PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Exploitation of Biotechnology in a Large Company

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Exploitation of biotechnology in a large company

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Almost from the outset, most large companies saw the 'new biotechnology' not as a new business but as a set of very powerful techniques that, in time, would radically improve the understanding of biological systems. This new knowledge was generally seen by them as enhancing the process of invention and not as a substitute for tried and tested ways of meeting clearly identified targets.

As the knowledge base grows, so the big-company response to biotechnology becomes more positive. Within ICI, biotechnology is now integrated into five bio-businesses (Pharmaceuticals, Agrochemicals, Seeds, Diagnostics and Biological Products). Within the Central Toxicology Laboratory it also contributes to the understanding of the mechanisms of toxic action of chemicals as part of assessing risk. ICI has entered two of these businesses (Seeds and Diagnostics) because it sees biotechnology making a major contribution to the profitability of each.

Introduction

I am grateful to the Royal Society and SERC for asking me to contribute to this symposium, Spinks Eight Years On; I think I would have added in parentheses 'Biotechnology after the Hype'. In the early 1980s there were too many symposia, too many multi-client surveys and not enough in the way of hard achievement. The people making money out of biotechnology were the venture capitalists, biochemical suppliers, conference organizers and publishers. Now the picture is clearly changing. There is much more focus on real rather than imaginary commercial targets and the routes to exploitation have been more clearly thought through. As the recent U.S. Office of Technology assessment survey shows (table 1), biotechnology research

Table 1. Concentration of biotechnology research effort

research area	biotechnology companies[a] (%)	companies with biotechnology operations[b] (%)
human therapeutics	21	26
diagnostics	18	11
chemicals	7	21
plant agriculture	8	13
animal agriculture	6	8
reagents	12	4
waste disposal and treatment	1	2
equipment	4	2
cell culture	2	2
diversified	4	11
other	18	0

[a] Two hundred ninety-six companies responded to survey.
[b] Fifty-three companies responded to survey. Source: Office of Technology Assessment.

effort of both small and large companies is concentrating on the health-care, agriculture and speciality sectors where the rewards are perceived to be greater for those who target their research correctly.

We hear less now about how microorganisms are going to synthesize bulk chemicals more cheaply, solve the problem of oil slicks or facilitate oil recovery from spent wells. We hear more about anticoagulants and anticancer agents, insect and herbicide resistant crops, transgenic animals for use in agriculture, drug manufacture and research.

To date nine biotechnology drugs have received Food and Drug Administration (FDA) approval and 81 are in development. Sixty-seven of these are in clinical trials and 14 are awaiting marketing approval by the FDA. This is very exciting and reflects a significant advance, but if I am honest there is still a remarkable clustering of companies around too few products and I suspect many patent litigations will result. We are witnessing one of these at present in the tissue plasminogen activator suit between Genentech and the Wellcome Foundation.

I fear the same thing is happening in the plant genetic manipulation field where ideas are so far ahead of achievement that companies are filing paper patents and claiming sun, moon and stars perhaps on the basis of an idea initially demonstrated in mammalian systems or one experiment in the petunia or in tobacco. I, for one, hope the international patent fraternity will take a tougher line on such filings in the future. At present the future looks as rosy for the lawyers as for the companies involved.

Over the past eight years we have learned much about what to do and what not to do in biotechnology and although ICI was making a significant investment in the late 1970s and early 1980s it was only a fraction of our investment in more traditional biological research into pharmaceuticals and agrochemicals. Many large companies, like ourselves, were accused of being slow off the mark; way behind in the biotechnology race. But unlike the biotechnology start-up companies, whose product horizons were solely biotechnology based, the successful large companies had good products in the market place, a full development portfolio and ideas queueing up for attention; all based on more classical proven technology. Against this background it was inevitable that unless biotechnology was to produce overnight miracles it would be introduced into the big-company research portfolio as products or ideas deriving from it were able to challenge or augment existing wisdom. At the time of the Spinks report that challenge was not immediately apparent. No company doubted the power of the technology for the future, but many would not have ranked the first generation of targets high on their own priority list. Sir Charles Reece said to the *Biotech '83* audience at the Wembley Conference Centre

> The science is fascinating: I have no doubt as to its future power in helping understand biological systems, but in reality we have taken the first few steps up a very long staircase. In medicine we have seen how these techniques provide us for the first time with a series of compounds whose therapeutic activity is at best uncertain. The timescales to clarify these uncertainties are likely to be long....

I think this still holds true today. Many cytokines like interferon (IFN) and tumour necrosis factor (TNF) are being developed for use in cancer therapy, but these potent chemical messengers show a surprising multiplicity of effect. IFN and TNF produce fevers. TNF has been associated with loss of weight, and given in large enough quantities to rats can reproduce the symptoms of a massive infection. A clearer understanding of these phenomena will doubtless emerge and our ability to manipulate these molecules will help dissect their biological roles and lead to better products.

