Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER

Journal of Biotechnology 65 (1998) 111–125

JOURNAL OF Biotechnology

Review article

Animal and plant cell technology: A critical evaluation of the technology/society interface[1]

R.E. Spier *

University of Surrey, Guildford, Surrey, UK

Received 26 November 1997; received in revised form 8 May 1998; accepted 25 May 1998

Abstract

The rate at which technology progresses is dependent on the nature of the technology/society interface. This is a complex interaction which involves the production of people capable of making technical advances, the physical opportunities for the deployment of those trained individuals in this task as well as cultural and social factors which will motivate the innovators to produce the advances we need to maintain the momentum of our continually improving situation. One particular aspect of the social situation which may be singled out for special attention is that of the ethics of the society in which people make and use the products of the innovation process. The ethical aspects of biotechnological activities has commanded a great deal of attention recently both from the professional and societal stake-holders. This paper, therefore examines in some detail the ethical aspects of the technology/society interface as it applies, in particular, to the development of animal and plant cell biotechnology. It focuses on the role of the regulatory agency and on the need for biotechnologists to acquire professional status so that they may develop a more trustworthy relationship with society.

Keywords: Technology/society interface; Cultural/social factors; Ethics; Innovation process; Animal/plant cell biotechnology; Regulatory agencies

1. The backcloth

While some 75% of the surveyed population of European adults would concede that ''Biotechnology probably does provide more benefit than harm'' (Eurobarometer, 1996) it is clear that some 25% of the survey sample did not think that the

* Fax.: +44 1 483259265; e-mail: r.spier@surrey.ac.uk

[1] Based on the Keynote lecture of the EFB Working Party event, 'Animal and plant cell culture technology', at the 8th European Congress on Biotechnology (ECB8) in Budapest, Hungary, August 1997.

0168-1656/98/$ - see front matter
PII S0168-1656(98)00136-9

balance was favourable to the beneficial outcomes of biotechnological activities. Moreover, it would seem that of the 75% who would commit themselves to a beneficial view some 50% were not firmly committed to that view and would examine each case critically on its individual merits. In particular, those aspects of biotechnology which lead to therapeutic capabilities were regarded as highly beneficial, while other developments in the generation of new food products or in the engineering of transgenic animals or plants or in the release of genetically engineered bacteria into the environment as part of a bioremediation program were not deemed to be of universal benefit, and were treated with sceptical caution if not outright antagonism (Kierman, 1996; Marshall, 1996). Other areas where biotechnology might generate products are those in which enhance features of well people (for example the kidney-derived hormone, erythropoietin, will increase the number of red blood cells in patients who repeatedly need kidney dialysis, but this hormone might also be used by athletes (Garewau et al., 1996), or examination candidates or others who might benefit from a higher degree of alertness and sustained activity). Such a use of a product dependent on the new biotechnology (it is made from a genetically engineered Chinese hamster ovary cell culture grown in roller bottles manipulated by computer-controlled robots) is either forbidden, unlicensable or illegal.

It may, therefore, be asserted that one of the bottlenecks to the development and use of our newly found capabilities to engineer and exploit animal and plant cells in culture is based on the suspicion with which society views the products made by these procedures. A second area where a restructuring of the social components could bring about an improved rate of generating biotechnological benefits based on the use of animal and plant cells in culture is at the interface between industry and the generators of new knowledge and capabilities; viz, the universities and government research establishments (GREs). It must be recognised that much new and important information and technology is generated by industry itself, but in some two-thirds of cases a university or dedicated laboratory was involved in the generation of a discovery of commercial importance in the UK between 1900 and 1990. However, at this time of writing the dogma which is followed is that industry and universities should work more closely together to achieve 'realising our potential' (CM2250 Waldegrave, 1993) based on the people engaged in contributing to the intellectual and economic life of the community. This simplistic approach has its drawbacks, yet as it contributes significantly to the configuration of the technology/society interface, I will examine it in more detail.

2. Industry, universities and society

Animal and plant cell technology is poised between industry on the one hand and three components of society, the universities, the GREs and the professional and learned societies, on the other hand, see Fig. 1A. There is also a direct relationship between society and industry in the provision of space, the collection of taxes, the compliance with laws and the generation and use of the products. In this section, I will explore some of the facets of the interface at which universities and industries interact. While I shall emphasise the animal and plant cell technology sector of the interface, much of what follows also pertains to other technology sector areas.

Whereas the current dogma seeks to enhance and extend the present university/industry interface, I will contend that the social imperative to 'realise our potential' may yet be more effectively served were there to be a restructuring of our social institutions such that the universities were enabled to achieve their principle objectives (see Section 2.1), and that the research which is intended to enhance the economic well-being of the country be focused in laboratories which have a remit to achieve, through dedicated research and development programs, particular goals which may then be taken up by the commercial sector and made available to society at large. Such laboratories may sit within the ambit of a university or may be independent of any

