THE BEGINNER’S GUIDE TO WINNING THE NOBEL PRIZE

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AMERICAN EDITION
Publisher: Columbia University Press
ISBN 978-0-231-13897-0

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CHAPTER 1: The Swedish Effect

The ceremonies surrounding the annual Nobel Prize presentations are for most Swedes an important reminder of great human endeavors, and of their own nation's place in promoting them. The awards have a high profile throughout the country: Swedish television carries live telecasts of the presentations and banquet, newspapers and radio programs feature the winners, and people talk about the prizes on the street.

Until they win, few laureates realize that the award ceremony is associated with an intense but exhausting week that thrusts them suddenly into the media spotlight, and requires a high level of energy and – unless they are teetotal – a reasonably tolerant liver. When the king confers that award, handing the winner a gold medal and a leather-bound certificate in an atmosphere of solemn dignity, he also bestows a kind of celebrity status that has its own rewards and limitations.

The latter mainly involves the loss of personal and professional time that goes with public attention, but the compensations are the broader awareness of your work, gaining a public 'voice' and the opportunities to meet extraordinary people. The presentation ceremony at the Stockholm Concert Hall is followed by the white-tie Nobel banquet – complete with gold-leafed plates and gold-plated cutlery – 1,200 in the town hall. Unlike the Queen of England, the Swedish monarch no longer has any statutory role and his function is essentially symbolic and ceremonial.

The following night, the king and queen hosted a spectacular dinner at the Royal Palace. The setting for the royal dinner was again formal, though the atmosphere was a little more relaxed than at the awards. The king described it as 'a family dinner'. The servers were dressed as footmen, the one standing behind the queen sporting an enormous feather projecting far above his head. This tradition was evidently started by an earlier king so that he could immediately find the queen in a crowded reception.

During the course of the Nobel week I delivered the lecture that every laureate is required to give, and in the evenings we were entertained by Swedish colleagues in the medical sciences. As new – and in some ways overwhelming – as it is, the experience of the Nobel week stand you in good stead for the reality of the very busy ‘Nobel year’ that all laureates face when the celebrations in Scandinavia end and they return home. You can avoid the endless rounds of engagements, of course, by either refusing invitations or by giving talks so appallingly bad that even the Nobel cachet cannot improve them – the word gets around. Most people take the responsibility seriously because it provides the opportunity to air issues they care about in a broad, public forum. The pressure generally tends to tail off after the next series of awards is announced. Although there are always invitations that seem to relate purely to the status of the Nobel Prize. The Nobel year's commitments consume a lot of time and take active scientists away from their research programs. Some, who are in the later stages of their careers, lose traction and never really get back to what had been their life's work. All laureates, at any rate, lose a measure of the personal space required for introspection and creativity. My year, however, like that of most senior scientists, was essentially booked and committed before the call came from Stockholm. Apart from my own ongoing work at St Jude Children's Research Hospital in Memphis, I was serving on various national committees and was booked to give numerous seminars. The Nobel adds a further level of invitations, many of which cannot be refused.

I received Australia's highest civil award, the Companion of the Order of Australia, from the then Governor-General, Sir William Deane, and gave masses of lectures associated with visits 'back home', including an address to the National Press Club in Canberra that was broadcast over and over. I was constantly giving public talks and appearing at public events while in Australia. There was never a spare half-day, or so it seemed. I also had to excuse myself from the review committee for the US Multiple Sclerosis Society, which was close to my heart. They had funded me in the past, and a dear friend had committed suicide years before because of her MS. It was all pretty exhausting, and even now I still have to be extremely judicious about the commitments I accept.

Deciding who should receive a Nobel is a considered and protracted process and is, even now, informed by the life and intentions of Alfred Nobel. The life of this wealthy industrialist and explosives manufacturer presents intriguing paradoxes. He invented the detonator, dynamite and a smokeless powder to propel cannon shells – all agents of destruction, in some sense – but many believe he intended all the prizes to operate to promote world peace. In that sense, they are all 'peace prizes' and clearly the words 'peace' and 'Nobel' go together in the broader public consciousness.

Before he died on 10 December 1896, Nobel instructed that the majority of his estate should be invested so that the accumulating interest could be used to fund what we all know as the Nobel Prizes. In his will he also specified the disciplines to be recognized, the institutions that should be responsible for decision-making, and guidelines about who should win. The most important single factor determining the status of the Prizes is the statement in the last sentence of the extract from Nobel's will that is published for all to read on the Nobel website. Translated from the Swedish, it reads: 'It is my express wish that in awarding the prizes no consideration be given to the nationality of the candidates, but that the most worthy shall receive the prize, whether he be Scandinavian or not'. Here we have it. These are international awards that try to identify the most important, the most significant work in physics, chemistry, medicine or physiology, literature, economics and peace, by individuals who have contributed most substantially to benefit humanity.

Nobel's executors were two young engineers who worked for his company – Ragnar Sohlman and Rudolf Lilljequist. Sohlman was instrumental in establishing the Nobel Foundation that is responsible for both the investments and the awards. The intent and scope of the prizes generally follows the brief instructions in Nobel's will, but practical considerations have required further interpretation by the Nobel Foundation. One consequence is that the award is given to a maximum of three people in each category, with the exception of the Peace Prize that can go to large organizations like the Red Cross or Medecins sans Frontieres.

The Literature Prize is decided by a committee drawn from the Swedish Academy, founded in 1786; the Physics and Chemistry Prizes by separate committees from within the Royal Swedish Academy of Sciences, founded in 1739; the Prize in Physiology or Medicine by members of the Karolinska Institute, which boasts its own alumni of Nobel winners; the Peace Prize by a committee selected by the Norwegian Parliament, the Storting. Although there is no prize in mathematics, the Nobel Foundation added the Bank of Sweden Prize in Economic Sciences in memory of Alfred Nobel in 1969. Responsibility for the Economics Prize – which some still consider to be controversial – was handed to the Royal Swedish Academy of Sciences, which sometimes chooses a mathematical economist.

Invitations to potential nominators go out in the later part of the year and they must forward any nominations they want to submit by the following February. The list of nominees is potentially enormous and varied, so there are strict rules around those eligible to nominate. For the science prizes, the general protocol is that major institutions and individuals prominent in particular areas are asked to provide names, a concise justification and background information. Though former laureates are always invited to submit nominations, they are restricted to the field for which they were recognized.

By October, the committees make their recommendations, and their decisions must be ratified by the broader body of the responsible academy. The discussions and deliberations involved in this painstaking process remain confidential, and are embargoed for fifty years. Whenever I read that someone has had the distinction of being 'nominated for a Nobel Prize', I wonder how the information emerged. Candidates in the sciences are most unlikely to be aware that they are being considered. They might be asked to provide up-to-date curriculum vitae, or a list of what they consider to be their achievements, but the enquiry is likely to have come from a third-party source that would not normally spark the thought of a Nobel connection. The nominators are asked to be as circumspect as the committees that make the decisions. Though the scientific community gossips about possible future winners and everyone assumes that the obvious people have been nominated, the details are generally known only to the proposers themselves.

The entire process is secretive, and the Swedes never leak. On the other hand, you do hear rumors that you've been nominated for a Nobel. I'd never tried to pursue this in any way – perhaps because, years ago, I was told by organizers I'd been nominated for another prestigious prize and became a bit fixated on it. Then nothing happened, so I've ignored anything like that since then.

Some people get very distressed about the Nobel because they think they should win. However, there is no 'court of appeal' and some never really recover from feeling they've been excluded. There is also the 'rule of three', which means that tough decisions must be made. At least in the medical area, people will have been nominated a number of times for different awards. Anyone who has a case will have been looked at pretty closely. I suspect that the same Nobel candidates come up year after year and, as I understand it, the leading cases are reviewed afresh each time.

Half the people who, like us, win a Lasker Basic science award later win a Nobel. American culture is very open, and being American, the Lasker committee leaks like a sieve. As I heard it, Rolf and I were added to a 'Harvard ticket' of Don Wiley, Jack Strominger and Emil Unanue after the immunologist on the committee said it would be outrageous to recognize them and omit us. Don and Jack provided the X-ray crystallography pictures that explained how our 'altered self' idea worked (see Appendix 1), while Emil worked on a related problem with 'helper' T cells (which is discussed in chapter 4).

