue the work at Oxford was immediately provided by the New York-based Rockefeller Foundation. Florey and his co-worker Dr Norman Heatley (who had worked out how to extract penicillin in a stable form utilizing a solvent extraction process) traveled to the USA in June 1941, where they were given a great reception, first at the Rockefeller Foundation, and then in further meetings in Washington involving officials from the National Research Council and the Bureau of Plant Industry (making a link with the mould as the basis of penicillin production). This then led to a series of major breakthroughs in scaling up production of the wonder compound.

The Wartime Production of Penicillin: A 'Second Manhattan Project'

It is well known that war accelerates the developments in technology that would otherwise occur but at a slower pace.[14] The case of penicillin is a classic instance of this observation and its impact on public administration. To the credit of the American wartime administration, the implications of penicillin as a new therapeutic agent, and the challenge of scaling up to industrial production, were grasped immediately by the relevant officials. Enormous resources were poured into solving the problems of scaled-up production of penicillin for therapeutic use. Florey's plea in 1941—'Give me one kilo of penicillin'—looked quaint within just a couple of years as the US built no fewer than 21 penicillin plants to produce the new wonder drug to protect front-line troops. The Office of Scientific Research and Development (OSRD) had been established, under the direction of the visionary Vannevar Bush, precisely to identify opportunities such as penicillin and channel the resources needed to bring them to fruition. The resources brought to bear in the USA on the scaling up of penicillin production were formidable, making it in every sense a 'second Manhattan project'.[15]

The discovery of penicillin and its identification as a therapeutic factor was one thing. Its production on a sufficient scale to be of use in the war effort, and in peacetime thereafter, was quite another matter. This is where penicillin's being the first biotechnology really counts. For every aspect of the production process—the manner of growing the mould, the medium on which it grew, the bioreactor vessels to be used, the means of extracting and purifying the active ingredient, the means of stabilizing it and preserving it, the means for distributing it, and the means for providing a safe way for it to be introduced into the body of a patient—all these features had to be developed, tested and improved in an industrial setting, and in a way that made the final product 'economic', i.e. so that costs could be covered, at least approximately, by revenues. This was an awesome challenge.

Florey had hardly returned to Oxford after his very successful trip to the USA (leaving Heatley to work at Peoria) when the influential Dr A. N. Richards, head of the Committee on Medical Research of the wartime OSRD, called a meeting in New York in December 1941 to secure commitments to make penicillin a project of national importance. At this meeting there were representatives of the Peoria laboratory (NRRL), of the National Research Council, plus three representatives each from the companies Merck and Squibb, two from Pfizer (then the leading fermentation company in the USA, with its revolutionary deep fermentation process for producing citric acid) and one from Lederle. This meeting was quickly followed by an outpouring of industrial energy, with the building eventually of 21 penicillin plants in record time by these and other companies to produce sufficient penicillin to support the Allied landing in Normandy in spring 1944.[16]

Likewise in Britain, at the instigation of both Florey and Fleming, steps were taken eventually to produce penicillin on a massive scale as a wartime measure. A meeting comparable in importance to that of Dr Richards in New York was called by Sir Cecil Weir in London at the Ministry of Supply in September 1942, to launch the production of penicillin under government control. Major pharmaceutical firms like Glaxo were involved in this effort, as well as government-built and owned facilities just outside Speke, near Liverpool.[17]

Now the really interesting part of this story is that Australia was a major player in this effort as well, not through the efforts of Florey and his Oxford team, but

through the dedicated and innovative commitment of a group of scientists and engineers at the Commonwealth Serum Laboratories (CSL) in Melbourne.

Australian Involvement in Wartime Penicillin Production: The Commonwealth Serum Laboratories

The early efforts to produce penicillin in Australia, at a time of military secrecy and the impossibility of securing normal commercial advice, were nothing short of extraordinary. There was no connection with Florey; he was virtually unknown in his home country, and most of those who knew of his work with penicillin assumed he was English. It was word of the efforts being made in the USA and UK to produce penicillin that galvanized the Australians, who felt, with good reason, that they might be at the end of the queue when it came to distributing penicillin to wounded servicemen in the Allied forces. The Pacific war was at its height, with Australian troops fighting the fight of their lives in New Guinea, when the decision to initiate production of penicillin in Australia was taken.

The decision was taken by the War Cabinet in mid-1943. Critical to this decision was Colonel E.V. (Bill) Keogh, the Director of Hygiene and Pathology for the Australian Army, and a former researcher at CSL in Melbourne, on secondment to the armed forces. The War Cabinet gave the go-ahead to produce penicillin at CSL, then the country's foremost public health laboratory and producer of vital materials such as vaccines, sera and products like insulin, and charged Keogh with finding an officer to direct the project.[18] Colonel Keogh knew just the man for the job, a former CSL colleague involved in veterinary research, then serving as a captain in the 2/8th Armoured Regiment, AIF, in New Guinea. This was Captain Percival (Val) Bazeley, a man of great energy and vision, then serving as a tank squadron commander. Bazeley took on his assignment with gusto, and after returning to Melbourne to CSL, set off on a fact-finding mission to the USA, with a view to getting penicillin production off the ground before the end of the year.