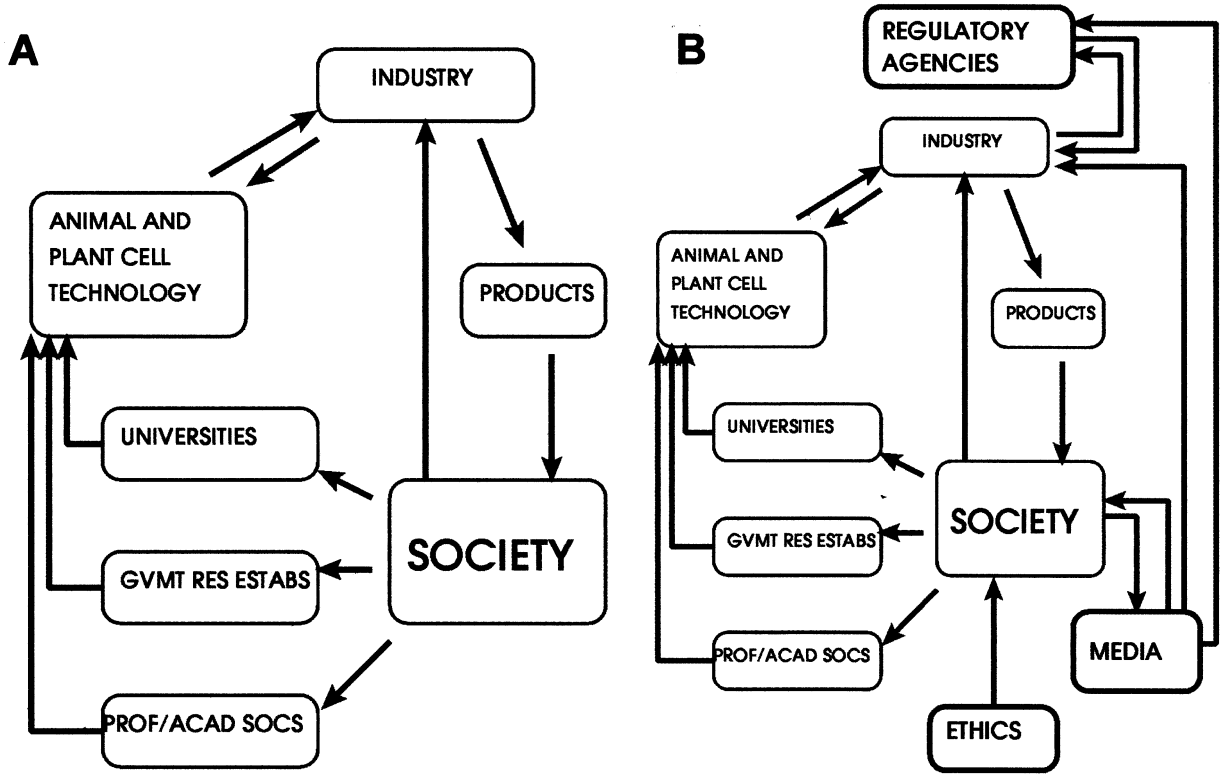

Fig. 1. Components of technology/society interface. (A) The inner circle; (B) the add-ons. GVMT RES ESTABS, government research establishments; PROF/ACAD SOCS, professional and academic societies.

one academic institution. Indeed, when the main commercial inventions and discoveries of the first 90 years of this century are examined, for the UK it may be surmised that some two-thirds of the inventions were the products of GREs or dedicated university laboratories. The residue of inventions derives from the activities of industry. That the dedicated research laboratory may be the most effective way of generating innovative answers to pressing social needs can be deduced from an examination of the way the universities and industry view their respective missions and the consequences of those approaches on the way the people who ply the university/industry interface modulate their behaviour.

2.1. The culture of universities

Academic institutions across the world are experiencing increasing financial stringency. In the UK the student population has increased by 100% while the number of academics has moved up by some 30%. Not only is the academic required to teach but he/she is engaged in administrative processes and is expected to effect world-class research. In turn, the latter has to be effected by obtaining funding following an extensive grant writing effort, of which some 60–90%+ is wasted through rejected applications. Nevertheless, the expectations of society for the university contain many of the objectives depicted in the following list: (1) to produce educated people with a sense of wisdom, culture, humanity, dignity, respect, honour, tolerance, discipline and ethics; (2) to inspire curiosity, to instil criticality, to inculcate capability; (3) to produce people with a second language and communication, numerical and literacy skills; (4) to screen such people for competence; (5) to survive as an institution; (6) to advance knowledge;

(7) to advance capabilities; (8) to interact with local communities and enrich them; (9) to set standards for behaviour both within the institution and beyond; (10) to market the intellectual property generated by the university activities.

It is generally assumed that the achievement of the above objectives may be effected with the most efficiency when the individual members of the university adopt a collegiate mode of operation which implies that academics are: (1) open in their communications with one another and their students; (2) individualistic in their approach to scholarship and research; (3) not concerned with monetary matters; (4) thorough, methodical and time consuming in the examination their data.

It is therefore, not surprising that certain tensions have emerged within the academic community, which, in spite of the expenditure of much good will, may have led to a decline in both the quality and quantity of the output of such institutions. This will become more evident when the interface between industry and the university is examined from the point of view of the ethicality of the behaviour of the so engaged individuals (Section 2.3). In preparation for that examination it is well to highlight the components of the culture of industry.

2.2. The culture of industry

It may appear that the sole function of industry is to make money. This superficial view is inadequate. In law, a company has roughly the same status as an individual; it can be sued, it can petition for an injunction, it has certain defined rights and responsibilities. It should not be surprising that this state is reflected in the objectives of industry which I have summarised in the listing as follows: (1) to survive and grow; (2) to make profits; (3) to make the purchase of its shares attractive; (4) to innovate and develop new products for social benefit; (5) to protect secrets; (6) to provide activity for employees; (7) to enhance the wealth of employees and investors; (8) to compete successfully often by being first to the market; (9) to achieve a monopolistic trading position; (10) to be accepted by the community; (11) to acquire and deploy the best in people, machines and materials.

Of crucial importance to the definition of the quality of the interaction at the university/industry interface are the following characteristics: (1) industrialists are secretive about unpublished information/ideas/hunches which may affect their profitability in the present or foreseeable future; (2) people in industry tend to work in teams, individual mavericks are not, in general, condoned; (3) people in industry work under time constraints and seek to get things done quickly to beat the competitors to the market; (4) money is important to all those who engage in the industrial endeavour.

The four characteristics cited above are in sharp contradistinction to the equivalent characteristics as cited for the individuals who occupy university positions (Section 2.1). Notwithstanding these inherent cultural differences and features, academics have been suborned into becoming more secretive and less open; press-ganged into teams to obtain grant monies and made supremely conscious of the value of monetary income and speedy performance to their respective universities. This has affected their behaviour in the light of the manners of their industrial counterparts. These attributes will be considered further below.