While the prize itself affects each individual differently, it's worth thinking about the general effect of theseawards on Sweden's place in the world. In the end analysis,the biggest, long-term winner from the Nobel Prizes maybe the land of Alfred Nobel's birth.

To my mind, the Nobel Prizes have proven to be a great device for focusing the broad attention of society on values that relate to rational, evidence-based enquiry, truth and peace, the basic building blocks of prosperity and of participatory democracy. Sweden is a modern industrialized nation. The country spends a very high percentage of gross domestic products – more than 4 per cent in 2001—on research and development.

It makes sense that the country that produced Nobel pays a lot of attention to its scientists and their institutions. Others do too: because the selection committees for the science prizes consist solely of people working within the responsible academies, ambitious people who believe they may have some chance of a Nobel will invite their Swedish colleagues to conferences and gatherings where their work is on show. In turn, the Swedish scientific community is very conscious of this and the standard of biomedical research at the Karolinska Institute, for instance, is extremely high. The population of Sweden is about 9 million, and five scientists from the Karolinska have been awarded the Nobel Medicine Prize. A surprising number of my friends doing medical research, in both the United States and Australia, have spent time working at the Karolinska in their younger days, simply because it is a great place to do science.

Though the modernization of Sweden is generally considered to have begun in the 1870s, a move forward thatincluded the personal efforts of Alfred Nobel, it is clear thatthe past 100 years have seen a major change in the country. Rapid technological advancement has been accompaniedby reasonably good relations between employers and trades unions. The university system is first-rate. It would be hard to measure, but it seems likely that the strong political commitment to, and participation in, higher education reflects an awareness of science and intellectual activity promoted by the Nobel Prizes. If you look at the rest of the world, both intellectual life and democratic governance continue to be in good shape in Sweden. I wish we could say that about all the developed countries.

Winning the prize is immensely gratifying both professionally and personally, but most scientists who enjoythe extraordinary privilege of a Nobel realize it also comes with responsibilities. One is to represent their particularscientific field. Many take a much broader view and speakout regularly in defense of science, reason and justice.

If we are to achieve satisfying and positive outcomes for humanity through this coming century, it is essential to bring together the different cultures that Alfred Nobel recognized by his prizes so that they interact in a mutually supportive way. Beyond that, it will be necessary to work with political and corporate power-brokers, financiers and religious leaders in the effort to build healthy and satisfying lives for all people on this small planet. How else can we ever hope to achieve harmony, peace and global prosperity? Though everyone has some understanding of humanitarian ideals, literature, religion, politics, and business and (perhaps) economics, the most obscure activity to many is what goes on in the sciences.

Many misinterpret the scope of science. The enormous successes over the past century have led to the widespread assumption that there will always be some sort of clever fix. In truth, science does some things very well, and others not so well. I strongly believe that though modern science is highly specialized and can speak in obscure tongues, an understanding of the basic nature of scientific enquiry and what scientists bring to the communal table is both straightforward and accessible to anyone. The task of the scientist through the twenty-first century is to advance discovery, evidence-based enquiry and the technological innovation that contributes to solving problems, alleviating suffering, and generating genuine and sustainable prosperity. This can only ever be just one part of the complex, multifactorial equation that operates to improve the human condition. Though there were many disasters through the twentieth century, the advances were extraordinary. We need to continue the best part of that trajectory.

CHAPTER 2: The Science Culture

The basic methodology of modern science is comparatively new in terms of the way human beings have traditionally approached the world. We are used to trial and error and the common sense approach, but science works by a much more formal process that leads often to counter-intuitive conclusions. The level of insight associated with award-winning science may not be vastly different from that found in great writing, but good books are much more familiar than what we now know as science.

The march of science from early times is much less well recorded. The science that we live with today is, in fact, only about *500* years old. To understand modern science, it helps to have a sense of how it developed. The earliest trace of the history of science dates from the beginning of the written word, and the available evidence tells us that science started well, but then fell on hard times. Science is neither a religion nor a substitute for religion (see chapter 7), but there was a time when the people in charge of using discovery and knowledge to promote the welfare of humankind behaved more like a priesthood than anything else.

Many who had the time and opportunity to pursue intellectual activity and enquiry were in fact priests and, as such, were constrained by religious authority. The Polish astronomer-cleric Nicolaus Copernicus (1473-1543) is said to have delayed the publication of his magnum opus on the earth orbiting the sun, *De Revolutionibus Orbium Celestium,* until just before his death from fear that he might be tried for heresy and burned at the stake.

In the ancient Greeks, we see the characteristics of what we now think of as science at its best in Archimedes of Syracuse (279-212 BC). If he were around today, he might have won several Nobel Prizes. Archimedes did what looked to be a simple experiment (had a bath), made an observation (the water rose), developed a hypothesis (he had displaced an equal volume of water), then reported the finding in a way that was both public and intellectually accessible to anyone who wanted to repeat the study. He noticed the displacement effect because he was already thinking about a problem. The king of Syracuse, Hiero II, wanted to know if the jeweler who had made a crown for him had cheated him. Was it solid gold, or part silver? Silver is lighter than gold so it will displace a greater volume for an equivalent weight: this was clearly the way to test the purity of the crown. It is impossible to believe that nobody had ever noticed before that a full bath overflows when somebody jumps into it – Archimedes simply took something that was commonplace, thought about it, stated a basic principle of physics and presumably got paid by the king. He would also have repeated the experiment (by having another bath).

The written archives that describe the life's work of Archimedes are thought to have been lodged in the Great Library of Alexandria, which was destroyed before 700 AD, probably by fire. Though called a library, this may well have been the world's first university. Recent excavations suggest a capacity to seat as many as *5,000* students. It seems to me that the dark ages that so stultified human enquiry for a thousand years – at least in the Christian world – began symbolically with the final suppression of the Alexandria Library by the Christian emperor, Theodosius IV. The modern scientific era had to wait for the upheavals of the Renaissance and the Reformation, and for figures like Francis Bacon (1561- 1626) whose writings provided the philosophical basis of the inductive method that drives scientific enquiry today. Scientists use inductive reasoning that progresses from specific observation (data) to generalization (theory), rather than deduction from some all-encompassing hypothetical construct. Bacon wrote that ‘ the only knowledge of importance to man was empirically rooted in the natural world’. We finally rediscovered what Archimedes had known more than 1,500 years previously: that nature cannot be explained by making statements about how we *think* it might work. Reliance on ex *cathedra* pronouncements that emphasize authority over reason, discovery and evidence is both death to the spirit of truth and enquiry and physically damaging for our species and our world.

What changed in the sixteenth century is that people again started to make systematic observations and to do experiments. At the University of Padua – perhaps the first great center for science-based medicine – the Belgian physician Andreas Vesalius (1514-1564) managed to get around the various laws that forbade dissection of the human body and wrote the first major anatomy text, *De Humani Corporis Fabrica.* While studying at that university, the English doctor William Harvey (1578-1657) began a series of experiments showing that Galen had been wrong and that the heart functioned basically as a pump, with valves that allowed unidirectional flow, enabling the blood to recirculate between the arterial and venous compartments. The discovery of the capillary circulation by Marcello Malpighi completed the circuit between artery and vein. Harvey had come to his conclusions by 1615 but, because of the power of the entrenched Galenic tradition, did not publish his seminal work, *De Motu Cordis,* until 1628.

By this time the science revolution was well established in Europe. In Paris, King Francis I established the College de France (1529) as a major intellectual institution that was totally independent of ecclesiastical authority. All lectures were free and open to the public. That continues today: I spoke there not long back at a scientific symposium, and any person who wished to attend was able to do so at no charge. The College de France remains one of France's most powerful institutions, located close to the Institut Pasteur. The sciences section of the Academie Frarncaise was established in 1666, four years after Charles II of England granted the initial charter of what continues as the British National Academy of Science, the Royal Society of London. Every major English scientist from Newton to James Cook to Darwin and on has been a Fellow of the Royal Society.