Bazeley and his associate, Lieutenant Kretchmar, a chemist, set off on their brief but momentous fact-finding tour of US penicillin operations, in September 1943. They visited all the facilities of the major US producers at the time—the Pfizer plant in Brooklyn, NY; the Merck & Co. plant at Rahway, NJ; as well as the facilities of the companies Squibb, Abbott, and Wyeth Laboratories—and the Peoria facilities of the Northern Regional Research Laboratory, where Dr Robert Coghill had built the pre-eminent penicillin research establishment in the USA. They obtained seed cultures of *Penicillium notatum* and basic process technology from this trip.

There followed a frenzy of activity at the Parkville facilities of CSL directed by Bazeley, with a small team of dedicated biochemists, bacteriologists, and engineers being assembled to get the project running. Incredibly, by Christmas 1943 the first ampoules of freeze dried penicillin were being shipped to New Guinea.[19] At the time, almost everything had to be innovated by the resourceful CSL group. Bazeley had taken rough sketches of what he and Kretchmar had seen in the US, and had made drawings and brief descriptions of the processes that would have to be followed at CSL. Everything else had to be invented on the spot.[20]

Extraordinarily enough, within six months the primitive CSL operations had been transformed into a highly productive bottle plant. Extremely large numbers of flasks had to be inoculated with the *P. notatum* and the contents shaken by hand over several days to achieve a solution of penicillin. This was very labor intensive, and was not as sophisticated as the deep fermentation process then being brought

on line by Pfizer in the USA—but it worked, and produced safe and reliable penicillin. By May 1944 the output of penicillin had increased from 10 million units daily at the beginning to 400 million units per week. This was sufficient to ensure that adequate supplies were reaching the frontline troops in New Guinea and elsewhere in the Pacific. It was also sufficient to allow Australia to take a step beyond that of any other country at the time, namely to allow penicillin to be supplied to civilians for certain stated infectious conditions.[21] This was an important milestone, placing Australia at the forefront in the development of the new biotechnology, and opening up its production of penicillin for civilian use and for the use of the Allies for the remainder of the war in the Pacific.

Postwar Penicillin and Antibiotic Production Industry in Australia

The rush to produce penicillin at CSL as a wartime emergency measure, was followed in the postwar period by a series of industrial developments that turned CSL into a world-class, leading edge producer of the most exciting biotechnological product of the age. This process began with a second study tour to the United States, Britain and Europe by Captain Bazeley, this time in the company of Dr F. T. Wheatland, the deputy director of CSL. The tour lasted six months, from September 1944 to March 1945.[22] The new technology of deep tank fermentation was studied in the USA, where Pfizer had introduced the method at its Brooklyn plant, and turned it into the leading edge industry standard.[23] Bazeley and Wheatley had then gone on to the UK to study aspects of the clinical applications of penicillin, and then for a short visit to the Allied armed forces stationed in Europe, to witness penicillin usage in the battlefield. Under wartime conditions, all such relevant information was freely shared between Allied forces—but Australia had to be a player in penicillin production and use to be able to make use of this knowledge flow.

The shift to deep fermentation tank technology was undertaken at CSL, under Bazeley's active direction, during 1946 and 1947, at the same time as bottle (or flask) production was further industrialized and mechanized. Pilot-scale production was undertaken in small 10-gallon tanks, to understand how the stainless steel piping, valves and pump systems would operate and whether sterile conditions could be maintained and stable product produced. Again there were heroic efforts by the small team of engineers and biochemists involved, so that by 1948, two 5,000-gallon fermenters were able to be installed and commissioned. This marked the start of truly industrial scale production of penicillin at CSL. It also marked a fundamental shift in the character of the facilities, from being a small, makeshift and laboratory-scale operation to a fully industrial plant with its own industrial heating, freezing, and chemical supplies operations feeding through a multitude of pipes. It was by now a world class bioreactor facility.