2.3. Ethics at the interface of the university and industry (see also Spier, 1995)

Ethics may be thought of as a suite of words which constitute the set points which humans use to control their social behaviour (Spier, 1996a). Generally, philosophers hold ethics to be synonymous with morals; being the Greek and Latin versions of the same concept. The word ethics is used in three contextually distinguishable ways.

(1) The first involves its use in discussions about systems of ethics or the way we may come to the overriding principles from which we may derive the detailed instructions or guidelines for behaviour; such considerations may also be thought of as meta-ethics.

(2) A second use is when we define a guideline for behaviour. I assert that all such guidelines can be considered as ethics. Note that these guidelines may be good or bad; right or wrong; beneficial or harmful. It is not material to the statement of ethics that they are necessarily as we would have them—they are just guidelines.

(3) Otherwise, there is a third use of the word ethics to describe those guidelines which are purported to be good, right and beneficial. Correspondingly we have unethical guidelines which are bad, wrong and harmful.

Let me be clear. There are many interactions between university academics and industrial employees which are wholesome and result in benefit for the individuals, their respective organisations and for society generally. Information is exchanged, advice given and taken, materials tested and evaluated and people move between the sectors. When such exchanges are equitable and not exploitative the ethics which has guided the interactions has been formulated to generate public benefit. Regrettably, not all the interactions in this domain are of this nature. Below I present instances where the ethics (the guidelines for behaviour) which have been followed need modification so that the improper behaviours alluded to become curtailed or eliminated.

It is rarely in the interest of an industry to acknowledge that either it has a problem; or that a problem it has had, has been solved by an external agency. Such a stance betokens weakness and something less than complete competency to do the job as set out. Therefore, industrialists do not find it easy to acknowledge the sources of their successes particularly when they come from an extramural origin. An example of this might be that a company having difficulty making a particular vaccine was in receipt of (1) a new, more competent, and productive cell line, (2) a new virus strain and (3) a worked out assay system to monitor virus production. Although it was clear that the company resolved its difficulties, when challenged as to the reasons for its success, it replied that they had used their in-house materials to solve their problems; and when their achievements where challenged publicly it appeared that they had not received any external help whatsoever. However, it was learned many years later that instructions had been given to company employees not to divulge the degree of help they had obtained from the extramural agency. The inequity in this interaction is apparent; the non-industrial researchers did not receive credit by acknowledgement for their contribution to the industrial success.

An industrial ploy which seems to pervade the interstices of the interface is one which involves shopping around the university sector to see which research projects the universities would like to do with the company. There are two sequellae to this; the first is that if the company has a defined project, it may hawk it around the rest of the university sector to see who would provide the results for the minimum expenditure and in the shortest time; and secondly, if there is not a particular project in mind then the industrialist might milk the ideas, which could lead to the generation of intellectual property, and then either take the ideas it likes to its 'pet' (low-cost/local) university laboratory, or do them in-house.

Unfortunately, there are not any easy solutions for a university wishing to sell some exciting research ideas to a company; in exposing the ideas, even after having signed a secrecy agreement, there is little to prevent the exploitative industrialist from taking advantage of his/her privileged position and engaging company employees along the line of research suggested by the academic. And because these employees are bound by the secrecy agreement they sign when they join the company, the academic is non-the-wiser until years later he/she sees in the literature or at a conference presentation the work which they had carefully and in detail expounded to that company. Of course, it might be argued that ideas have their time and place and the same idea can crop up in two or more places simultaneously; but the nagging suspicions remain.

In the heat of negotiating a contract for a research investigation the representatives of the university may overstate their case for industrial commitment. It is facile to make unrealistic projections for the length of time a project might take (shorter than in reality), the actual costs incurred in the project (less than the actual commercial

costs as the overhead costs to the institution are rarely levied above 100% of salary costs while commercial operations tend to use figures of 250% salary costs) (Motluk, 1997), the virtuosity and commitment of the academics involved (conveniently forgetting their teaching and administrative duties), the adequacy of the laboratory provisions on site (where antiquated, much used and multipurpose equipment may give less than accurate and reliable performance) and where trained support personnel are available to do the work (individuals on short-term contracts whose chief objective is to obtain a more stable position to regularise their extramural lives). It should be noted that in undercutting commercial rates to acquire contracts other commercial companies which would otherwise be in the running for the contracts (and would do them more efficiently because of the dedicated personnel and equipment) are disadvantaged. The money for such underpinning has to be obtained from other university budgets which does not necessarily decrease the quality of provision in the so-depleted areas.

Although the above might be thought of as ways in which the university takes advantage of a gullible company, the latter too might have ways of augmenting its return from its university investment. Apart from having an academic in tow, the latter can be exploited to divulge thoughts on a wide range of issues stemming from the original contract. Such academics may use university facilities which were not included in the contract negotiation, including the peers of the principle investigator on the contract; these individuals may be providing help and support to the principle investigator and receive neither recognition nor financial reward for their pains. It may even be possible to unwittingly involve undergraduate students in contractual activities by setting the subject area for their undergraduate research project to overlap the area of contracted research with a company.

As the company ethos is to protect as secret any information which can in any way aid a competitor, the publication of the results of a project can be impeded in a way which may seriously disadvantage the academic contractee even though there may have been provision in the contract for conditional publication. While it is clear that the company needs to be able to patent any intellectual property which results from the project, the time taken to achieve this cannot be extended unreasonably; although on occasion this provision can be exploited to delay publication due to 'difficulties with the patent lawyers'. Publication can become a particularly contentious issue when the company does not wish the negative and damaging results of tests on one of its proprietary products to become public (Marshall and Vogel, 1997). Under these circumstances it is not the academic institution which is damaged, rather society at large is the looser as it may be misled into thinking it is buying a beneficial product where the product may be inactive, or worse still, damaging.

Another situation in which the ethics of company practice might be questioned is the soliciting of university laboratories to effect what might be difficult or dangerous work to which it does not wish to expose its own personnel. Two examples come to mind; one involved the requirement to produce and assay mycoplasma organisms (an invidious contaminant of animal cell cultures) and a second involved the chemical synthesis of β-propriolactone a potent inactivation agent for the rabies virus and a toxic material to humans also. Universities might also be exploited for their willingness to host experiments with animals; this decreases the likelihood of animal rights activists disrupting work and destroying company property.