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A biotechnological snapshot of ICI at the start of this decade would show us dominated by our investment in single-cell protein ('Pruteen'). This was an outstanding technical achievement, but with soya and oil prices turning against us it was not a commercial success. This experience taught us much about how to grow microorganisms on a large scale (1.6×10^6 l) but it also highlighted the inefficiencies inherent in the fermentation process. Volume for volume, fermentation processes are much more capital intensive than their chemical counterparts, and we learned that the challenges for those wishing to compete at the bulk end of the market with new fermentation products centred around the need to get rid of all that water. Having to work in dilute suspensions and subsequent separation and dewatering contributed heavily to product costs. More than anything else this focused our biotechnological attention on higher added-value products at the speciality end of the chemical business.

Through this period we established two world firsts in the application of recombinant DNA technology. Both came from collaborations between scientists in our Corporate Research Laboratory in Runcorn and their colleagues in Billingham and Alderley Park. The first related to 'Pruteen' and involved the introduction of an energetically more efficient ammonia-fixation pathway into *Methylophilus methylotrophus*, (Windass *et al.* 1980). The glutamate dehydrogenase (GDH) gene from *Escherichia coli* was introduced into the methylotroph and its own glutamate synthase (GOGAT) gene was rendered inactive by mutation. This saved 1 molecule of ATP for every molecule of ammonia fixed as glutamate and was the first example of metabolic pathway modification using recombinant DNA technology.

Our second contribution was the first total synthesis of the genes coding for α1- and α2-interferon (Edge *et al.* 1981, 1983). We went on to explore whether this technology could generate interferon analogues in which we could enhance the beneficial effects of interferon

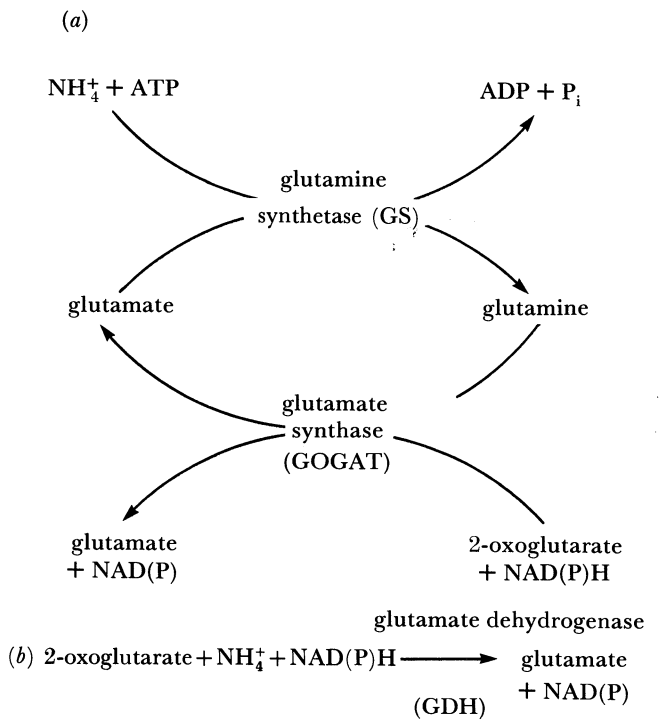

FIGURE 1. Pathways of ammonia assimilation in bacteria. The *Methylophilus methylotropus* GS/GOGAT system (*a*) was replaced by *E. coli* GDH (*b*).

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while minimizing its side effects. In all we made over 80 analogues, convinced ourselves of the power of protein engineering, and managed to show some separation of anti-viral and anti-proliferative effects. Now, of course, gene machines carry out in days or weeks a project that took us many person-months to achieve.

Though our entry into the recombinant DNA arena had its highlights, much of our pharmaceutical and agrochemical research carried on as before. Hindsight shows that we got it right. Our Pharmaceutical business focused most of its attention on the use of modern non-biotechnological science to hit major therapeutic targets. As a result we launched Diprivan, our new intravenous anaesthetic, in 1986 and are following this with four cardiovascular drugs, an anticancer agent and a compound for treating diabetic complications. Behind them are some 15 high-quality compounds in early clinical and preclinical phases. The situation has been similar in our Agrochemicals business. They spent the last ten years looking for novel pesticidal activity by using traditional technology. Over this period they were responsible for about 10% of the new product introductions within the industry. Notable ICI newcomers have been soyabean selective herbicides, a corn root worm insecticide, cereal fungicides and herbicides, fruit and vine fungicides, a family of plant growth retardants and a new, highly active, foliar pyrethroid insecticide.

Although it is perhaps too early to make comparisons, I do not know of any major biologically based pesticide that has been produced over the same time period. To be fair there are no shortages of projects and ideas for creating biological pesticides: insect-specific viruses carrying recombinant toxins; introduction of toxin genes into root-colonizing bacteria; combining toxin genes into one host to broaden species specificity; the use of endophytic bacteria to carry toxin genes into plants. All will require sufficient rewards from the market place to fund business requirements and research and development expenses, but increased specificity will mean smaller market share and rewards will only be worthwhile if regulatory costs are contained.