The motto of the Royal Society is *nullius in verba,* which means 'nothing by words alone', which in turn translates to mean, 'You have to do the experiment'. The idea of experimenting is not foreign to us: children do it all the time. But experiment alone is not enough. The experimental results have to be reported publicly in such a way that anyone who has the resources to do so should be able to confirm or refute the study. It has to be repeatable. No scientific finding becomes fully legitimate until it is published and discussed. I always tell my young colleagues, 'If it isn't published, it isn't done'. The oldest scientific journal in English is *The Philosophical Transactions of the Royal Society of London.* The *Phil. Trans.* has been in continuous publication since 1665.

The seemingly simple technique of moving from hypothesis to experiment to publication and independent verification has transformed our world over the past *500* years. This change was part of a larger Western intellectual awakening which began with the European cultural Renaissance and the Protestant Reformation and culminated, in the mid-to-late eighteenth and early nineteenth centuries, in the Enlightenment. The Enlightenment in turn provided the intellectual framework for the founders of the new American Republic, particularly for Thomas Jefferson. The questioning of received custom, tradition and authority, and the encouragement of individual reason and freedom of thought, meant that the business of explanation shifted from assertion and 'revealed truth' to evidence.

The big problem with building an increasingly complex body of knowledge on successive insights, experiments and discoveries is that both the technologies that are required to do the work and many of the important conclusions become less and less accessible intellectually to the non-specialist. Living in the sixteenth and seventeenth centuries, Francis Bacon and William Harvey could readily encompass the known world of science. This would also have been true for the initial group of seven who got together as the first members of what was to become the Royal Society, at Cheapside, London, in 1645 to discuss the 'new philosophy' or 'experimental philosophy'. A little later, Sir Isaac Newton (1643-1727), who famously discovered gravity from watching an apple fall, and the diarist Samuel Pepys, who was elected to the Society in 1665,would have understood everything that went on at themeetings.

How do we foster a more sophisticated understanding of what science can and cannot do in the broader public consciousness? There are good books on science and scientists, many of which are written by dedicated science journalists. The ABC-TV *Catalyst* programs that I've seen have been excellent (quite a few of them sourced from outside Australia, presumably for financial reasons). In the United States, the *Scientific American Frontiers* programs, narrated by Alan and Nova's *Elegant Universe* are consistently first-class.

Another way to bring the science culture more into the general domain is to take a leaf from the book of the Nobel Literature laureate, the Italian playwright Dario Fo, and inform via the medium of the theatre. Stage plays and intelligently made television dramas and movies (a scarce product when it comes to science) can be very powerful mechanisms for communicating. Michael Frayn's *Copenhagen* shows that a human dilemma created by a possible application of science can be transformed into an entertainment that is both enjoyable and intellectually challenging.

What also needs to happen is to move science from the realm of remoteness and embed it much more in the normal human experience. Everyone can achieve at least a measure of scientific literacy and, what is more, people will gain both personal satisfaction and even a sense of wonder and delight from having a better understanding of the natural world around them. Perhaps it would also be useful to develop ways of conveying the sense that a measure of frustration and uncertainty is also a normal part of the reality with innovative science. There can be a worm in the shiniest apple and sometimes, of course, the worm is more interesting than the apple. Do kids get bored with school science because they don't see that intriguing worm and, instead, come away with the impression that the whole game is predictable and mechanistic? Nothing, of course, could be further from the truth. Science museums with creatively designed interactive exhibits are found in most major cities. Visiting them is an experience that both children and adults can enjoy greatly, as we did when we lived in Philadelphia – our kids had a great time in the Saturday morning science program at the venerable Franklin Institute. Increasingly, as is already the case with the Nobel e-museum, it will be possible to visit on the Web reconstructions of some of the experiments that led to major discoveries.

Both the British and the French governments make heavy use of their national science academies, the RoyalSociety and the Academie Frarncaise respectively. The USNational Academy of Sciences has traditionally played amajor role in providing well-researched, dispassionate anddetailed advice to both the Congress and the President, thejob that it was set up to do at the time of its foundation byAbraham Lincoln. There is nothing to stop a US president drafting a top scientist for a Cabinet post. Though scientistscannot and should not dictate policy, it doesn't take muchinsight to realize that every major political decision should, where applicable, be informed by the best possible scientific insights.

Some groups in society are simply unlikely to ever be sympathetic to science, even though they may have no qualms about taking advantage of what science and technology have to offer. Perhaps the biggest disconnect is in the minds of those at the extremes of religious fundamentalism who, if their wishes were implemented, would return to social models that depend on 'revealed' truth andauthority. The growth of knowledge-based economies dependson flexibility, creativity and the capacity to retain thosewith the greatest abilities and the best minds, no matterwhat their belief system, sex or sexual orientation may be. Regressive social models quickly drive those people away, or even destroy them.

Fundamentalism is not, of course, confined to religious groups. The extremes of the environmental movement are absolutely opposed to the application of genetic engineering approaches to improve plant varieties. Nothing in the human experience provides more fertile ground for faddism than the food we eat. Though traditional plant breeding has changed most of the items in our food basket to the point that they would be unrecognizable by those living in the fourteenth century, the thought that techniques based in contemporary gene technology should be used for further, targeted improvement is apparently unacceptable tomany environmental activists.

Part of the problem is that the first applications of plant gene technology were fostered by a large chemical company, Monsanto, in a way that horrified those who believed that plant varieties, seed supplies and so forth should not be controlled by international conglomerates. Many entirely reasonable people share this perception, including most of the Aid agencies operating in the developing world. There were few, if any, regulatory controls, and the scientists didn't help by simply telling people that there was no danger, and that they should just be allowed to get on with it. The trust-us-and-accept-what-you're-told approach doesn't work too well anywhere any more. A more judicious approach that invites openness and accountability would no doubt serve both the public and the scientific interests much better.

The reaction against genetically modified organisms (GMOs) has generally been greater in Europe than in the United States. Part of the reason is the relative strength of the environmental movements. A further component that feeds into the European discomfort is that there is a general and justifiable distrust of regulatory authorities. In part, this may stem from, for example, the way that the then British government and bureaucracy handled the BSE (mad cow disease) outbreak. Americans have much more confidence in agencies like their FDA, which controls the approval of drugs and vaccines for human use.

The negative reaction has also compromised the distribution of products like saffron rice, which is freely available and was engineered in Swiss public sector science laboratories to correct the blindness caused by vitamin A deficiency and the iron-deficiency anemia that afflicts people, particularly women, in some parts of the developing world. We recently saw the tragedy of Zambia refusing GM corn, which has been eaten by millions of Americans without any untoward consequences, in the face of a disastrous situation where many were starving. Not only is there a complete absence of any evidence that GM corn or saffron rice has any deleterious effect, there is no good scientific reason either for thinking that there could be such effects.

Every time I talk to plant scientists, whether they work in the advanced nations or in developing countries, I get the same message: they want to use GM approaches for applications like the production of higher yield crops, disease resistant varieties and plants that grow on poor soils, especially those with a high salt content. The same is true for the Consultative Group for Agriculture Research (CGIAR), the organization started in 1971 by the former US Secretary of Defense and president of the World Bank, Robert McNamara, and the Australian economist Sir John Crawford, for channeling international resources to science directed at feeding the poor of the world. The CGIAR currently operates some twelve agricultural research institutes in developing countries. In the past, they funded the research done by the maize breeder Norman Borlaug that led to his Nobel Peace Prize for contributions to the 'Green revolution' of the 1960s. Borlaug is an energetic, enthusiastic and infinitely decent human being, now in his eighties, who is still doing everything in his power to promote science-based agriculture as a partial solution to the joint problems of starvation and social degradation. He was a conventional plant breeder and is a passionate advocate for the use of GM approaches to speed up what needs to be done.

The fact of the matter is that at least 800 million people of the 6.4 billion or so that inhabit this planet do not get sufficient to eat each day. Aid certainly helps, but moving food internationally requires ships, trucks and the associated consumption of energy. Care has to be taken to ensure that what does cross the seas isn't stolen to end up being sold to starving people. If that food transfer strategy worked, however, there is no reason – given the global surpluses – why the problem should not already have been solved. Nobody and no country wants to live as a charity case. The ultimate aim must be to ensure local sustainability in food supply, whether at village or national level. Pride and psychological well-being are at least as important as efficiency when it comes to the food/agriculture equation. The GMO approach is certainly not the whole solution, but it does have the potential to play an important part.