When contracted to an industrial project academics may have conflicts of interest. In the USA such contracts are examined by an internal review board (Werhane and Doering, 1997) and where an academic or a member of the academic's immediate family may be a beneficiary of the contract in amounts of money of over $5000 then actions have to be taken to limit and control any further benefit which may accrue. But there could be other benefits in kind which could affect promotion prospects or the attainment of tenure (where that still exists). Additionally, academics might feel conflicts when it comes to guiding students or fellow academics towards or away

from particular areas of scientific investigation because of knowledge which has to be held in secret. This may also spill over into the lectures and publications of the academic which could thereby mislead audiences and cause confusion where reason should prevail.

Industrialists too have to wrestle with conflicts of interest when they participate on grant review bodies or act as referees for journal publications. In principle the referee or reviewer should not gain one iota of personal benefit from the intellectual material to which the industrialist has been exposed (except of course that the task is, of itself, meritorious). However, this does not always hold. Most academics have a war-chest of stories as to how they were maltreated by grant reviewers and publication referees (it should be noted that industrialists are not the only malefactors in this context). Yet the insider knowledge which an industrialist might purloin back to the secretive enclave of the industrial base cannot be obviated. Not only are ideas appropriated but projects are discredited and disallowed as they may conflict with industrial ambitions which have not yet been revealed. I would contend that the introduction of industrialists into such situations is fraught with problems and the adage that 'industry knows best' (Coleman, 1983) should be erased from the set of principles which have been used to control the activities of universities.

(Parenthetically, if we are to have peer-review processes for grants as the least of evils, then because it is inevitable that the reviewer is in an advantageous position in relation to those who are not involved in the review process, it is essential that each of the peers, that is, all those who are active in the grant application process, should be given an opportunity to participate in the grant review process and thereby offered an equal bite at the reviewing cherry.)

The nature of these interactions is antithetical to the university achieving its objectives as stated above (Section 2.1). It is also not in the interests of industry to have the energies and imaginations of academics devoted to the survival of the university through its monetary contracts with industry. In the end, 'that which is inexpensive, becomes expensive' and it may be that the underpinning research that industry can best exploit is more efficiently accomplished by specifically targeted and appropriately staffed and financed GREs or by industry itself as stated by Richard Sykes the CEO of Glaxo-Wellcome (Cohen, 1996) and Sir John Cadogan, Director-General of the Research Councils (Cadogan, 1997).

Universities should be given the task for which they are accepted, which is of the training of students in the research activity. It is well known that when an institution has a clear and unambiguous remit it will perform to that remit with greater success than when the remit is multifarious and the outcomes are obscure and blurred. Such clarity of function is also required for the establishment of a suite of ethics from which both the university and industry can only benefit.

But the university/industry interface is one facet of the society/technology interface. Other aspects of society such as the regulatory agencies, the media and the ethics held by the people also impinge in the way the technology is progressed. It should be noted that the laws of the land are codified ethics and tend to be written in such a way as to proscribe particular behaviours. As they are included within the ethics issue they will not be considered further here, but it is necessary to remember that the general laws about fraud, misrepresentation, safety and others apply at the interface between technologies and society. The three generic aspects referred to previously will be examined in more detail below.

3. The influential agencies

In Fig. 1B, I have added to the components of the inner circle of Fig. 1A three additional agencies; the regulatory agencies, the media and ethics. The impact of these agencies on the way in which animal and plant cell technology develop has already been alluded to in Section 1 and will be further developed in this section.

3.1. The regulatory agencies

Society needs to be protected against the prospect of the promulgation of drugs or products

which in widescale use may cause damage to people. These agencies are relatively modern and began in the 1960s (Dunlop, 1973; Spier, 1996b). While novel foodstuffs are also subject to regulation, the majority of cosmetics and natural foods do not require a certificate before marketing and distribution. The products of the animal and plant cell technology effort are mainly in the pharmaceutical area and each such product has to go through a regulatory procedure, which, in three stages determines whether a putative product is safe, efficacious and can be made consistently. Although it is not yet mandatory, people in the agencies have an eye on the social value of the material which is under evaluation. In each of the parameters used for the assessment, judgements are made and those determinations are themselves influenced by the state of mind of the people in the regulatory agency (Spier, 1996b).

For example, the issue of safety is not one which requires a product to be 100% safe; there is no such product (Editor, 1996). Therefore, we are left with a balance between the cost of the product (monetary cost plus and social damage [which may be assessed by determining the risk of damage and multiplying it by the magnitude of the damage] caused by the product) to be balanced against the benefits of the product. This relationship will differ for different cultures, societies and times. There are societies which are prepared to accept the damage caused by alcohol, cars and smoking because there are sufficient people to attest to the benefit of such life-destroyers. There are other societies which find a modified polio vaccine (genetically engineered to prevent the type III component from reverting to the wild type) (Burke et al., 1988) almost unlicensable, even though the new product is designed to be safer than the one in current use.

Even the issue of efficacy is not as clear cut as one might expect. In the presence of a life-threatening disease (such as the acquired immune deficiency syndrome (AIDS)) drugs may pass through the agency which are hardly effective and have serious side effects. However, to license a new measles vaccine is much more difficult as there is already and effective vaccine and the cost of showing that there are significant advantages to the new vaccine may be prohibitive (over $100 million).

The ability to manufacture a product to a particular specification is a regulatory agency requirement. But what are the tolerances which are built into such a specification? For example, in a virus assay (such as that in the target animal, cows, for foot-and-mouth disease vaccines) may have a standard deviation of $\pm 300\%$, so that a given vaccine, which has to be at least one standard deviation above a base level of two, must have a titration value of not less than six. Indeed assay variations are notorious. Samples of the products generated from animal and plant cells in culture measured in different laboratories can vary considerably; and unless there is considerable effort expended in standardisation of assay procedures the achievement of a licence to produce is retarded substantially.