A new wing was added to CSL's penicillin facility, and first an additional five, then a further three, 5,000-gallon tanks were installed, making 10 in all. The 50,000-gallon capacity resulting from these extensions was comparable to leading biopharmaceutical producers elsewhere in the world. Yields were also dramatically improved, through relentless application of R&D to the process—from use of new, higher-yielding Penicillium strains, to use of new media for growing the mould, to use of new and improved methods of extraction, stabilization and bioassay. To give a feel for CSL's world-class ranking at this time, consider the fact that biochemists Gilbert Anderson, Leo Davis and Viv Davey developed a medium for growing

the Penicillium mould based on dried skimmed milk, as an alternative to the US-developed corn steep liquor medium. This was the subject of one of CSL's rare patents, and the technique was successfully used for a time as an alternative, high-yielding medium for penicillin production at CSL.[24]

Innovative research was also being conducted on wider aspects of penicillin use by members of the penicillin team at CSL. For example, work was directed towards finding a less painful form of penicillin to be used in injections. Whereas in the rest of the world the potassium salt of penicillin was utilized, because of its ease of purification, at CSL work was undertaken to find a less painful but still reliable form, which was eventually found to be the sodium salt. This helped to make penicillin an antibiotic of choice because its injection was now a much more comfortable procedure.[25]

The 1950s and 1960s saw CSL expand its range of penicillins produced, by keeping abreast of the development around the world of a range of semi-synthetic penicillins. The industrial scale of production of penicillin transformed CSL's production of other biomaterials, particularly vaccines.[26] CSL was keeping up with technical developments in the world of penicillin and antibiotics generally, through its own R&D and through collaborative arrangements with pharmaceutical giants like Eli Lilly, Wyeth Laboratories and Beecham Research Laboratories.[27] But CSL was also isolated, both from other potential pharmaceutical firms in Australia, and from its overseas counterparts. This was to take its toll on the technical and industrial aspirations of the organization.

Indeed CSL on its own did not constitute a national penicillin industry. Beyond CSL, there was very small-scale production by fermentation at the South Australian producer, F.H. Faulding—still smarting from the refusal during wartime to grant the company access to technological data shared amongst Allied governments—and from 1955 onwards, by small branch plants of pharmaceutical multinationals. The British firm Glaxo was the first of these, opening up a small penicillin fermentation plant in Port Fairy, regional Victoria, in 1955.

The domestic market was a small one, and without any encouragement to engage in exports, or develop production links with overseas partners, CSL's world-class facility was falling behind the best world standards. The market suffered a downturn in 1960, and the CSL fermentation plant was in fact shut down for 15 months, from December 1960 to February 1962—but with expensive maintenance being continuously applied. This led CSL to seek restrictions on imports of penicillin, through an approach to the Advisory Authority on Tariffs, leading to the imposition of temporary direct import controls in August 1962 (lasting until June 1963), and the raising of tariffs. Thus Australia was going down the route of domestic industry protection but without the associated industry development measures being put in place. A second multinational, Abbott Laboratories, was allowed by the Commonwealth government, to open a plant for penicillin production—despite the domestic over-capacity. The Abbott plant was established at Kurnell, on the southern outskirts of Sydney, in 1964.

At the same time, the scale of production of penicillin at CSL was further expanded, with two new 25,000-gallon tanks being installed in 1964–65. This effectively doubled CSL's capacity from 50,000-gallons to 100,000-gallons. With a protected domestic market CSL was able to meet all production requirements, and built up a considerable strategic stockpile of various forms of penicillin, which might be needed in any national emergency. Again a market downturn led to shutdown of the plant, due to over-capacity, for periods in 1971–72, with full

production resuming in January 1973. By this time, things were not looking good for penicillin production as an industry in Australia.

Rundown of the Australian Penicillin Industry

By the 1970s the Australian penicillin industry (if this is what one public sector producer and two branch plants of multinationals could be called) was in crisis. Production was being undertaken just for the small domestic market; over-capacity was rife; the scale of production was so small compared with the largest and most efficient plants overseas that costs were high; and imports were kept at bay only by a high tariff. CSL was by far the dominant domestic producer, with a new large-scale plant installed in the first half of the 1960s, but periods of enforced shutdown because too much product was being stockpiled.

The new Director brought in early in the 1970s, Dr Neville McCarthy, was resolute in enforcing commercial discipline on CSL's activities, in a long-overdue review of its basic operations. He brought in consultants from the US pharmaceutical firm Squibb to advise on improving efficiency in the deep fermentation tanks. These recommendations were acted on, and yields and efficiency improved dramatically. But inefficiency was not CSL's fundamental problem with penicillin. Its public-sector character, with a focus on the public welfare and its oversight by the Commonwealth Department of Health (which had an overwhelming medical and consumer perspective rather than any kind of industrial development perspective) meant that it could not develop into a serious multinational producer of antibiotics. And paradoxically, CSL's existence retarded the entry of any other domestic Australian company into the wider antibiotic business—even though some, like F.H. Faulding in South Australia, were keen to do so.