What is to be done? Open, rational public dialogue would help, but that's difficult at the moment. Some organizations have made opposition to GMOs an article of faith, and so many individuals assess the issue in a very emotional way. There are, however, a number of obvious steps to take.The first necessity is to ensure that the types of regulatorycontrols and monitoring procedures that elicit public confidence are not only in place but can be seen to be working.The second is to strengthen public sector biotechnologyresearch and development, in Africa particularly, so that thecountries themselves have 'ownership' of both the science and the applications of the science. The third is to build economic structures that make GM seeds available free, orat cost, to farmers at the village level. There is no reasonwhy large-scale agriculture operations in Africa or anywhere else should not pay commercial rates. There is nothing to stop farmers whoplant GMOs from also maintaining their own, conventional seed stocks produced in traditional ways. It must beobvious that GM plant varieties will be used in the firstplace only if they are associated with reduced fertilizer and insecticide costs, or give substantially higher yields.

The irony is that many scientists who support GMO approaches are also passionate advocates of environmental conservation. Why should strategies that have the potential to bind marginal soils together, or limit the use of insecticides and nitrate fertilizers, be considered 'anti- environment'? There are enough really bad guys out there in positions of power without having those who are concerned with promoting human well-being and the health of the planet taking opposite sides on this important issue. It is surely time to initiate a more sensible and balanced discussion.

Unlike the situation with plant GMOs, people in general have relatively few problems with modern medicalscience. Everyone is happy to benefit from a new cancercure and there is no doubt in anyone's mind that a moreeffective treatment is a real plus. The next generationinfluenza vaccines are likely to be GMOs engineered by aprocess called reverse genetics. I doubt there will be any problem with their acceptance in the face of an influenza pandemic, especially if, like the H5N1 bird virus that is a looming threat (see chapter 4), there are indications that it may cause severe infections and human deaths on a massive scale.

Perhaps the main area of debate relates to the use of embryonic stem cells, where the lobby groups termed 'pro life' (the life of the fetus, not the woman) condemn elective or medically advised abortion in the belief that success with stem cell research in some way legitimize the 'pro choice' (by the mother and doctor) position. This debate is a social and moral one that will not be swayed by scientific and argument. Apart from deeply held religious convictions, there is also a broader cause for concern that any wide spread use of early human embryos from terminated pregnancies could become a means of providing 'spare parts'.

Ask yourself whether some of the totalitarian monsters that so blighted the twentieth century would have had the slightest qualm about paying (or forcing) a young woman to carry a fetus to three or four months if the tissue from that embryo would have ensured a further year of life for them. Might there just possibly be people like that around today? This has to be a broad debate that is informed by both science and ethics. Fortunately the great majority of medical science research has nothing to do with embryonic stem cells.

Few would object if, for example, we could take ‘self’ stem cells from an individual’s own blood or bone marrow, then manipulate them in some way so that they return to the embryonic state. Such cloned, pluripotent cells would be of immense medical benefit to the individual providing them. In addition, this strategy would circumvent the difficulty with tissues derived from aborted fetuses, which bear foreign transplantation molecules that can promote rejection (see Chapter 4). As with a transplanted kidney, such host-versus-graft responses can be controlled with suitable immunosuppressive drugs, but the situation is notideal. An alternative, and utterly abhorrent, possibilitywould be to use 'identical twin' cells from an embryonic 'clone' of the person to be treated. This is one of manyreasons why the cloning of whole human beings should bebanned permanently. At the same time, great care has tobe taken that any anti-cloning legislation is not drafted so broadly that it would inhibit the useful application of cloned cell lines and so forth that I've mentioned above.

The interaction between science and government is both complex and long-term. Early examples relate to weapons technology and fortifications. Archimedes designed effective war machines. Rene Descartes (1596-1650), who is regarded by many as the first modern mathematician, earned his living as a military engineer. Thepublicly funded voyages of exploration from Europe fromthe sixteenth century to the eighteenth were concernedboth with acquiring territory and with discovering preciousmetals, plant varieties and so forth that could be exploitedfor economic advantage. Early successes fostered by this approach included the importation of tobacco, the tomato and the potato, which comes from the South AmericanAndes. Sir Joseph Banks became the longest serving president of the Royal Society and it was he who suggested the 1788 establishment of a penal colony in New South Wales, which marks the beginning of European Australia. Modern Australia may be the only country on earth that was established on the suggestion of a scientist as a result of a scientific expedition.

There are many stories of how government-funded science has served the public interest, a well-known example being the development of radar which was so instrumental in the defeat in World War II of the short-lived Nazi empire. More recently, the NCI Special Virus Cancer Program of the 1970s helped put in place the technology that allowed the relatively rapid isolation of the human immunodeficiency virus (HIV) that causes AIDS. If AIDS had hit the Western world a hundred, or even fifty, years earlier, the confusion and fear about what was happening would have been infinitely greater than it was, as there is no way that we could have isolated the causative agent using the available methods. The history of witch-burning, killing minorities and so forth that accompanied the disastrous plagues of the Middle Ages in Europe might well have been repeated in modern guise if AIDS had continued to spread unchecked in the democracies.

In general, democratic governments from both the liberal and conservative ends of the political spectrum haveno philosophical problem when it comes to supportingmedical research. The expense of medical research is infinitely less than the cost of health care delivery, which is now consuming such a high proportion of national budgetsin every advanced country. Research scientists also plough any grant money back into the economy by buying expensive chemicals, isotopes, plastics and sophisticated equipment from private industry sources.

The discoveries made by the publicly funded bio-medical research community flow on to the private sector in the development of new biotechnology start-ups and larger innovative companies. The drug industry, in particular, depends heavily on this transfer of novel findings from the public to the private world as a source of new product development. Major pharmaceutical companies set up their own laboratory complexes close to, or even inside, the top research institutes and universities. Such partnerships make good economic sense, as it is only the private sector that can ultimately assemble the resources needed to bring a new drug or vaccine to the market.

The tension between science and government comes to the fore when the best advice that the scientists can provide is seen by politicians as having acute, negative consequences on the economic (and thus the political) front. The classic case at the moment concerns the predictions of progressively escalating temperatures, melting ice caps, raised sea levels and disrupted weather patterns as a consequence of increased carbon dioxide levels. At least in the United States and Australia, the oil companies, the mining companies, the timber-cutters, the automobile industry and others do not want even to hear about global warming. On the other hand, much the same sensitivities that influenced the GMO debate have led to an acute awareness of the issue in European countries. The global warming equation is, of course, extremely complex.

Given the widely expressed doubts that come, in the main, directly or indirectly from industry sources, it might be thought that governments would want to increase the amount and depth of the research being undertaken so that better predictions can be made. Where there is doubt, more experiments need to be done, more observations must be made. Whether or not that is the intent, any moves to inhibit such enquiry suggest a deliberate strategy to suppress the truth. There is too much concern, and too many players involved in too many countries.

If there were even the hint of a military threat as serious as that being put forward by the informed science community about the consequences of rapid climate change, the response by governments would be both immediate and dramatic. Why is there such a difference? A facile argument is that military spending is a traditional way of transferring public money to powerful corporations, while at the same time facilitating the type of pork barrel politics that allows local representatives to bring home the bacon. This dynamic is yet to emerge in the environmentally friendly industry sector, but there is no rational reason why moving towards the development of sustainable technologies should not be just as good a mechanism for spending tax dollars to support private sector job creation.

There are also, I think, deeper reasons that rest in the biology of what we are. Human beings are programmed by their evolutionary history to react very rapidly to the possibility of imminent attack. There was no problem, for example, in getting the global community to work together to limit the SARS epidemic. The response was universal, rapid and efficient, partly because it built on the global influenza surveillance network that operates out of the World Health Organization (WHO) in Geneva. The existence of this WHO program reflects that influenza is a continuing, immediate threat, with new strains emerging constantly. When it comes to insidious, long-term environmental damage, though, we are much less concerned about what is happening. The worm has turned now, but many agricultural communities in the developed world came very late to measures that would minimize erosion, the saltation of soils and so forth. Deforestation continues globally at alarming rates.