The introduction of the 'social value' parameter might make more transparent some of the thinking of the regulatory agency personnel. However, this measure of the licensability of a product is not easily determined. How is social value determined? By the amount one has to pay for something? By its contribution to the survivability of individuals/groups/society? By one's emotional reactions of like/dislike, want/reject? A vaccine protective against AIDS would be valued greatly and prevent several tens or hundreds of thousands of deaths per annum; a vaccine protective against infant diarrhoea is not as highly valued although it might prevent the deaths of millions of infants world wide.

Not all is well with the regulatory process. Apart from the ambiguities and judgement calls which are inherent in the process, the cost to companies of obtaining a licence to sell a product may range from $10 to 500 million. (These costs are passed on to the consumer and explain the $2000 a dose for a material which is probably less expensive to produce than the bottle in which it is contained!!). It should not be beyond the capabilities of a modern society to abbreviate this process and bring down these costs without the forfeit of too great an increase in the dangers to which people may become exposed.

3.2. The media

Bad news sells newspapers. Disasters fascinate and hold people spellbound; particularly if they are infrequent and large. Even the hypothetical potential for a disaster is newsworthy in some parts of the media. This latter propensity is particularly damaging to the newly emergent biotechnologies amongst which animal and plant cell products feature in a significant way.

At this time of writing, considerable effort is being expended to achieve the genetic transformation of humans using viruses grown in animal cells in culture which have been engineered to inculcate into human somatic cells and cure genetically derived diseases, such as cystic fibrosis. From such therapeutic attempts some media pundits have extrapolated beyond what is reasonable in science fiction and have proclaimed the arrival of a monster of Frankensitinian proportions. We do not have to go back in time a long way (50 years or so) to remember the stories told to children about the wide variety of monsters/witches/goblins/trolls/griffins/serpents/gods/demons who would 'get them' if they strayed from the path of good behaviour (ethicality). This evocation of our primeval fear complex is a potent generator of phobias and resistance to modern biotechnology and the social benefits it can bring. Such extreme views need to be curtailed. It may be possible to achieve this were there a more open communication system between biotechnologists and the public (Fox, 1996; Golub, 1997; Woolley, 1997).

A second source of problem with the media (generally at the level of the page editors rather than the reporter/journalist) is the generation of hype. It is easy to see that if a putative product or method might in some circumstances lead to an earlier diagnosis of cancer, a vaccine protective against AIDS, or a possible cure for Alzheimer's disease, the media with headlines blazing would proclaim the arrival of the ultimate cure for cancer/AIDS/Alzheimer's, respectively; notwithstanding the admonitions of the startled biotechnologist who did not go anything like as far as the media would have him/her go. Not all the opprobrium is attributable to the media, however. Some of the newer biotechnology company public relations people have been known to enlarge on their company's new discovery or capability well beyond the limits of the actual development. All who are engaged in preparing and providing news for the people of our societies have a duty of care to elicit those reactions which are fully justified by the developments reported; but no more and no less.

In a genetically engineered product it is often held that we have something which is unnatural. But what is natural? If it exists can it yet not be a part of 'nature'. Although this is a semantic issue, hinging upon a definition of nature that may exclude some of the entities which palpably exist within that domain, it is a concern for those whose concept of naturalness is informed by what is traditional and part of conventionality. It is easy to show that what we hold to be conventional or traditional today was otherwise before those conventions/traditions came into being. Therefore, as change is inherent in the condition of nature and as genetic engineering is but one such change, it may also be regarded as a natural activity and its products, natural products.

A common complaint levelled at the biotechnologist is that in genetically engineering a cell, there has been an interference with the work of God(s). In essence, the technologist is accused of playing God and attempting to influence the state of nature. I would answer such a criticism with a statement like; in writing this article, I am attempting to put into the mind of the reader certain concepts/ideas/memes (Dawkins, 1978) which might even be replicated by communication between readers and others; in giving a speech or preaching a sermon, a similar process is afoot; building a shelter, tending cattle, growing wheat are all processes in which humans alter nature. Are all such alterations of nature to be denied because they have not been ordained by a deity? If such alterations are allowed then it is difficult to see a difference in principle between these changes and the ones effected by the biotechnologist. A corollary to this issue is that if all which exists on earth is as a result of the intention of a deity, then genetic engineering as an earthbound activity is also at the wish of the self-same deity and is therefore allowable.

Were the media to become better informed on these issues then we might expect that society might be better served by its communication practitioners. In the absence of this development we will have to continue to struggle to get the good news properly presented and our societies appropriately informed.

3.3. Ethical issues in animal and plant cell technology

New developments require us to behave in new ways. How then are we to modulate our behaviour in the light of the novel products and processes which are emanating in great numbers from the technologies which are the subject of this article? One such way to provide additional guidance for behaviour is for biotechnologists to adopt a code of conduct. Two kinds of codes may be distinguished; the one being an advisory code, which, in the breach, leads to admonitions for better behaviour, while the second is a disciplinary code, where breaches result in actions which may deprive the reprobate biotechnologist of the right to continue to work as a practitioner in the area of biotechnology. The latter code may become part of the machinery which enables biotechnologists to practice as professionals, to which I shall return in Section 4.

3.3.1. Plant cell technology

Conventional wisdom might assert that, other than for questions of principle, the genetic engineering of plants would not throw up issues which require us to make behavioural or ethical decisions. After all, humans have been making new plant varieties for centuries and selective procedures have been in place for even longer periods of time, such that, even before the advent of the new biotechnology (say 1975) the dangers of monoculture were becoming apparent and as particular crop varieties became popular, the diversity of the plant life of a country or continent was declining rapidly.