In spite of all the commercial uncertainty associated with biotechnological developments, ICI biotechnology has changed significantly over the past eight years. Our Pharmaceuticals and Agrochemicals businesses have significantly increased their in-house effort. Our Central Toxicology Laboratory is integrating biotechnology techniques into their research programmes hoping to shed more light on chemical carcinogenesis; and three new businesses have been created (Seeds, Diagnostics and Biological Products) all driven by the promise of biotechnology.

Agricultural biotechnology

For many years now our agrochemical business has been selling one biotechnology-derived product, gibberellic acid. This is produced by the fungus *Gibberella fujikuroi* and its main application is in producing seedless grapes.

But gibberellic acid produced by fermentation is costly, even by speciality chemical standards, and it is arguable that such expense has limited its use in agriculture. In fact the activity of any fermentation-derived pesticide has to be extremely high to compete with its chemical counterparts. The avermectins meet this challenge and for vegetable lepidoptera they are between two and five times more active than the highly active, chemically synthesized pyrethroid insecticides. At this level of activity formulation and packaging costs become more important than the cost of the active ingredient (figure 2).

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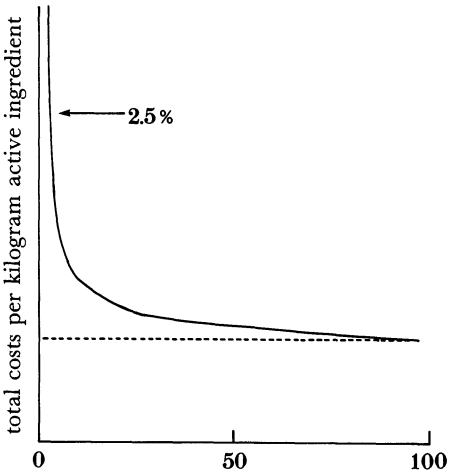

FIGURE 2. Schematic graph of the cost of escalation of a typical pesticide formulation with reducing concentration. At concentrations of less than 2.5% the active ingredient becomes less important. Modern pyrethroids have reached this level (Deltamethrin and Karate). Some formulations are less than 1%. The broken line shows the cost of 1 kg of active ingredient.

Some microbial isolates are also used by the industry, and many more are under field test (table 2). Two of the best known are the various *Rhizobium* species for nitrogen fixation in legumes and *Bacillus thuringiensis* (*Bt*) for treating lepidopteran pests such as spruce budworm and European Corn borer. Like many other companies, small and large, we in ICI screen for natural microbial antagonists of major plant pests. We have our own strain of *Bt* in trials and we run natural-product screens in the hope of identifying new toxophores from microbial species. But of equal importance to us now is the use of biotechnological techniques to aid the invention of new pesticides. Thus cloning and expressing genes for key target enzymes in bacteria, isolating and crystallizing the resulting proteins and using X-rays, nuclear magnetic

TABLE 2. EXAMPLES OF POSSIBLE BENEFITS INVOLVING THE RELEASE OF GENETICALLY MODIFIED ORGANISMS

organism	where developed	benefit
Pseudomonas + *Bt* gene	Mycogen, U.S.A.	killed before release – controls lepidoptera pests
Pseudomonas syringae: ice nucleation	AGS, University of California, U.S.A.	increased frost protection
Pseudomonas + *lac* Z	Monsanto, U.S.A.	study movement of rhizosphere
Bacillus thuringiensis	Ecogen, U.S.A.	conjugated strain to control organisms
Clavibacter xyli	Crop Genetics, U.S.A.	control of European corn borer
Pseudomonas spp.	EPA, U.S.A.	degrade 3-chlorobenzoic acid
Rhizobium meliloti	BioTecnica, U.S.A.	increased N fixation
Trichoderma harzianum	Cornell, U.S.A.	control of damping off
Agrobacterium tra	Rood Nodule, Australia	control of crown gall
Autrographa californica NPV	NERC, Oxford, U.K.	control of insects
Pseudomonas fluorescens + *Bt* gene	Monsanto, U.S.A.	control of soil pests
Myxoma virus	CSIRO, Australia	control of rabbit
Pseudomonas aeruginosa + *Bacteroides nodosus*	CSIRO, Australia	vaccine against sheep foot rot
Pseudomonas syringae (natural strain)	Snomax Technologies, U.S.A.	snow making

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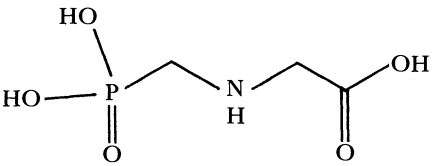
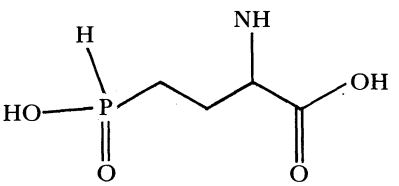
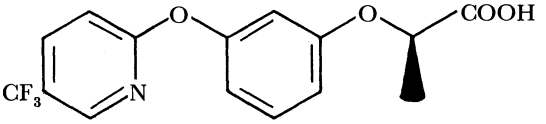
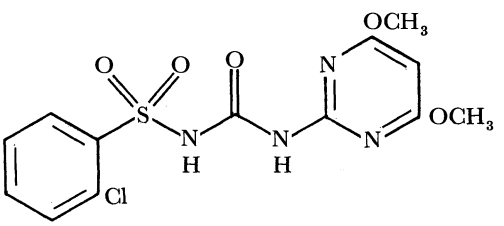
resonance and computer graphics to facilitate the design of novel inhibitors will be a key feature of our future activities.