Apart from CSL there were two multinational branch plants, one operated by the British company Glaxo and one by the US company Abbott Laboratories.[28] Both these plants operated at way below the best scale and process standards of their overseas sister plants, and presumably were seen by their corporate headquarters as small producers for the local market, economic only because of the tariff barriers. However, as at CSL, over-capacity forced the companies to curtail or halt production at times, and Glaxo actually stopped penicillin production altogether at Port Fairy in 1975.

It was in these circumstances that the Industries Assistance Commission (IAC), successor to the former Tariff Board, examined the penicillin and wider antibiotics sector in 1974–76, as part of a review of the pharmaceutical and veterinary products industry. The IAC report was totally unsympathetic to the prospects for penicillin production, and in particular showed indifference or even hostility to the plight in which CSL found itself. It noted all the features mentioned above (small-scale production, over-capacity etc.) and concluded that 'local manufacture of penicillin and streptomycin is not economic'; and that 'On economic grounds there is no case for assistance to the industry'.[29] This was code for allowing the industry to be phased out, subject only to countervailing social considerations which the government might have (e.g. regarding the desirability of maintaining domestic production of vital antibiotics as a strategic supply). The IAC recommended that if such social considerations were to apply, then the government should wind down the tariff and support the industry with direct subsidies.

The IAC report with its damning indictment was not acted on immediately. Instead the government ordered a further review of the recommendations. By this

time there were only CSL and Abbott producing penicillin, and both at well below world standards and at high cost. Abbott argued that it had started producing penicillin in Australia only because it had received government assurances of continued support; it was in effect calling for indefinite subsidies to maintain its Kurnell production facility. CSL for its part argued that its penicillin production could be maintained at full capacity only if it were given sole supply status to the local market. The review fudged the issue, and recommended that bounties be paid on production, with Abbott to receive a bounty on production of penicillin V (the major product) and CSL a bounty on penicillin G (the minor product). This was in effect a death sentence for penicillin production at CSL, and the penicillin plant was indeed terminated in 1980. Abbott maintained sporadic production for a time, buttressed by public handouts, but without making any serious investment in technology or scale of production.

A further antibiotics plant had been established in Victoria by Cyanamid, to produce tetracycline, but this plant was soon the victim of the economies of scale that overseas plants serving much larger markets enjoyed. CSL too had tried to expand from penicillin to other antibiotics, including streptomycin and chloromycetin, but these had short runs before being closed in the face of foreign competition.[30]

This then was the sorry end to which a dramatic and promising industrial start in biotechnology in 1945 had been brought. No one seemed to lament the phase-down of the penicillin and wider antibiotic industry in Australia. Lack of investment and lack of vision had brought the industry to this state by the 1970s, when closure seemed to be the only reasonable option. But what makes for such sad reading, with the perspective of hindsight, is how narrow were the options considered.

Paths Not Taken in the Australian Penicillin Industry

At the time of the dismemberment of the penicillin industry in Australia, there was only a limited understanding of the options available for industry promotion and development. From our current perspective, we would recognize that a very important seed had been planted in Australia during the war years. It was capable of growing into many diversified industries involving different forms of antibiotic production and export, as well as associated entities such as vaccines. Moreover a revitalized penicillin industry would have stimulated related industries such as biological fermenters, specialized glassware and a host of other areas, but instead the industry was simply shut down because it was judged to be 'uneconomic' by the narrowest criteria of current costs and market size. All possibilities of these other diversified industry developments died with it.

At the very same time that this industry was being dismantled in Australia, the Europeans were building up their pharmaceutical industries, and becoming major players in antibiotics (led by firms such as Glaxo, Beecham and Hoffman LaRoche). In many cases public sector laboratories played critical roles as depositories of fundamental knowledge—the very role that CSL could have played if it had not been constrained to be a commercial producer. In Japan and other East Asian countries like Korea and Taiwan, new industries were also being created, with very different understanding of how an industry could be nurtured to the point of becoming internationally competitive and a source of national wealth generation.

In Japan in the postwar era, one new industry after another was seeded and developed. Through the 1950s, the Japanese economy went through wrenching structural change, as older industries based on coal-mining, foodstuffs and textiles were phased out, and newer 'heavy and chemical industries'—steel, petrochemicals, cement and machinery—were phased in. This process continued through the 1960s, with industries such as synthetic textiles, plastics, automobiles and electronics being introduced and 'nurtured'. In each case the steps invoked by Japan's Ministry of International Trade and Industry were more or less the same, and followed a seven-step sequence.[31] Johnson illustrated the process using the example of the petrochemical industry, which was created *ab initio* in the mid-1950s. It is striking that none of these steps was ever taken, or even contemplated, in the case of the penicillin and wider antibiotic industry in Australia.[32]

After the brilliant start, with penicillin being produced at the best levels of world practice and in quantities exceeding on a per capita basis any other country, there was no effort ever made to grow the market or seed the industry to a wider circle of players. The efforts of one Australian domestic producer, F.H. Faulding in Adelaide, were actually rebuffed.[33] A 'Japanese' approach would on the contrary have given every encouragement to Fauldings to invest in advanced technology and open up an export market for its product, treating CSL as lead domestic producer and source of technology for a small circle of private sector players who would be encouraged to grow and internationalize and become an internationally competitive industry.