Also, in the pre-biotechnology period, many (countless) experiments were effected which involved the transfer of a plant which was found in one environment/country to a completely different environment/country. This is akin to the release of a new genotype in a foreign environment. In this sense it is not different in any way to the deliberate release of a genetically engineered organism into a particular environment. Clearly many of the transfers prospered. Potatoes and rubber palms transplanted well as did the mulberry bush (a native of Asia and North America) which enabled the production of silk in France in Pasteur's day. Some plants did become weeds when transposed. But it has never been beyond the bioingenuity of humans to find an antidote to an uncomfortable biological gaffe. (for a review of such transfers see Williamson (1996)).

However, plants constitute a common basis for human foods. When tomatoes have their shelf-life increased by inserting a gene which codes for an inhibitor of the gene whose expression leads to the production of the enzyme polygalacturonase (an enzyme which accelerates fruit softening and overripening) into their genomes, there was much concern expressed in the press and by people. A consensus conference was held on this specific issue in London in 1996 (Lloyd-Evans, 1995) the outcome of which was to affirm that people should be given the opportunity to choose not to have such tomatoes and that the genetically engineered version (the puree and sauce derivatives) should be labelled accordingly (Recent information has it that these products, labelled as being derived from genetically engineered tomatoes, are preferred to the products not so derived). A somewhat different situation is developing in the area of soya beans where an engineered variety of bean has been mixed in with beans which have not come from a genetically engineered plant. The American farmers who produce these beans do not distinguish between them and hold them for storage in hoppers where the beans are mixed. When they began to export such beans to Europe and refused to label the mixture as a commodity which contained genetically engineered material, there was a concern expressed at all political levels. Whether this issue was aggravated by economic considerations and the issue of the mixed beans was used as a device to reduce American imports to Europe is still moot. There is clearly a mixture of ethical issues based on economics, the

issues in principle about the edibility of a genetically engineered material (this in spite of the administration by injection of millions of doses of genetically engineered insulin and hepatitis B vaccine) and issues based on labelling practice and the analytical methods which may or may not determine the presence of the genetically engineered material in a sea of non-engineered beans.

What is new is that we can now make herbicide-resistant plants which implies that a farmer who takes advantage of this property will be tied into purchasing the appropriate herbicide which goes along with the plant. Of course, disaster scernarioists envisage the gene for herbicide resistance being transferred to weeds thus making them resistant and requiring the farmer to use a plant which is resistant to another herbicide so as to continue the 'progression'. Although there may be advantages in the decrease of the amount of herbicide used, because of its specificity, the locking-in of the farmer to the seed/herbicide supplier may lead to an exploitation of the farmer with increases in the price of seeds and chemicals. A variant of this situation may be seen in the production of plants by genetic engineering which are resistant to insect attack. Again it is possible that the insects may mutate to become resistant to the toxin which was engineered into the plant thus engendering the re-engineering of the plant with a different insect toxin gene. Clearly in both of these cases there will be changes in the ecosystem. Whether the changes will be beneficial or harmful has to be determined by careful observation and quantification of all the relevant parameters. It is not enough to point out that a change has been made and therefore harm has been committed. Rather, a pragmatic experimental approach should prevail in which limited uses are made of the above possibilities and increases in the scale of the operations are kept in line with increases in our confidence that the outcomes are more than likely to be beneficial.

When moving a genetically engineered plant or micro-organism into the uncontrolled environment of the field one immediately incurs a risk of doing harm as well as an opportunity for achieving benefit. The magnitude of the risk is generally unknown and the magnitude of the potential damage or benefit is also unknown. But humans have faced this situation countless thousands of times before as, and when, they have transported seeds from a 'home' country to a new country far abroad. Would Johnny Appleseed be decried in today's world for spreading apple tree seeds about the American continent? However, it has also to be recognised that in certain states and countries the unofficial introduction of foreign and viable biomasses is forbidden (the state of California, Australia) but the controlled ingress of useful biomaterials is also encouraged. Were we not to accept any risk of damage then such developments would cease; the prospects for progress would likewise terminate. As we must develop and change or perish, we may respond to the opportunities to insert newly engineered biomaterials into a variety of environments and learn from the outcomes the basic lessons which will enable us more effectively to use the tools that the genetic engineer has put at our disposition.

3.3.2. Animal cell technology

As there is a more direct connectivity between human cells in culture and human beings the use of such cells throws up a welter of additional issues to consider. Also, while plant cells enrich human populations via their modification into foods, flowers or pharmaceuticals, animal cells provide a basis for the production of viruses for vaccines and gene vectors for use in the modification of the human genome, and in recent months have been used to initiate clones which has caused the reissue of the concern about the establishment of cloned populations of humans (Spier, 1997; Wilmut et al., 1997). Animal cells in culture are used for a widening range of applications (Editor, 1995). Whereas the initial uses were based on attempts to understand the way the human body differentiated from a fertilised embryo to an adult, in the 1950s animal cells in culture began to be used to produce virus vaccines (polio, followed in the 1960s by mumps, measles and rubella); in which position they stayed until in the 1970s when additional uses were discovered. These included the manufacture of monoclonal antibodies, the production of cytokines and immunoregulators, the generation of therapeutically active enzymes

and hormones and, most recently, the making of human organs from cells grown in bioreactors and the use of animal cell cultures to provide the cells used for the cloning of animals (op. cit. Spier (1997)) and possibly humans also (Dickman, 1997) were the legal situation to permit this development (Editor, 1997a,b; Wadman, 1997a,b). As a result of these developments many questions have to be answered as to how we use these potent product materials and, in particular, whether we can only make products aimed at either the therapeutic, diagnostic and prophylactic markets, but can also make products which will enhance the human condition both in the life time of an individual and also, through the germ-line modifications, the life time of subsequent generations.

Most citizens would concur that virus vaccines have been an unalloyed boon to their societies. Yet it is also clear that the widespread use of vaccines can be problematic. For example, as vaccines are effective in preventing infant mortality in the developing world there may result an increase in the number of surviving infants who may incur dietary deficiency diseases (kwashiokor or marasmus) later in life. However, it is encouraging to note that the number of children born to such mothers during the period of their fertility has dropped drastically in the last 30 years from 6 to 3.5 live births (UNICEF, 1996) so that projected increases in population may have to be revised in a downwards direction.