For those not familiar with pesticide mode of action, table 3 lists some of the major herbicides and their target proteins.

TABLE 3. TARGET SITES FOR HERBICIDES STRUCTURE

compounds	structure	target site
glyphosate		EPSP synthase
phosphinothricin		glutamine synthase
fluazifop *R*-acid		acetyl-coA carboxylase
chlorsulfuron		acetolactate synthase

SEEDS

Working alongside these scientists are our plant biotechnologists, who now form an integral part of our Seeds business, which ICI entered in 1985 with the acquisition of the Garst Seed Company. We became involved in Seeds because we saw it as the logical way of exploiting plant biotechnology. We chose to acquire knowledge of plant breeding, seed multiplication and marketing through acquisition and added to it by expanding our in-house effort in plant bioscience. By the end of 1987 we had established a major presence in the two biggest developed world markets, the U.S.A. and the E.E.C. By adding SES in Europe, Sinclair McGill and Miln Marsters in the U.K. we now have a seed company that is in the world's top ten and a crop portfolio that spans maize, sorghum, wheat, barley, sugar beet and oilseeds.

As Dick Flavell has indicated (Flavell, this symposium), plant science has developed rapidly

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over the past five years and now some 40 plants are transformable by DNA, with the monocots steadily succumbing to DNA technology. Protoplast regeneration in rice is now routine and isolated reports of maize and barley transformation are likely to expand into a flood of activity over the next few years.

The new benefits that biotechnology is likely to bring to the industry are shown in table 4. In the short term the use of restriction fragment length polymorphism technology will help the breeders track useful characters through their breeding programme and shorten the breeding cycle. In the medium term a set of single gene resistances to broad spectrum herbicides will enable the farmer to benefit from crop–weed selectivity through genetics rather than chemistry.

TABLE 4. BENEFITS OF BIOTECHNOLOGY IN PLANT BREEDING IN THE MAJOR CROPS

short term	restriction fragment length polymorphism technology
medium term	virus resistance
	herbicide resistance
	insect resistance
long term	fungal resistance
	yield and quality improvements
	processing benefits
	hybrid technology

Insect and viral resistance genes at present demonstrated in tobacco, tomato and potato (table 5) will be extended into the broader acre crops as transformation technology develops. It is interesting to note that pesticide chemistry has had similar problems to pharmaceutical chemistry in dealing with viruses. There are no effective anti-viral agrochemicals. The industry keeps viruses under control through control of their insect vectors, often involving the use of insecticides. By contrast there are now three or four biotechnological solutions to producing virus-resistant plants, which include coat-protein genes, satellite RNA sequences, anti-sense RNA and now, possibly, genes coding for ribozymes.

In the longer term advances are expected that benefit the food processor or the consumer directly. One early example in which we have been involved is the control of the ripening process in tomatoes (figure 3). We recently reported on a collaboration with Professor D.

TABLE 5. EXAMPLES OF GENETICALLY MODIFIED PLANTS RELEASED INTO THE ENVIRONMENT

quality	where developed	plant
herbicide resistance		
glyphosate	Calgene	tobacco
atrazine	Ciba-Geigy	tobacco
sulfonylurea	DuPont	tobacco
phosphinothricin 'Basta'	PGS	potatoes, tobacco
disease resistance		
crown gall	Agracetus	tobacco
tobacco mosaic virus	Monsanto	tomatoes
leaf roll virus	AGRC	potatoes
pest resistance		
tobacco hornworn	Rohm Haas/PGS	tobacco
lepidopterous pests	Monsanto	tomatoes
others		
kanamycin resistance	IPSR	potatoes

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Grierson's laboratory in Nottingham on the down-regulation of polygalacturonase (PG) by the use of anti-sense RNA technology (Smith *et al.* 1988). The particular benefit to the processor would be the retention of pectin polymers, obviating the need to add natural thickeners to soups and fruit juices.

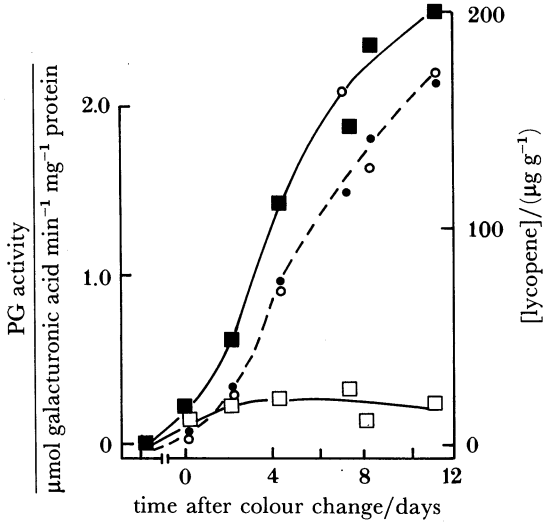

FIGURE 3. Development of PG activity and colour in normal and anti-sense tomatoes. ■, Normal PG; □, anti-sense PG; ●, normal colour; ○, anti-sense colour.