It makes no sense to be locked in to old, dumb technology. No matter what the future, energy independence and technologies that are clean, green and minimize waste is clearly the way to go. Why isn't this seen as a major priority? Is it because entrepreneurs operating on a small scale in what will initially be high-risk ventures do not constitute a significant source of political contributions? My bet is that those nations that focus on environmentally friendly, innovative industrial development will be the economic power-houses of the future. The scientists, the economists, the industrialists and the politicians need to be in a process of continuing dialogue. Both the carrot of R&D funding and the stick of regulatory requirements can help to lead the innovation donkey to water!

At some stage there inevitably comes a tipping point where the basic realities change for the worse and political leaders who have allowed a disastrous situation to develop pay a severe penalty. The first sign of a tipping point with global warming may be starting to emerge in what look to be extremely atypical weather patterns.

Education is clearly the key if we are to build a greater appreciation of science into both the political and the public consciousness. People don't have to know the details of this or that scientific discipline, but it is important to develop a reasonable understanding of how science works and where the strength and limitations of the scientific approach lie. I would, however, reiterate that innovative approaches like science theatre and the creative use of the Internet merit further development and thought.

As the Nobel physicist Richard Feynman put it: 'For a successful technology, reality must take precedence over public relations, for Nature cannot be fooled'. Science is the best tool we have for not fooling ourselves and for probing the reality of what faces us. Humanity will ultimately pay a heavy price if those of us alive today choose to inhabit a self-serving fantasy world that denies reality.

CHAPTER 3: The Scientific Life

The2004 Physics Nobel, for 'a colorful discovery in the world of quarks' went to the theoretical physicistsDavid Gross, David Politzer and Frank Wilczek from the University of California at Santa Barbara, the CaliforniaInstitute of Technology and MIT respectively.

The theoreticians I know need to talk a lot with at least one close colleague who understands intimately what they are saying, and even the purest of pure mathematicians, who may be reluctant to reveal what they're thinking to the person in the next office, tend to gather at places like the Princeton Institute of Advanced Studies. The life of John Nash, an applied mathematician from Princeton who won the 1994 Economics Nobel – andgave his name to the 'Nash equilibrium' that is central to game theory – was portrayed recently in a Hollywood film, which tells the story of the support he received during the course of his long struggle with schizophrenia, which has now achieved a great measure of remission. The impact of mathematically based theory on the biomedical research community is a relatively recent phenomenon. The theoreticians who develop mathematical models of biological systems are generally keen to get together with experimentalists like me so they can access real data – but I fear we often disappoint them. The process of generating the numbers they would like to have could consume our whole lives and millions of dollars. Even so, theoreticians are an amiable bunch: they tend to drink a lot of coffee and beer, wave their hands around and write equations on white boards. Sometimes it is even possible to grasp what they are on about.

The cultures in the various areas of experimental science differ greatly, though we all talk a language based on hypothesis, experiment, observation, open reporting and independent verification. The scale of the 'small science' done by most biologists can, however, seem a long way from the world of the experimental physicists, what many scientists think of as 'the big end of town'. The new CERN particle accelerator located on the border of France and Switzerland cost $US2.5 billion, but will provide a unique international facility to address the most fundamental questions in physics. When the CERN people talk about an experiment, they may be describing a commitment that involves years of construction, preliminary testing and preparation. A single 'big science' experiment can cost millions- especially if it requires shooting things intospace – and involve hundreds of people. Many university astronomers and physicists, though, work on the smaller scale that is familiar to a biomedical scientist like me. However, even if the world of cosmic scientists probing the beginning of the universe seems very different from that of the research biologist, the common link is that we all come down at one point or another to dealing with new data.

Laboratory scientists work in groups. A typical group of ten or twelve will be led by the 'principal investigator',or PI, the senior scientist responsible for raising the funds,setting the overall direction of the research program, seeingthat the primary papers and review articles get written,and travelling to talk about the work at scientific meetingsand research seminars. Every major university and research institute has a regular seminar series and, in a big scientific environment like the United States, any PI who is doing substantial and interesting research will be on one circuit or another. The cachet of a Nobel Prize, of course, only adds to this load. The more successful people are often booked for a year or more ahead, and are also solicited regularly to write review articles or chapters for books of collected papers.

The key resource person in any sizeable research program is likely to be the head technologist. Typically, thisis a very experienced and competent individual with an undergraduate or master's degree who has always workedunder supervision at the hands-on end of research. MyMemphis laboratory is managed by Elvia Olivas, whogrew up in Mexico, trained in science, worked as a technician and then took a business degree. Sometimes a PhDscientist who has decided not to pursue an independentcareer fills the head technologist role. Their job is to makesure the laboratory runs properly by ordering equipmentand research supplies, supervising junior technologistsand developing new technical approaches. The head technologist will often look after the budget, no small responsibility in any lab. Experimental biology, for instance, is nolonger done solely with small items like test tubes and petridishes, though buying plastic plates and flasks does consume a lot of the budget in many laboratories.

Even the 'small science' pursued by medical research workers commonly costs between $US600,000 and $US1.2million a year per laboratory, including salaries, if it is to runat a competitive level. A further major expense is the priceof various types of counters and analytical instruments;such resources will generally be shared between groups, but they come in the range of hundreds of thousands of dollars and have to be regularly upgraded or replaced. If a competitor can measure something new and different, or get the same result more quickly with a novel piece of equipment, a program will rapidly fall behind. Equipment generally comes under the heading of infrastructure costs and, as machines aren't particularly glamorous - unless they're so impressive physically (like a Jupiter rocket) that politicians can put them on display – they are often a goodtarget for philanthropists who want to help the medical research enterprise.

At least in laboratories in the United States, junior technologists are likely to be learning the science tradewhile earning some money as they apply for entry tograduate school or medical school. The other members ofany given research group will consist of PhD students and postdoctoral fellows (postdocs), with greater numbers ofpostdocs in the high-profile research universities and institutes. Individuals in both groups will have in mind the goalof becoming independent scientists in academia, thougha few may already be aiming for a job in a science-based industry setting. Most, if not all, of the postdocs will havecome to the laboratory after completing their PhD workelsewhere.

It's at the postdoctoral stage that many young people make their first international move. Depending on thesociety they come from, they may or may not be aiming togo back. For those from less well-resourced countries, thepostdoc transition is often 'the great escape'. It is an extraordinary but true fact that many societies, even some thatare quite wealthy, are led by politicians who provide such limited support for science that they effectively export theirnation's best and brightest. The universities and science-based industries of Western Europe and the United Stateshave been the great beneficiaries.

The best advice for those who go overseas for postdoctoral training and want to come back to their home turf is to learn different skills and approaches that will allow them to establish a new, independent area of activity on return. Still, though no nation should be complacent about losing top talent, it is important to recognize that there will always be a 'global churn' when it comes to the movement profiles of innovative scientists. Controlling the migrations of such people is a bit like herding cats, a rather useless exercise. It does nonetheless help to offer quality cat food (funding) and plenty of it if you want to attract the attention of a top cat.

The decision about where to continue the scientific apprenticeship begun as a graduate student can be the most important in any scientific career. Though it may look overwhelmingly attractive to go as a postdoc to the laboratory of the person who seems to be at the cutting edge of the subject, a lot of other, bright young people will have the same idea. Sometimes it can be hard to get your work noticed: one colleague I like and respect greatly for his scientific achievements told me he doesn't even bother to talk with postdocs who aren't generating interesting data. This is fine for highly competitive and aggressive young people, but it doesn't suit others who may ultimately turn out to be very good scientists. The best way for an intending postdoc to get the feel of a program is to visit and talk with the junior members of the laboratory, preferably over a coffee or a beer. It can often be a good experience to work with a younger PI who is still on the way up, runs a smaller operation, travels less and is able to give more personal attention. All leading PIs know that they will be only as effective as the young people who work with them. They are the ones who do the hands-on experiments, look first at the results and process the data sets that are the life-blood of experimental science. What comes out in the end analysis is the product of an intense and continuing dialogue between the members of the group. Different PIs operate in different ways, but most encourage open discussion and debate.

Classically, the others in the group may first see a new set of results and hear the possible interpretation at a weekly laboratory meeting that all are required to attend. They can then add their own ideas about what a particular finding may mean in the broader sense, or what could happen next. In a dynamic program all ideas are up for discussion, whether they come from the PI or the newest graduate student. Sometimes fresh, young minds that are not loaded down with what went before will see a particular set of data, or a possible opportunity, from a new and interesting perspective.