Instead it was foreign multinational pharmaceutical companies that were allowed to set up production plants, but without any stipulations governing transfer of technology, growth of export activities, or commitment to invest in advanced scale activities. Is it unreasonable to suggest the feasibility of applying such conditions? At the same time, in the late 1960s and 1970s, these were the very conditions being applied to multinationals wanting to invest in Singapore, by a market-savvy government and its agency, the Economic Development Board in Singapore. The result was that multinationals in Singapore were forced to play the role of powerful vehicles of industrial development, with local firms benefiting through supply contracts—or what economists call 'forward and backward linkages'.[34] But no such demands were made in Australia. Instead a perverse policy was pursued, of tariff protection of the domestic market and encouragement of multinational production behind the tariff barrier wall, at small scale and at declining technology levels. This did indeed 'crowd out' any hope of private sector production buildup, all the while encouraging the sole public sector producer, CSL, to maintain its activities for purely 'social' reasons.

The result was, predictably, the gradual rundown of the industry to the state where the IAC was quite correct to describe it by the mid-1970s as 'uneconomic'. But things could have turned out so differently had there been some vision and leadership in Canberra—or even a different set of institutional matrices. CSL could have been placed under the aegis of the Commonwealth Department of Postwar Reconstruction, instead of the Department of Health. As such, CSL could have been developed into a vital and dynamic source of technology, maintaining a world class production capability and R&D capability, not in order to be a monopoly supplier to the local market, but to transfer this technology and expertise across to a developing private sector as quickly as possible. CSL could have been encouraged to develop its links with the universities, particularly the newly founded ANU, to act as a dynamic source of knowledge and expertise in biotechnology.[35] This domestic

sector could have been nurtured, initially by tariff barriers but more directly by technological collaboration with CSL and pharmaceutical multinationals, to become a competitive supplier not just of the domestic market, but of a broader export market, in competition with European, American and eventually Japanese producers. The costs of this domestic industry could have been kept low through encouragement of local production of supply materials and production equipment, such as the corn steep liquor needed as a medium for penicillin production, and its Australian equivalent in the form of dried skimmed milk. Specialist chemicals like amyl acetate, as well as fermenter tanks, bioassay equipment, sterilizing equipment and all the associated instrument and equipment supplies that could have developed, with suitable encouragement, into a self-supporting industrial cluster. This would in turn have stimulated the launch of new rounds of biotechnology production activity, and new rounds of instrument and equipment supply, in a self-reinforcing cycle that is now recognized to be the core of the 'Silicon Valley' model.

As things actually happened, a peculiar kind of industrial dynamic was set in motion, where a public sector institution was forced to become both public R&D facility and also monopoly supplier to the domestic market. Had CSL been able to expand abroad and behave like a business, it may have been able to overcome these limitations of its origins, and evolve into a pharmaceutical multinational. But it was kept on a tight leash by the Department of Health, and this did not happen. In the apparent absence of alternatives, the Commonwealth government opted for a protectionist domestic policy, creating import barriers, but failing to develop corresponding industry nurturing institutions. At the same time it allowed in foreign multinationals which erected branch plants purely for the supply of the local market. Thus the local industry was caught in a pincer movement, with a state-owned monopoly on the one hand being prevented from developing, and a private sector being prevented from emerging in such a small market, and multinationals setting up branch plants to serve the local market, thus inducing over-capacity. A more pathological set of industrial dynamics could scarcely be imagined.

This then is one plausible solution to our starting puzzle, namely the paradox of how a country which was amongst the world's leaders at the birth of the modern biotechnology industry, in 1945, could have fallen behind so decisively and so rapidly as to see its penicillin industry completely dismantled by the end of the 1970s. The explanation lies in the perversity of a set of institutions and the pathological industrial dynamics that they generated. The lessons are all too clear.

Concluding Remarks: Building a Biotechnology Industry in the Twenty-First Century

The penicillin story is pregnant with lessons for the twenty-first century—the 'century of biotechnology' as one famous activist put it.[36] There are clear signs that Australia is building critical mass in a range of biotechnologies, backed by major public sector research laboratories, and with an understanding of the need to seed and nurture new enterprises within these laboratories, as well as to attract foreign capital, technology and knowledge. Other places are racing ahead. There is already a major bloc of biotech companies in the USA, emerging from their own 'Silicon Valley' like environments, and poised to make maximum use of the potential opened up by the publishing of the details of the human genome.[37] In Europe, Germany has taken a leap forward in biotechnology, fostering 'bio-regions' and encouraging dozens of new companies to sprout up.[38] In the

Asia–Pacific, places like Singapore are forging ahead with their plans to develop a cluster of biotech industries, focused not just on human and medical products, but on transgenic plants and farm animals and new kinds of DNA-engineered vaccines for the huge China, India and Indonesia markets. This is the competitive environment within which Australian firms are venturing in the new century of biotechnology.