HEALTH CARE

Our other major established bio-business, Pharmaceuticals, is also increasing its commitment to biotechnology by expanding its own effort and incorporating the Health-Care-related science of the Corporate Bioscience unit. Here, as in Agrochemicals, biotechnology is seen as providing both products and techniques; novel proteins with therapeutic activity, and aids to traditional drug discovery by providing information on key enzymes, receptors or cell-growth regulators. In the last decade we have witnessed the cloning of many of the membrane proteins upon which modern drugs act. Many of the specific subtypes of these proteins have been found to retain their properties when expressed in heterologous mammalian cell lines. They therefore offer a relatively simple system for looking for drugs that distinguish between subtypes and hence only hit their intended target receptor. The current range of β-blockers are a case in point. They are effective anti-hypertensives because of their action on the β-adrenergic receptors of the cardiovascular system. However, they also have activity on the β-adrenergic receptors in the central nervous system, a fact that has not gone unnoticed by some well-known snooker players!

But one major biotechnological focus in ICI is our cancer molecular biology programme, which aims to build on our success with the anti-oestrogen 'Nolvadex', used in the treatment of breast cancer, and 'Zoladex', a decapeptide leutinising hormone – releasing hormone (LH–RH) agonist for use in treating prostate cancer. It is worth noting that the key to the success of 'Zoladex' is the development of a slow-release formulation that circumvents the need for multiple injections.

Our investment in cancer molecular biology recognizes the incredible surge in knowledge generated by the application of modern biological techniques. Their combined power is

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uncovering the roles of growth factors, oncogenes and tumour suppression. Out of this should come new approaches to cancer therapy.

The molecular biology of the 1980s has also given us access to whole families of chemical messengers whose utility in cancer is being examined in the clinic by a variety of companies, small and large.

The anti-proliferative agents such as the interferons and tumour necrosis factor are beginning to find application in spite of side effects. α-Interferon looks like being the agent of choice for hairy-cell leukaemia, renal carcinoma and various papillomas.

Colony stimulating factors may exert anti-tumour activity by promoting differentiation of tumour cells at immature stages of development, but also look like being a valuable adjunct to chemotherapy through the stimulation of white-cell production.

Studies on the role of growth factors such as epidermal growth factor and platelet-derived growth factor in neoplastic growth are likely to open routes to therapy, as might immunological approaches based on monoclonal antibodies alone or as conjugates with toxin molecules.

Our own immunotoxin programme, which began with a collaboration with Warwick University, is attempting to produce selective agents based on monoclonal antibody conjugates with the castor bean toxin, ricin. Ricin consists of two polypeptide chains: the A-chain kills cells by stopping protein synthesis, and the B-chain binds non-specifically to cells and facilitates the entry of the A-chain. Our present work focuses on recombinant A-chain antibody conjugates with collaborative work continuing on B-chain modification to separate non-specific binding from cell entry characteristics. But with such potent toxins the major challenge is to find a monoclonal antibody that is highly selective to the tumour cell of choice.

Toxicology

But what of cancer from the other perspective? Ensuring that the products of our industry are non-carcinogenic. Our Central Toxicology Laboratory has had this as its major focus for many years, and is one of the world's leading laboratories in chemical carcinogenesis research and testing.

The first breakthrough in identifying potential chemical carcinogens came in 1973 when Professor Bruce Ames produces his *in vitro* mutation assay. (Ames 1973). The test system developed rapidly in the 1970s and was readily adopted by both the regulatory authorities and industry as a rapid screening test for carcinogens. The Ames test has proved remarkably effective in identifying electrophilic chemicals with potential carcinogenic properties. Most studies have shown it to be more than 80% effective. Its great advantage over standard animal studies is that it only takes two or three days to complete and costs £1–2000 per chemical. Compare this with animal studies, which take $3\frac{1}{2}$ years to complete and cost £400000.

By 1980 the Ames test was routinely used to screen out mutagenic chemicals from those that could progress into development programmes and hence into long-term animal studies. By 1988 and subsequent experience of such animal studies we find that a proportion of these non-mutagenic chemicals are capable of producing cancer. Such chemicals are known as non-genotoxic carcinogens. Several are shown in table 6.