There are a suite of issues which pertain to the production of vaccines (Spier, 1998). In the private enterprise operations which prevail in the vaccine production area for humans, vaccines which are not economic (will show a profit on the R&D investment) are generally not produced. Also, other vaccines whose efficacy would decrease the demand for successful drugs (stomach ulcers and the common cold caused by a mixture of rhinoviruses, coronaviruses and adenoviurses) are not high-priority items for the pharmaceutical companies. Finally, the actual charge levied on the vaccine is a matter of concern for those vaccines which have more than paid off their R&D costs. In some cases a two-tier system is in operation and some vaccines are sold to the WHO or to a government sponsored vaccination program at a fraction of the price that would be charged to a private physician treating an adult patient.

Figures denoting expenditure on health-care R&D by governments will evidence that the proportion spent on research into prophylactic medicine is a small fraction (generally $< 5\%$) of that which is spent on therapeutic R&D. As the cost of hospitalisation increases inexorably it behoves our well-developed societies to pause and review this situation. Were we to come to an ethic which promotes the prevention of disease (infectious as well as non-infectious) then research into the additional vaccines which could be made in animal cells in culture and whole plants (Hamilton, 1997, this symposium) would have to be augmented significantly in addition to research on diet, exercise and ways of controlling and decreasing mental stress.

Testing vaccines before licensure is both a costly and ethically sensitive issue. This is particularly the case when the vaccine is targeted at preventing disease in a developing country but could also provide benefits to developed countries. While local people may be used in the vaccine trials there has to be a commitment by the investigating company that the vaccine, if, and when, it obtains its product licence, will be made available to the people of the country in which the tests were done under especially favourable financial terms. Furthermore, provisions have to be in place to obtain informed consent (which is not a trivial issue when there are considerable differences in language, culture and basic understandings). There may be additional problems in that the removal of blood samples (necessary to determine the efficacy of the vaccine) may raise taboo issues for a person and may not provide access to another part of his/her essential body parts for fear that they maybe used to damage or harm the tissue donor.

Vaccines may be used as technical fixes to obviate ethical problems (Spier, 1989). Rather than modify behaviour, people may prefer a technical vaccination which would protect them against infection. Thus, in the case of AIDS, it is possible to prevent the spread of this infection by the appropriate use of contraceptive condoms and

the abstinence from the practice of unprotected anal penetrative sexual intercourse. Hepatitis A virus transmission has been shown to be markedly decreased when people are willing to wash their hands thoroughly before eating, and hepatitis B transmission responds to the same prohibitions that apply to the AIDS situation. This evokes the question as to the necessity for the raising of vaccines for these diseases. In this determination we have to assess the costs and benefits to society as a whole for each course of action and bear in mind that in a freedom-promoting political environment the inculcation of changed behaviour patterns is difficult if not impracticable. We are, therefore, at this time, left without a choice but to follow the technical route to achieve the control and elimination of disease through the widespread use of effective vaccines; many of which are made in animal cell culture.

A final issue in relation to vaccines is the prospect of providing vaccinations via the water supply or via a commonly eaten foodstuff (bananas). This prospect coupled with the possibility of the development of a vaccine which will protect a female against pregnancy can provide both acceptable and unacceptable opportunities. Clearly the surreptitious application to society of any material is not condonable. We need to have an open society in which the biotechnologist and the people work together to achieve mutual benefit.

Monoclonal antibodies are monomolecular antibody preparations made from a selected clone of antibody secreting animal cells. They are used as components of diagnostic kits, for preparative processes based on affinity chromatography methods, for the delineation of cancerous tissue and/or the attack of such tissue by bifunctional reagents; they may even be used for their enzymatic properties (abzymes). Few ethical issues pertain to these reagents though the intellectual property disputes in the early days of their use were not insignificant. Otherwise, as these antibodies may be used as hormones, in that they can be targeted to hormone receptor molecules, issues which pertain to hormones can be raised for these antibodies.

A wide range of hormones can be made from animal cells in culture, These include growth hormone, erythropoietin, insulin, follicle-stimulating hormone, leutenising hormone, somatostatin, prolactin and others. These substances can control the nature of the animals into which they are injected. Additionally it is possible to use the genes which code for these hormones as a means of generating transfected animals and humans which permanently secrete larger amounts of the hormone than normal. This may lead to larger animals or cows with increased milk yields or animals which are deliberately rendered sterile. A consequence of effecting such changes is that the economics of particular industries may be affected, with the displacement of groups of farmers (for example) from the workforce. There are also a series of concerns based on the production of unusual animals. However, the latter eventualities may be likened to the selective breeding programmes which have been used for dogs, camels, turkeys or horses, whereby breeds have emerged which are incapable of survival except through the offices of human carers. As each development is novel, it may be most appropriate to deal with the issues which arise on a case-by-case basis.

Our societies are quite clear on what they regard as desirable. It is not only the monetary value and incomes of sports people, stars of the stage and screen and purveyors of popular music which can provide the clues as to the way society values particular personal properties, but there are equivalent rewards for shrewdness in business, artistic flair and ruthless determination. Other attributes, such as height, strength, mental ability, hair/eye/skin colour and symmetry may be taken as elements in the construction of an individual who can excel in the other denoted areas. The question which falls from these considerations is whether we would wish to produce more people with attributes of higher value as depicted above, or otherwise. How we proceed in this matter will depend upon the establishment of the necessary control systems and upon the careful, sensitive and open way by which we engage in society-wide experimentation with alternative forms of using the techniques which have been made available to us via the production of animal cells in culture.