Misty Jenkins, a Koori scholar who traces part of her genetic heritage back to Australia's Indigenous people, is agraduate student in my Melbourne program. She is working on influenza virus-specific 'killer' T cells, the assassinsof the immune system which I discuss at greater lengthin chapter 4. She was recently at the Australian Society ofImmunology meeting in Adelaide when she chanced to talkwith another young scientist who is using digital imaging approaches to analyze visually how immune cells kill. Now she will get together with him to take a look at some of the processes that we have been studying, using an entirely different approach, one that nobody else in the laboratory, including me, had been thinking about. Will it tell us anything new? We don't know yet, but it sounds intriguing and that's often the way that something different and exciting gets off the ground.

The postdocs and graduate students in any good laboratory are generally driven by an intense sense of excitement and intellectual curiosity. Science at its best is, in the end, like a good detective story. It offers a chance to ask questions, search for clues, uncover what is hidden and come to a conclusion, or even better, a solution. The main word for the scientist at every level is 'interrogate' – and most Nobel Prizes go to the 'hard' scientists who interrogate nature itself. The classical interrogation technique of the scientist is the experiment and, as with any detection task, the first step is to ask the right question.

The key insight about the right question might come initially from reading or talking with theoreticians who think full-time but don't do experiments – rather like the paralyzed detective, Lincoln Ryme, in Jeffrey Deaver's crime novels, who is all intellect and no praxis. As the investigation progresses, more questions will be provoked by what is discovered, and they will drive successive experiments. Like any human activity that seeks to intrigue and inform, the whole task is concerned with putting together a good story. If the team is both lucky and skilled, the ultimate account will be novel and interesting. Often, though, despite a promising start, the conclusions can be mundane and boring, and many of the resulting research papers are at the level of 'not proven'. If the experiment does lead to a good result, it has to be confirmed before we can accept that it can indeed be believed. The experiment may be repeated exactly as before, or changes could be made that might fill in a few gaps in the story while still providing support for the initial analysis. Sometimes an experimental result can look just too good to be true, and a repeat study will bring us back to Earth.

What has generally made me very comfortable about the results I see from my research group is that the data sets are never too perfect. This approach works with a complex field like viral immunity, but it isn't appropriate, of course, for a mechanistic analysis like determining the sequence of a gene or a protein. The sequence has to be correct. The analysis is readily repeatable by anyone with the right expertise and equipment and there are real penalties in terms of the individual's reputation for being wrong.

However, if the results are informative and the study repeats, we might then go on to ask a further question, or may decide that it looks pretty good as it is. The next step is then to write the scientific paper and report the results for the scrutiny of our colleagues and competitors, our peers (the process termed 'peer review'). As Karl Popper, the influential philosopher of science, pointed out, only the written record is valid in science. No matter how honest we may be, memory is easily distorted. Besides, some of the key insights may not emerge until we look really closely at the research data and assemble the findings into a convincing story.

It is important to discuss ahead of time how any particular study will operate in terms of who pulls all the data together and does the initial write-up. That person will normally have her or his name as the first author on the eventual research paper, a point that needs agreement from everyone involved. Order of authorship is enormously important in the business of credit for biomedical scientists.

In biology, at least, the usual convention is that the first name on the manuscript is that of the junior scientist who has the greatest responsibility for, and involvement in, the particular project, while the PI is the last, or senior, author. Sometimes the technical work of the study divides equally between two young scientists, so the agreement is that they will alternate as first author on successive research reports. Running a successful research laboratory demands both time and attention. Because of my other commitments, I now work directly with experienced colleagues, and will often put my name in the middle rather than at the end of a list of authors. My program at the University of Melbourne is operated jointly with Steve Turner, an Australian who worked with me as a postdoc at St Jude, then returned to establish the laboratory and he is now an independent university faculty member.

I am sometimes asked why I continue to operate two such physically distant research efforts. The great strength of the St Jude program is the continued collaboration with the virologists Rob Webster and Richard Webby, which allows us to work with viruses that have been engineered to address unique questions concerning the influenza-specific immune response. Rob also runs one of the few bio-security laboratories where it is possible to do protection experiments with the extraordinarily lethal avian influenza viruses that are a looming threat to humanity (there is more on this in the next chapter). Melbourne, on the other hand, offers a sophisticated immunology community where we have developed a spectrum of effective collaborations with structural biologists and molecular geneticists interested in the regulation of immune effector mechanisms and the nature of T cell memory (see chapters 4 and 8). In fact, we exchange both reagents and personnel between the two locations. Cutting-edge science is an international activity that is driven, in part, by the principle of selective advantage. So, though the arrangement may perhaps seem cumbersome, it works, the science benefits and a few very talented young Australians and Americans gain in their level of international experience and exposure.

Early in my career I wrote pretty much every word of anything I ever published. Nowadays my starting point is often a draft manuscript from a young associate. As I agonize over and re-work the text, I am constantly checking back with questions like 'How exactly was this done?', 'Do we have a repeat experiment?', ‘What do you think of this result?', 'Could it mean that ...?', 'Do you remember who said ...?' We eventually end up with something that is mutually acceptable and, hopefully, understandable by others in the field. The next step will be to submit our manuscript of 1,000-2,000 words of carefully reasoned argument, plus diligently cited references to other studies, and illustrative figures and tables full of results. Sometimes we may go for a rapid publication format, but if we aren't in too much of a hurry, our latest 'baby' generally will go to the most prestigious scientific or professional journal that we think might accept it.

Sometimes we write longer, solicited reviews of our own work or of the field in general; these are usually under *5,000* words long and rarely more than 10,000. Most research journals appear monthly. This can also be the case for short review formats, though the longer accounts come out as annuals. Timely, specialist reviews are very important, as the magnitude of the scientific literature is such that only those intimately involved in a particular sub-field are likely to have either the time or the inclination to read the primary research reports.

A submitted paper will often bounce straight back with 'thanks, but no thanks' from the editors of one of the top journals, like the weeklies *Nature* or *Science* that are as much newspapers as research report formats. If the editors decide after a preliminary read that they might want to publish, the article will then be sent to two or three informed colleagues for anonymous peer review. They may have lethal criticisms that will ensure rejection or, quite commonly, they may suggest additional experiments that need to be done or arguments that should be made. Anonymous review can be open to abuse, but most behave responsibly as everyone lives by the same rules. In my experience, the famous aren't cut any slack in the peer review process, and indeed they shouldn't be. The integrity rests in the validity of the data and the intrinsic interest of the conclusions, not in the personality or prominence of a particular author.

Publication means credibility when it comes to securing research grants, jobs and promotions. Science is very competitive and there is always the possibility of being beaten to the post. Credit for a big discovery that can lead to a Nobel Prize requires the recipient to be first to publish the primary research data or the spectacular new idea, even though the report of the actual discovery can be very brief indeed. The 1953 paper on the DNA double helix by Jim Watson and Francis Crick that started the molecular biology revolution occupied fewer than two pages of *Nature.* The key findings and ideas that led to our 1996 Medicine Prize appeared in three research reports (reproduced here in the appendices) that took up fewer than four pages in the same journal, and in a four-page hypothesis article that appeared in *The Lancet.*

What experienced scientists do when it comes to the stage of writing-up is to start by laying out the experimental results in tables and figures, then develop a closely reasoned account of the data set that provides the basis of the story that is to be told. The account may well support the idea that stimulated the study in the first place, but it can equally be true that a novel conceptual thread emerges as a consequence of looking at the new evidence that has been generated. This is then reflected in a discussion of the results and in the summarizing abstract, which should convey the strongest points in an exciting way. The last step may well be the introduction, laying out why this particular study was done. At this point a research paper can be a little disingenuous: the introduction may reflect more what we might have thought if we had been really smart and knew what the results were going to be, rather than the ideas we had when we set out on the journey.