The relevance of these findings in relation to the potential effects on human health is unclear. Some, such as trimethylpentane producing kidney cancer in rats or propionic acid producing

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Table 6. Non-genotoxic carcinogens

carcinogen	site
thiocarbonyl compounds sulfamethoxazole	rat thyroid
KCl, NAOH prolonged irritation	mouse skin
propionic acid	rat stomach
trimethylpentane	male rat kidney
diethylhexyl phthalate	rodent liver
diethylene glycol	rat bladder

rat stomach cancer, are thought to be species specific, but it is this area where we are hoping that modern biotechnological techniques can play a major role. We aim to understand why it is that non-genotoxic chemicals can cause cancer and whether the effects observed in rodents, often thought to be hypersusceptible, is capable of occurring in human tissue, particularly at the very low doses often encountered in environmental situations.

Diagnostics

Our third Health-Care-related activity started in late 1984 when we recognized the potential synergy benefits between our pharmaceutical interests and the role foreseen for DNA technology in clinical diagnosis.

The ICI Diagnostics business has chosen to commercialize developments in biotechnology in six areas: infectious disease diagnosis, genetic disease testing, genetic fingerprinting, tissue typing, cancer testing and disease predisposition. Of these it is the genetic fingerprinting sector that has advanced most rapidly and gained the most publicity.

The opportunity to commercialize Professor Alec Jeffreys' DNA fingerprinting innovation came to ICI from the Lister Institute of Preventive Medicine, the source of Professor Jeffreys' funding for this work (Jeffreys *et al.* 1985*a*, *b*). An agreement was signed in July 1986, and less than a year later Cellmark Diagnostics opened for business in Abingdon. Soon after, a U.S. laboratory was completed and it began operating towards the end of 1987.

Professor Jeffreys was working on the structure of the human myoglobin gene when he discovered a repeated DNA sequence that, when isolated and probed against the DNA of unrelated individuals, gave a complex pattern of bands. Each band represents a length of DNA which has a match with the DNA sequence in the probe. Now, after several years of research and thousands of comparisons, it is very clear that these patterns are unique to every person except identical twins.

Figure 4 shows an example that was featured on Italian television, where the DNA pattern of a hypothetical suspect's blood was compared with those from several suspects. Inspection shows that suspect Regolini committed the crime!

One of the first real tests of the technology occurred in a major criminal case in England in which two incidences of rape, several years apart, were shown to be committed by the same man. A screen of a thousand local villagers eventually identified the suspected culprit who then admitted the offences.

DNA 'fingerprinting' analysis is also playing a major role in the resolution of family relationships, particularly in paternity disputes. Everyone inherits half their genetic make up

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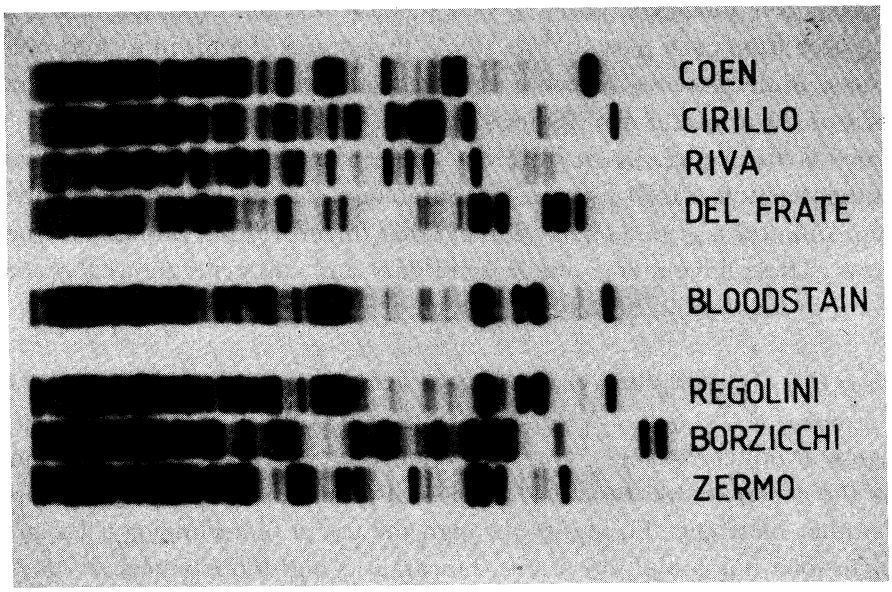

FIGURE 4. Comparison of DNA fingerprints of 'scene of crime' bloodstain with those of the hypothetical suspects.

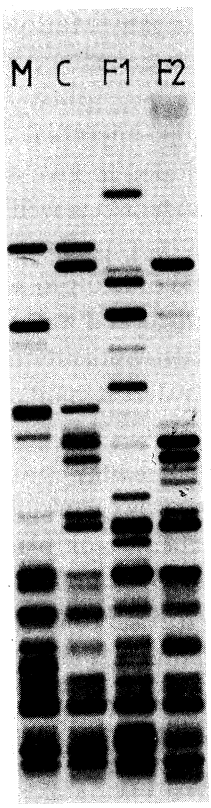

FIGURE 5. DNA fingerprints in a typical paternity dispute showing F2 to be the real father.