A flourishing Australian biotech industry in the twenty-first century would be a fitting memorial to the efforts of the pioneers who created a world-class penicillin industry here in the 1940s and 1950s; but it will not happen through the imagined operation of 'market forces' alone. Intelligent intervention is called for to nurture the fledgling industry, and allow it to develop to the point where it can hold its own in the face of international competition. These are the lessons that have been learnt from the successful creation and nurturing of industries, and from the failures such as Australia's loss of its penicillin capacity.

Notes and References

1. Much helpful advice and insight was provided by Dr Neville McCarthy, former Director of the Commonwealth Serum Laboratories (CSL) and until recently a board member of Autogen; by Mr Alf Brogan, author of the definitive history of CSL (see Alf Brogan, *Committed to Saving Lives: A History of the Commonwealth Serum Laboratories*, Hyland House, Melbourne, 1990); and by Dr Mike Dyall-Smith, of the School of Microbiology and Immunology at the University of Melbourne. The research assistance of Dr Jane Ford is gratefully acknowledged. Above all I wish to acknowledge the help and advice of my late father, Mr Alwyn G. Mathews (1919–2008), who was an important player in the story of penicillin retailed here.
2. This has changed somewhat since the centenary of Florey's birth in 1998, which was celebrated by public events in Adelaide, his home town; by programs on ABC Radio National; and by the 'Tall Poppies' website created by the Australian Institute of Political Science.
3. D. K. Aylward, 'Diffusion of R&D within the Australian wine industry', *Prometheus*, 20, 4, 2002, pp. 351–66.
4. Possible parallel cases included the Connaught Laboratories attached to the University of Toronto, and the State Serum Institute in Copenhagen. Generally speaking, public sector bodies engaged in fundamental research, and vaccines and antibiotics were produced by private-sector corporations.
5. See M. E. Porter, 'Clusters and the new economics of competition', *Harvard Business Review*, November–December 1987, pp. 7–90.
6. Since its privatization, this is in fact what CSL has become. It is now a very successful chemotherapeutic and biotech multinational corporation based in Melbourne.
7. There are two biographies of Florey, by R. G. MacFarlane, *Howard Florey: The Making of a Great Scientist*, Oxford University Press, Oxford, 1979; and a more popular account by L. Bickel, *Rise Up To Life: A Biography of Howard Walter Florey Who Gave Penicillin to the World*, Angus and Robertson, London, 1972 (reprinted as *Howard Florey: The Man Who Made Penicillin*, Melbourne University Press, Melbourne, 1995). His own textbook account of penicillin and other antibiotics is given in H. W. Florey *et al.*, *Antibiotics: A Survey of Penicillin, Streptomycin, and Other Antimicrobial Substances from Fungi, Actinomycetes, Bacteria and Plants*, Oxford University Press, Oxford, 1949.
8. The sulphonamide series, and in particular sulphanilamide, was developed at the I.G. Farben Industrie research laboratories at Eberfeld in the 1930s, particularly by Gerhard Domagk.
9. See A. Fleming, 'On the antibacterial action of cultures of Penicillium, with special reference to their use in the isolation of B. influenzae', *British Journal of Experimental Pathology*, 10, 1929, pp. 226–36.

10. For a recent overview of the discovery and development of antibiotics from the perspective of innovation theory, see W. Kingston, 'Antibiotics, invention and innovation', *Research Policy*, 29, 2000, pp. 679–710.
11. A former colleague of Florey's, Dr Hugh Barry, visited the team at Oxford on the next day, and described the atmosphere in the lab as follows:

> Chain was beside himself with excitement and Florey, as usual, was trying to conceal any outward sign of emotion. Eight mice had been injected with streptococci the previous day and four of the mice had also been given penicillin powder. The four controls had died but the other four were still alive. From that day on there was no doubt that a miracle drug had been found. (See B. Heagney, *Half a Century of Penicillin: An Australian Perspective*, Royal Australasian College of Physicians, Sydney, 1991, pp. 3–4)

There were of course many more mouse trials as well as trials in other animals before the decisive clinical tests on humans with otherwise untreatable infections. But these all called for large supplies of the penicillin, which stretched Florey's laboratory facilities to their limit.