The 'firearm-barn wall' strategy has recently been formalized by the description 'discovery science'. Generally, this has been defined as 'science that is not limited by an hypothesis' – and the processes will usually lead to a mass of new questions which will then need to be followed up by the usual, hypothesis-driven research strategies. Discovery science is coming into its own in biology, and particularly in the new science of genomics. A century after the first Nobel Prize, the efforts of people like Craig Venter, Francis Collins and others resulted in the first published sequence of the human genome, the complete DNA code that ultimately determines the nature of our physical beings. The mouse genome soon followed. There are now published genomes of many life forms, ranging from the malaria parasite to the fruit fly to the chimpanzee, the chimpanzee's being about 98 per cent identical to ours. Knowing the genome can perhaps be likened to having a telephone directory that lacks many of the names and addresses. The massive task ahead of us is to associate the numbers with names, then work out what these individuals do and how they fit together.

The cultures within 'small science' laboratories are as different as the personalities and characters of the key players. Some PIs are quite controlling and will want to supervise the planning of every experiment very closely. They may also require each young scientist to work on avery different project and report only to them. Others aremore open and hands-off. My personal style is to encourage people to collaborate. Viral immunity is particularly complex and any one experiment can require the 'person-in-power' to look simultaneouslyat a number of diverse variables measured by different techniques. Though each young scientist will do individualsmall, often preliminary, experiments that probe their ownspecific ideas and refine their technical abilities, the capabilities they develop also contribute to larger investigations.A big experiment may typically start at seven in the morning and, because there are a number of time-consumingsteps that require incubations, staining and so forth, theday's work may not be completed until midnight. Peoplemake mistakes when they are exhausted, so groups oftenarrange to operate in different shifts.

The lead player in any particular experiment may be in a support role for another investigation. My job as a PI might be to bring the coffee and doughnuts, and to discussany last-minute changes in the experimental protocol that result from some unforeseen difficulty. Though I servedmy apprenticeship and worked for years at the bench, any 22-year-old technician will do hands-on laboratory workmuch more quickly and efficiently than I can.

The initial success that every scientist must achieve is to make the transition from postdoc status to establishing their own independent laboratory. Many institutions,particularly in Europe, will try to retain extraordinarilytalented people who emerge from within strong researchprograms. However, the usual situation in the United Statesis that people move on at this stage of their career. There isa constant search for bright young candidates – and talent is what matters. Some young scientists become fixated ongoing only to a high-prestige institution. My approach inthis has always been a bit idiosyncratic in that I have been happiest in situations that had a strong collegial feel, whereI also had the sense that I would be able to concentrateon my research. Others prefer to work in high-status, very competitive environments.

With e-mail, and with FedEx to transfer samples for analysis, it is easy to have strong collaborations at a distance, at least within the United States or Europe. As young scientists come to the end of their post- doctoral training, some decide that though they might wish to continue in research, they would be more comfortable in an industry setting. The latter is likely to be better paid and, though it was almost unknown twenty years ago, it isn't uncommon now for biomedical PhD candidates to start out with an industry career in mind. Joint business-science or economics-science degree courses are increasingly popular as the realization dawns that high technology will drive a great deal of future industrial activity.

So you've got to be multi-skilled: the work of theexperimental scientist covers the spectrum from student to public speaker, from funding generator to administratorof all aspects of very substantial programs. Then there is service on various national and international committees,though it's important for anyone who is working creativelyto avoid being consumed by committee activities.

Day to day, the scientific life is exciting and fulfilling. Big experiments often benefit from the involvement of people who like to start and finish at different times of the day. Some senior investigators may come in at midday and work late into the night. The international cooperation and competition that are an essential part of science also mean frequent communication with those pursuing similar research questions in other countries.

Smart people who are working on similar problems will often come to the same conclusion. I've sometimes decided not to take a particular course when I learned from a brief chat or a formal talk that what I had been thinking about was already well underway elsewhere. Another great clarifying experience, and increasingly a feature of the scientific meeting circuit, is seeing some of the extraordinary presentations made by people like Mark Davis, fromStanford, or Ulrich von Andrian, from Harvard, who use contemporary imaging approaches to provide visual insights into, for example, the ways that the cells involved in immune responses behave (see chapter 4). If one picture is worth a thousand words, one short movie can be worth a thousand pictures in a research journal. Such material is increasingly available from the Web, but the first encounter often comesfrom the totally unexpected experience of seeing a sixty- second clip in a scientific talk.

At the beginning of a scientific career, of course, the money is not high, but stipends for bright young PhD students are generally paid at a level that is sufficient to maintain life. Support may come from a national scheme, from training grants to substantial universities or from the budget of a research grant to a senior scientist. Graduate students often supplement their income by undergraduate teaching or tutoring. Postdoctoral fellows are paid considerably more. After they're established, most scientists live reasonably well, and job security is generally good for those who achieve long-term university positions.

Maintaining both tenure and a high salary in a top research university will inevitably mean being competitive in the research grant scene, though some leave the laboratory and move on into university administration. Scientists are increasingly prominent as university presidents or vice-chancellors, usually the best-paid jobs in any academic setting.
A few scientists become very wealthy. All academic institutions have mechanisms that ensure that anyone who makes a commercially important discovery will at least share in the resulting profits. Some launch their own companies. Even if they didn't achieve fame and fortune, most scientists in the latter part of the twentieth century benefited from the first mass 'culture of creativity' in the history of humanity, as governments facilitated and funded discovery and the generation of knowledge. The success of the enterprise is, perhaps, reflected in the fact that elements in the entrepreneurial-business culture now focus heavily on biology and biotechnology. Though it was not the case for researchers of my generation, who have had to learn such matters late in life, young scientists are increasingly well educated on issues relating to intellectual property rights, patents and so forth. In turn, young lawyers and business trainees are being drawn more into science-related areas. There were in the past, as described in Dava Sobel's *Longitude,* occasionally nationally resourced competitions to seek solutions for important national problems, but government-funded research on a broad scale is a recent phenomenon.

Once the political process triesto direct research, disaster inevitably results. Scientists at the top are no longer funded, and the politicians end up paying third-rate 'cannon-builders to put a man on Mars'. It takes a sophisticated political process to deal with this reality. The US style of government, where the division of powers between the executive (President and Cabinet) and the legislative branch (House and Senate) makes for a quite open political dialogue, may be the ideal form of government for promoting innovation.

The populations of Nobel laureates and leading research academics overlap, of course: the difference is that theNobel Prizes go to scientists who have had the good luckto hit on a stellar, breakthrough discovery, or the intellect tomake some immensely powerful theoretical contribution.Most will be long-term achievers, but this is not always thecase. Nobel Prizes aren't won by simply accumulating scientific brownie points. The prospect of winning prizes isn'twhy people go into science and stay there. When they reach*65,* many successful scientists are still so excited by what they do that they choose not to quit. There are plenty intheir seventies who are still seriously committed to researchand the promotion of science-while others walk awayfrom the job like people elsewhere, and find new interests.Fred Sanger, who won two Nobel Prizes, quit at *65* to growroses and sail his yacht. He'd done what he came to do.

Scientists do make mistakes and the less scrupulous can and do lie when it comes to the business of allocating credit, particularly for the source of an idea. However, the actual scientific data cannot be faked. Apart from matter for criminal investigation if the research is by federal research grants, for instance, developing their set of experiments or theoretical interpretation basis of wrong information will inevitably lead to a long-term scientific investigation can be thought ever-branching tree. The worst scenario is when evidence emerges that research data has been manipulated, or even invented. In the United States this can lead ultimately to an FBI investigation, but the truth must out no matter how painful consequences.

Sometimes, however, there is indeed clear and irrefutable evidence of deception. A famous instance is the case of the painted mice. The story is told in Joseph Hixson's *A Patchwork Mouse* (Anchor Press) and by Sir Peter Medawar in a chapter entitled 'The Strange Case of the Spotted Mouse' in his book *The Threat and the Glory* (HarperCollins). A young medical scientist generated some exciting evidence of long-term survival when he first cultured black mouse skin tissue in a particular way, then grafted it across a histocompatibility barrier onto a white mouse. Normally, of course, the 'host' white mouse would have rapidly rejected the 'donor' black skin (see chapter 4). After a week or two, only an all-but-undetectable scar should remain. As others were to show later, his first, promising results may well have been right. The problem was that he could not repeat them and eventually faked the result in a quite crude way by painting a 'patch' on a white mouse with a black marker pen. Not surprisingly, he was soon found out. Many cases of fraud show this same profile of a 'good' early result, followed by a failure to repeat, although there are also a few cases where there was deliberate deception from the outset. Sociopaths are found in all walks of life, and science is no exception.