Using animal cell cultures to produce enzymes, such as tissue-plasminogen activator or blood clotting factor VIII may seem to be unburdened

with ethical problems; the two enzymes are therapeutically active and useful. However, there are issues which relate to the most cost-effective treatment of blood clots in heart attacks as substances, such as aspirin and the bacterially produced asparaginase may also be efficacious. A new suite of over 40 immunomodulatory proteins/glycoproteins has been discovered in the last 20 years. Manipulation of the composition and concentration of these chemicals can be used to improve the immune response to vaccines, infections, cancers and autoimmune diseases, such as the rheumatic disorders. Again the main ethical issue which emerges is the affordability and availability of these materials.

4. Conclusion

At the interface of technology and society there is a continual thrusting up of new issues and opportunities to improve our condition which, in turn, leads to the requirement to review the way we behave. This is particularly acute when we survey the way in which the products of animal and plant cell technology impinge on the public domain. This paper has highlighted some of the areas where ethical issues have been raised. In particular we can see that the regulatory agencies are a focal body in the determination of what products enter the market place; and part of the decision-making process is dependent on the ethical views held by the regulators. Notwithstanding this hurdle to the emergence of new products we have also to be aware that the way the media handle these issues does not always comply with the realities of the situation.

While there are many new products derived from animal and plant cells in culture presently in the market, there are hundreds more waiting in the wings. Some of these products will require us to review the way we see ourselves as human beings. This can only be done if there is an effective and open interaction between all the individuals who are involved at the interface, as well as those who may become concerned and who have not yet developed the sensitivities to realise that many changes to their way of life may be inherent in the manifestation of the new products. It would also help were the biotechnologists to agree to become professionals like the doctors, lawyers and architects, so that a more formal contract between the biotechnologists and society may become operational.

Because the developments we are considering are momentous, we have to resist the temptation to issue blanket declarations to ban all such developments. Rather we have to carefully and collectively explore the new regions of capability which these modern technologies have made available to us. A cautious, open and inviting approach is what the citizens of our respective societies require. As scientists and technologists we can no longer remain the back-room and foist on to an unprepared public whatever we have concocted for their edification. This is an unprecedented era of intellectual and technical advancement; it is best done as a conjoint effort in a caring, deliberate and well considered manner.

References

Burke, K.L., Dunn, G., Ferguson, M., Minor, P.D., Almond, J.W., 1988. Antigen chimaeras of poliovirus as potential new vaccines. Nature 332, 81–82.

Cadogan, J., 1997. From pure science to profit. Chem. Industry 1 December, 937–939.

Cohen, J., 1996. Research 'summit' ponders health funding shortfall. Science 274, 49–492.

Coleman, R., 1983. The then Government Chief Chemist. Speech Made at Biotech '83, On-Line, Wembley, London.

Dawkins, R., 1978. The Selfish Gene. Paladin, London, pp. 206.

Dickman, S., 1997. A real culture shock. New Scientist 155 (2091), 4–5.

Dunlop, D., 1973. Medicines In Our Time. The Nuffield Provincial Hospital's Trust, pp. 67–89.

Editor, 1995. Biotechnology medicines and vaccines approved and under development. Genet. Eng. News 15 (14), 12–16.

Editor, 1996. UK medical chief suggests 'safe' does not mean 'no risk'. Nature 383, 371.

Editor, 1997a. European research programme faces rough ride ahead. Nature 386, 639.

Editor, 1997b. Human cloning requires a moratorium, not a ban. Nature 386, 1.

Biotechnology and the European Public Concerted Action Group, 1997. Eurobarometer Survey of 1996. Europe Ambivalent on Biotechnology. Nature 387, 845–847.

Fox, J.L., 1996. BASIC takes bioremediation public. Nat. Biotechnol. 14, 1077.
Garewau, R., Audran, M., Flowers, C.H., Baynes, R.D., Duvallet, A., Senecal, L., Brission, G.R., 1996. Erythropoietin abuse in athletes. Nature 380, 113.
Golub, E.S., 1997. Genetically enhanced food for thought. Nat. Biotechnol. 15, 112.
Hamilton, W.D.O., 1997. This symposium.
Kierman, V., 1996. New agers cast a spell on science. New Scientist 24 February, 10.
Lloyd-Evans, L.P.M., 1995. Representation of the people? The UK's first consensus conference. Sci. Eng. Ethics (quoted in Science 274 (1996) 491–493) 1, 93–96.
Marshall, E., 1996. Rifkin's latest target: genetic testing. Science 272, 1094.
Marshall, E., Vogel, G., 1997. Publishing sensitive data: who calls the shots. Science 276, 523–526.
Motluk, A., 1997. When the sums don't add up. New Scientist 155 (2091) (19/7/97), 18–19.
Spier, R.E., 1989. Ethical problems? Get a technical fix. Vaccine 7, 381–382.
Spier, R.E., 1995. Ethical aspects of the university–industry interface. Sci. Eng. Ethics 1, 151–162.
Spier, R.E., 1996a. Ethics as a control system component. Sci. Eng. Ethics 2, 259–262.
Spier, R., 1996b. On the acceptability of biopharmaceuticals. Sci. Eng. Ethics 2, 291–306.
Spier, R., 1997. Clones on stage. Sci. Eng. Ethics 3, 106–108.
Spier, R.E., 1998. Ethical aspects of vaccines and vaccination. Vaccine (submitted).
UNICEF, 1996. The State of the World's Children. Oxford University Press, London, p. 99.
Wadman, W., 1997a. US senators urge caution on cloning ban. Nature 386, 204.
Wadman, W., 1997b. White house bill would ban human cloning. Nature 386, 644.
Waldegrave, W., 1993. Realising our Potential. UK Government White Paper.
Werhane, P., Doering, J., 1997. Conflicts of interest and conflicts of commitment. In: Elliot, D., Stern, J.E. (Eds.), Research Ethics: a Reader. University Press of New England, London, pp. 165–189.
Williamson, M., 1996. Biological Invasions. Chapman Hall, London, pp. 1–244.
Wilmut, I., Schnieke, A.E., McWhir, J., Kind, A.J., Campbell, K.H.S., 1997. Viable offspring derived from fetal and adult mammalian cells. Nature 385, 810–813.
Woolley, M., 1997. The comfort zone. Science 275, 1243.