12. And also of his wife, a distinguished clinician. Dr Ethel Florey was indefatigable in her efforts to establish the clinical guidelines for the use of penicillin. She summarized her work in a textbook, see M. E. Florey, *The Clinical Application of Antibiotics: Penicillin*, Oxford University Press, Oxford, 1952.
13. With characteristic modesty, Florey allowed Chain to be the lead author in this paper: E.B. Chain and H. Florey *et al.*, 'Penicillin as a chemotherapeutic agent', *The Lancet*, 24 August 1940, pp. 226–8.
14. For the definitive statement of this view, see W. H. McNeill, *The Pursuit of Power*, Basil Blackwell, Oxford, 1983. Weiss provides an elaboration in terms of the role of states and state institutions. See L. Weiss, *Creating Capitalism: The State and Small Business Since 1945*, Basil Blackwell, Oxford, 1988. This provides the context for a discussion of the wartime development of penicillin.
15. See the short review 'Medicine's Manhattan project' in *Technology Review*, July/August 1999, in the 'Trailing Edge' column. *Technology Review* is the magazine of the Massachusetts Institute of Technology.
16. For the eyewitness accounts, see R. D. Coghill, 'The development of penicillin strains' and A.L. Elder, 'The role of the government in the penicillin program', both in R. I. Mateles, (ed.), *Penicillin: A Paradigm for Biotechnology*, Candida Corporation, Chicago, IL, 1998. The main US pharmaceutical companies contributing to the penicillin effort were Pfizer through its Brooklyn, NY plant; Merck & Co through its Rahway, NJ plant; Abbott Laboratories (North Chicago, ILL); Lederle Laboratories (Pearl River, NY); Eli Lilly & Co. (Indianapolis, IN); Reichel Laboratories/Wyeth (West Chester, PA); E.R. Squibb & Sons (New Brunswick, NJ); the Upjohn Company (Kalamazoo, MI); and the Winthrop Chemical Co. (Rensselaer, NY). In addition there were suppliers of materials such as corn steep and specialist chemicals like the solvent amyl acetate.
17. The British wartime efforts are vividly described in a monograph produced just after the war by David Masters. See D. Masters, *Miracle Drug: The Inner History of Penicillin*, Eyre & Spottiswoode, London, 1946. Five pharmaceutical companies—May & Baker, Glaxo, the Wellcome Foundation, British Drug Houses and Boots—joined forces in a consortium, named the Therapeutic Research Corporation, to investigate the biochemical, bacteriological and biotechnical features of penicillin. This was an important institutional innovation associated with the exigencies of war.
18. The alternative candidate facility was the Institute for Medical and Veterinary Research in Adelaide, Florey's home town, where some research was being conducted on moulds, and where the firm F.H. Faulding was keen to become involved in penicillin work. But CSL was chosen with the support of Keogh and of the Director-General of Health, Dr J. Cumpston. The encyclopaedic *Technology in Australia 1788–1988* provides a summary of the histories of both CSL and Fauldings. See AATSE, *Technology in Australia 1788–1988*, Australian Academy

of Technological Sciences and Engineering, Canberra, 1988, available at: http://www.austehc.unimelb.edu.au/tia.