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from each of their true biological parents. This means that about half the DNA 'fingerprint' pattern is inherited from each parent. The DNA 'fingerprint' bands in a child must therefore match with those in the parents DNA fingerprints. The paternity dispute shown in figure 5 is typical and shows F2 to be the real father.

Great interest is also being shown in DNA 'fingerprinting' for immigration cases, animal pedigrees, authentication of cell lines in biotechnology, canine paternity disputes and even cattle rustling. And now a second generation of DNA fingerprinting probes have been isolated by Alec Jeffreys. These have much greater sensitivity and can generate a DNA pattern from 1 μl of blood or, in favourable cases, from one hair root.

Biological products

The Biological Products business represents another new venture for ICI. Formed in 1984 and based on the expertise that produced single-cell protein, its remit is to seek opportunities outside ICI's other bioscience businesses through the use of biotechnology. Its current range of interests span food, microbial inoculants, biocatalysts and biopolymers.

In the food sector we have combined our knowledge of fermentation scale-up with the food expertise of Rank Hovis McDougall on the development of Quorn mycoprotein. This product can be readily textured into a human food and has the benefits of excellent taste combined with healthy eating characteristics such as low fat, no cholesterol, high fibre and high protein. It is now marketed from a dedicated food company Marlow Foods from their factory in Stokesley, North Yorkshire. It is currently selling in Sainsburys and British Home Stores and will soon appear in other outlets.

A second product in the market is the microbial silage additive 'ECOSYL' which was launched two years ago. This was developed to give a high microbial count and is safer and easier to handle than its chemical equivalents, as well as producing greater animal benefits.

A third interest relates to enzymes and biotransformations, the latter activity focusing on the use of enzymes to effect syntheses that are difficult to achieve chemically. This technology will be particularly useful to the pharmaceutical and agrochemical industry, who increasingly are looking for cost-effective ways to synthesize optically pure products. Recently, we announced the sanctioning of a production facility to exploit this and subsequent developments in biotransformation.

One survivor from our 1980s biotechnology programme is the biopolymer poly-α-D-hydroxhybutyrate (PHB). Like the rest of our work, attention here has turned to high-value applications. The world is awash with cheap bulk plastics and to compete against these with a fermentation product was asking the impossible. However, in 1988, against a background of increasing environmental concern, there is a growing interest in the material. The product, which is a bacterial energy storage component, is biodegradable and can be melt-processed on reasonably conventional equipment into bottles, films, etc. This, coupled with its increasing availability and improved process technology, has created the stimulus to evaluate its applications in many areas.

In summary, ICI is exploiting biotechnology by a variety of routes. In our established businesses it is offering the prospect of new products but centres around techniques that will help new product invention. In our Seeds business we have chosen to exploit by investing in plant bioscience and acquiring businesses to provide us with the downstream skills we lacked.

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In Diagnostics we have responded rapidly to a new technology and are building the business through organic growth, as indeed we are in Biological Products. It is in the latter two businesses where we have products in the market place as a result of 1980s' technology.

Our large competitors have also chosen pathways to exploitation that vary with the nature of the business. DuPont are investing heavily in their own Health Care business in both drugs and diagnostics, but have chosen to research in plant biotechnology without entering the seeds business. Monsanto see biotechnology as their passport into the next century and have invested more heavily. They have a similar strategy to DuPont in plant biotechnology, but have purchased G. D. Searle to exploit their health care biotechnology. Unilever, BP and Dow have joined ICI, Ciba-Geigy and Sandoz in investing in Seeds and each has a significant supporting biotechnology effort.

Our 1988 snapshot sees biotechnology beginning to deliver on its promises. The science is still advancing at a breathtaking rate, but the top of Charles Reece's staircase is still a very long way ahead. We still require a great deal of hard work and investment in the basic science fully to exploit this exciting technology.