19. The lead biochemist, Harold Cochrane, who was charged by Bazeley with the job of extracting the penicillin from the liquid, has left a graphic description of those first few months and years in his personal memoir. See H. Cochrane, *Penicillin: The Australian Story*, unpublished memoir, 1990 (ISBN 0646034936, National Library of Australia reference No. Nq 338.47615329230994 C663).
20. The author's father, Mr Alwyn G. Mathews, was a member of this group, from March 1944 to August 1946; at the time, he was a young biochemist, transferred across from his work on Vitamins A and D in fish oils. He was responsible for developing the freeze-drying aspects of the penicillin work, and its dispensing into ampoules for clinical use.
21. This important regulation was published in the *Commonwealth of Australia Gazette*, No. 85, on 3 May 1944. It was called the 'Control of Penicillin Order' and was issued under the National Security (Medical Coordination and Equipment) Regulations. In less than one page it covered the supply and use of penicillin for civilians suffering from such scheduled diseases as septicaemia, meningitis, osteomyelitis, pneumonia, gas gangrene and tetanus—all killers at the time. The Order was issued under the name of Alan Newton, Chairman, Medical Equipment Control Committee.
22. The atmosphere of the time can be gauged from the fact that Bazeley and Wheatland needed the personal approval of the Prime Minister in order to undertake this trip; any journey overseas was viewed with suspicion.
23. Deep tank fermentation was undoubtedly the step that turned penicillin production from a heroic laboratory-based affair into a major industry. Pfizer already possessed major expertise in deep tank fermentation for its major pre-war product, citric acid. It put its very profitable citric acid production at risk by utilizing its fermentation tanks for production of penicillin—but when this process turned out to be successful, Pfizer reinvented itself in the early postwar period as a pharmaceutical firm. This was the first of many corporate transformations that have marked the biotechnological era.
24. Australian patent 215879. See Brogan, *op. cit.*, p. 89. Other innovators at CSL were not so lucky. The public service culture of the establishment meant that recognition of individual achievement through the award of patents was actively discouraged.
25. The author's father was involved in this innovative work. In the CSL at that time, there was no question of seeking to patent the innovation.
26. Penicillin production on an industrial scale revolutionized the production of vaccines at CSL, so that it was able to produce immense quantities of Salk polio vaccine in the 1950s and early 1960s using such industrial methods. The polio vaccine project was also energetically led at CSL by Dr Bazeley, who had by then acquired a medical degree, and became Director of CSL from 1955 to 1961.
27. Collaborative agreements with Eli Lilly in the 1950s and 1960s covered procaine penicillin initially, then phenoxymethyl penicillin (penicillin V), penicillin process technology, and the antibiotic streptomycin. An agreement with Wyeth International covered the long-acting benzathine penicillins, while agreements with Beecham Research Laboratories covered the semi-synthetic penicillins such as phenethicillin, ampicillin, amoxycillin and others. However CSL did not become a producer of chloramphenicol, the first purely synthetic antibiotic. This was a major strategic error, despite there being expertise available. See Brogan, *op. cit.*, pp. 90–1.
28. Glaxo commenced production of penicillins V and G at a plant in Port Fairy, Victoria, in 1955; this plant also produced bulk streptomycin. Abbott started producing penicillin at its plant at Kurnell, on the southern outskirts of Sydney, in 1964.
29. IAC, *Pharmaceutical and Veterinary Products. Industries Assistance Commission Report*, *Parliamentary Paper 135/1977*, Parliament of the Commonwealth of Australia, Canberra, 2 August 1976, p. 1.
30. See the paragraph on these episodes in the entry on the Commonwealth Serum Laboratories in AATSE, *op. cit.*, pp. 627–8.

31. See a classic study by Chalmers Johnson, *MITI and the Japanese Miracle: The Growth of Industrial Policy, 1925–1975*, Stanford University Press, Stanford, 1982, p. 236. These steps started with the need for the industry and its prospects being spelt out in a founding document. Second, foreign currency allocations were authorized by MITI and funding was provided for the industry by the Japan Development Bank. Third, licenses were issued to Japanese firms for the importation of the needed technology (subject to MITI oversight, to avoid technical duplication or payment of excessive royalties). Fourth, the nascent industry would be designated as 'strategic' in order to give it special and accelerated depreciation allowances on its investments. Fifth, the nascent industry would be provided with improved land on which to build its installations, either free of charge or at nominal cost. Sixth, the industry would be given tax breaks, such as exemption from import duties (to assist import of capital goods), refund of duties paid on imported components, and exemption from export duties. Finally, MITI would create through 'administrative guidance' a small group of firms as players in the industry, in order to avoid 'excess competition' and to coordinate investment among the firms in the industry.
32. The exception is perhaps Step Five, where the Commonwealth provided the land, adjacent to Royal Park in Melbourne, on which CSL, as a government-owned entity, was built.
33. Fauldings started up a penicillin production plant at more or less the same time as CSL, in 1945, with the same idealistic intentions, to supply a wonder drug for the war effort. But unlike the case of the UK and USA, where private pharmaceutical firms were encouraged to take a lead role, and there was free sharing of information between firms (to the point where Pfizer, the lead producer in the USA and originator of the deep tank fermentation method, made its techniques freely available to competitors), in Australia the War Cabinet and in particular the Department of Health refused to allow Fauldings access to any government data. Thus its penicillin plant was a makeshift affair utilizing flat bottles (like CSL's initial production plant); they never made the transition to deep tank fermentation.
34. This and similar experiences are analyzed in the creation of a semiconductor industry in East Asia. See J. A. Mathews and D. S. Cho, *Tiger Technology: The Creation of a Semiconductor Industry in East Asia*, Cambridge University Press, Cambridge, 2000.
35. It is noteworthy that CSL was in fact closely linked with the foundation of the ANU in 1946, and actually provided the home for the ANU Department of Biochemistry in its early years. But the emphasis on production for the domestic market led to the devaluing of these academic links, which in turn contributed to a siege mentality at CSL that was rife by the 1970s.
36. See J. Rifkin, *The Biotech Century: Harnessing the Gene and Remaking the World*, J. P. Tarcher, New York, 1999.
37. See the special issues of the journals *Nature* and *Science* devoted to the human genome project published in February 2001.
38. See, for example, the review by S. Momma and M. Sharp, 'Developments in new biotechnology firms in Germany', *Technovation*, 19, 1999, pp. 267–82.