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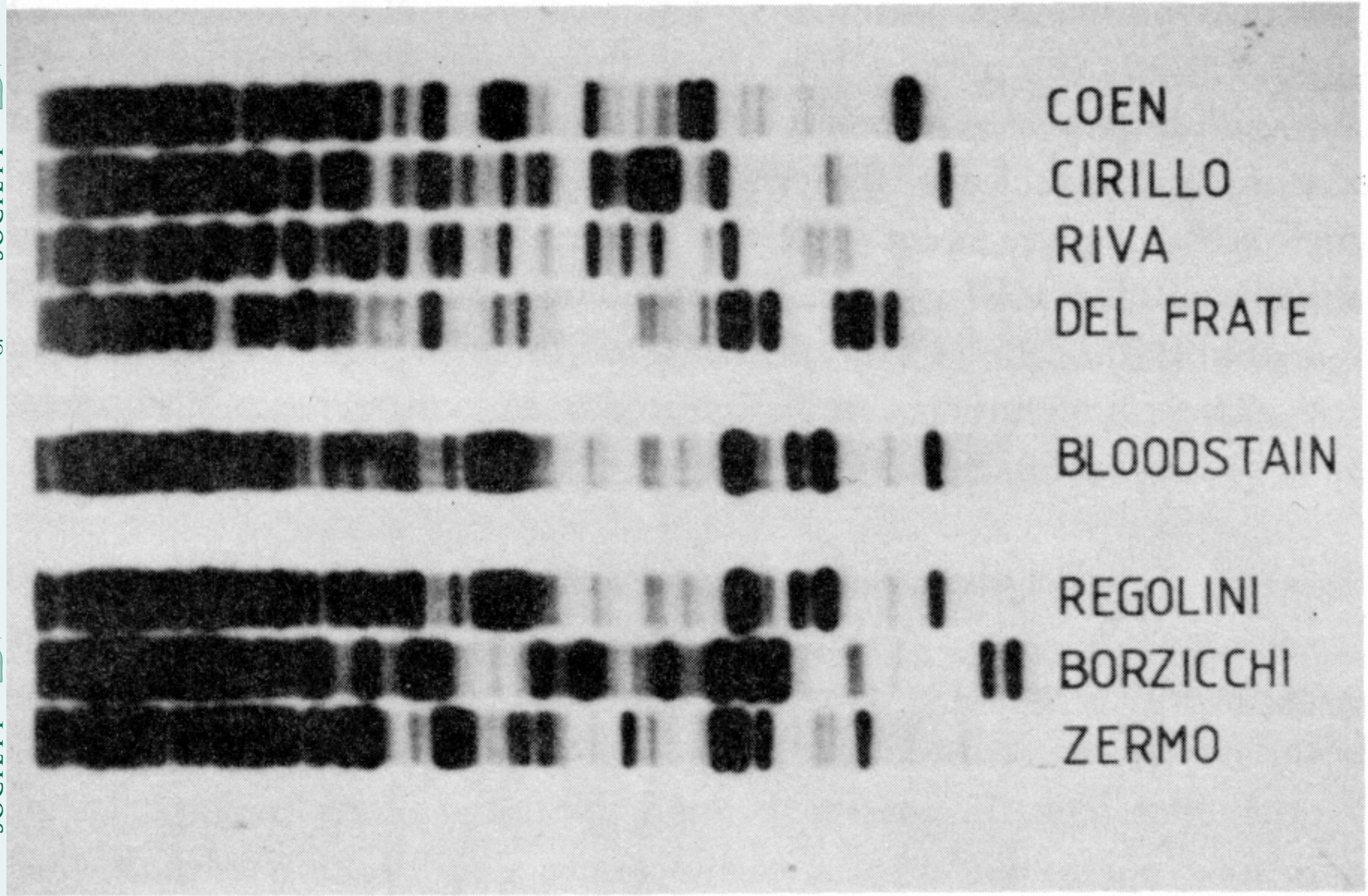

FIGURE 4. Comparison of DNA fingerprints of 'scene of crime' bloodstain with those of the hypothetical suspects.

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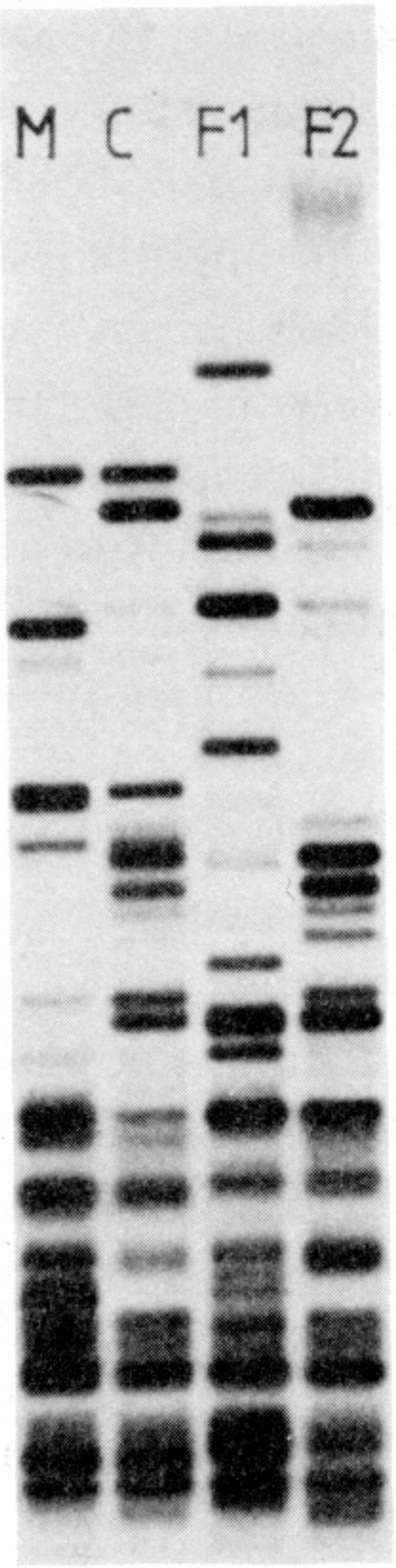

FIGURE 5. DNA fingerprints in a typical paternity dispute showing F2 to be the real father.

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