Science fraud generally occurs in high-profile institutions, often in the medical research area where expectations can sometimes be raised way beyond the scope of the available evidence. There have been prominent instances in both the United States and Europe, and I know of one such story in Australia. I was peripherally involved in this case because, while I was living and working in Philadelphia, I was asked to review the research report for publication as a letter to *Nature.* I knew the PI to be a first-class scientist,and both he and I were fooled by the exciting 'data' that hisyoung colleague had generated. The article was published,though the deception was soon discovered and the claimswere immediately withdrawn.

Of course, most mistakes in science don't come from deliberate fraud. This is one reason we repeat experiments.An interpretation can be wrong because the technology wasimperfect and unknown variables were at play. The mistakewill become apparent when new approaches or instruments become available. When it is recognized that an idea basedon a flawed finding has gained some credibility in a field, it is essential that the originator make the effort to pointout very publicly why and where the hypothesis was wrong.This is as much a matter of self-protection as anything else.If the initial protagonist fails to do this, there is an absolute certainty that someone else will.

Joint programs can be an enormously effective way to do science. The Nobel Prizes for Medicine to Mike Bishop and Harold Varmus in 1989 'for their discovery of the cellular origin of retroviral oncogenes', the genetic elements that contribute to the development of cancer, and to Joe Goldstein and Michael Brown in 1985 for their work on cholesterol metabolism, reflect efforts of this type. Though Rolf Zinkernagel and I shared the 1996 award, we worked together for only about two-and-a-half years at the beginning of our respective careers in immunology.

Programs led jointly by a wife and husband can also work well with, not uncommonly, the woman scientist taking the more public profile and the man staying closer to the laboratory bench. The most famous Nobel couple is, of course, the Paris team of Pierre Curie and Marie Sklodowska Curie, who shared the 1903 Physics Prize for radioactivity with Henri Becquerel. Their daughter, Irene Joliot Curie was, in turn, awarded the 1935 Chemistry Prize with her husband, Frederic Joliot, for the discovery of the radioisotopes that remain so important in the research laboratory, diagnostic medicine and therapeutics. The expatriate Czech scientists Carl and Gerti Cory shared half the 1947 Medicine award for their discoveries concerning energy metabolism, while working at Washington University of St Louis, in Missouri.

Perhaps the best known husband and wife team in my own field of immunology are Philippa (Pippa) Marrack and John Kappler; they are both HHMI investigators (see chapter 6) working at the National Jewish Medical and Research Center in Denver, Colorado. Pippa is English and Cambridge-educated, and John is American.

Early Influences

What sort of family experience might be expected to form a future Nobel Prize winner? The pattern is that there's no pattern. There are some Nobel families. Among these the father, mother, daughter combination of Pierre, Marie and Irene Curie, the father and son team of William and Lawrence Bragg was awarded the 1915 Physics Prize, and the chemist and neuroscientist Ulf von Euler (Medicine, 1970) followed his father, the enzyme chemist Hans von Euler-Chelpin (Chemistry, 1929). Fritz Zernik (Physics 1953), who invented the phase contrast microscope which I used in my early research, was the uncle of Gerardus 't Hooft (Physics 1999) .Other Nobel laureates in science were also raised in academic families, and some came from prosperous business backgrounds. Many grew up in very modest circumstances and were the first in their family to attend a university, or even to complete high school. Science is, after all, a common 'up and out' path for bright kids who come from a social context where there is little understanding of the realities of power and privilege. The Nobel laureates in science also went to all sorts of schools. Some spent their childhood on farms where the quality of the available formal education was limited. A few were home-schooled. Because most are from the United States or Europe, the majority attended taxpayer-funded primary and secondary schools, or Catholic schools of equivalent wealth and status.

It makes sense that a high-quality selective schooling, whether the selection is based on the merit of the child or the economic circumstances of the parents, does foster talent, but it is also apparent from the record (www. Nobelprizes.org) that this is not an essential prerequisite for later academic stardom. Being accepted at a top institution is likely to be a

plus, but it isn't essential. While 40% of the British laureates were at Oxford and Cambridge, another 40% were at Birmingham, Manchester or Sheffield.
The United States is unique because, in addition to great state universities like UCLA, Berkeley, the University of Washington, the University of Michigan and the University of North Carolina, it has a number of first-class private tertiary institutions: Harvard, Yale, Cornell and University of Pennsylvania to equivalent campuses in middle America and to the small liberal arts colleges.

Scientists have to learn an enormous body of highly specialized knowledge before they can pursue their craft. The university and college systems I've mentioned above provide the training for the first step in a science career, which is generally the Bachelor of Science (BSc or BS) degree achieved after four years of undergraduate study. The next step is to gain the 'science ticket', the Doctor of Philosophy (PhD or D Phil) degree that requires the candidate to do research under the broad supervision of an established scientist. Again, this will generally go on in a major university, though there are also 'partnering' arrangements that allow students to work in top research institutes like the laboratories of the Institut Pasteur, the Max Planck Society, or places like the Walter and Eliza Hall for Medical Research, Melbourne, and St Jude Children's Research Hospital.

One difference between the United States and the rest of the world is that the undergraduate experience is dedicated to the idea of providing a liberal education, which means that those working towards a BSc degree are also required to take English, a foreign language, history and so forth.
Not every future Nobel laureate followed a typical academic path, and some didn't even complete a research PhD. This is most common for medical graduates, where the MD plus a couple of years in a first-class laboratory is often enough to set people up for a stellar research career. Of the medical Nobel laureates reviewed in *my* twenty-year survey, 60 per cent had a PhD alone, 30 per cent an MD alone, and the remainder had both degrees. Of the US laureates, some 40 percent list only an MD.

A few of the physical scientists, particularly those with an engineering background who went straight into industry, did not bother with any form of doctoral degree, though all will have been awarded honorary doctorates by universities wishing to hear from them at undergraduate graduation ceremonies. As with any human activity, there are exceptions that prove the rule. It generally makes sense for the trainee scientist to work in the best available places with the smartest people. There are no absolute standards that determine where, how and by whom creative science is done.

CHAPTER 5: Personal Discoveries and New Commitments

The practice of science is still high on the list of what drives me, and I am as excited by intriguing new data as are my young colleagues who do the experiments and generate the results. I remain 'hooked' on discovery. At some stage, however, I will quit laboratory science and, depending howwell my brain is functioning then, devote my remaining time to either staring at the waves or trying to deal intellectually with the 'bigger picture'. This would be an easierdecision if I felt that I did not still have some useful role toplay in research teams working on AIDS and influenza, both of which are pressing human problems. Still, I have also long held the view that there is a point where senior scientists should metaphorically hang up their pipettes and, like the emperor Cincinnatus, who cleaned up theRoman state and then quit, rusticate themselves. Nobody isindispensable, and I regularly ask my colleagues to let me know when it is becoming obvious that I have passed my use-by date. Senior scientists (like politicians) sometimes go on too long and lose their sense of perspective: age can play bad tricks on what have been incisive minds.

Although I no longer head the department of immunology at St Jude Children's Research Hospital in Memphis, I still maintain a small, but active, laboratory there and enjoy the many contrasts with my other, and equally enjoyable, research life at the University of Melbourne. The University of Melbourne is a highquality research university, comparable to many similar institutions in the northern hemisphere and several in otherparts of Australia. St Jude, on the other hand, is unique.This private pediatric research hospital fosters top quality research in the clinical and laboratory sciences. Desperatelysick children are accepted for treatment from every state ofthe United States, and there have been many patients from other countries, including Russia and a number of MiddleEastern and South American nations.

All children are treated free at St Jude whether or not they have insurance. St Jude Hospital not only provides free treatment for its young patients, but also travel and accommodation expenses for accompanying family members, counseling and psychological support for siblings, and so forth. All this costs a great deal of money. The hospital has a truly extraordinary fund-raising organization that, in the financialyear 2004, for instance, raised more that $US350 million inpublic subscriptions. Being awarded the Nobel gave me theopportunity to help with this by appearing on televisionand in other publicity formats, speaking at lunches and dinners, talking to potential donors. Needless to say, I embraced this with total enthusiasm and will continue with it as long as Ican.

The second commitment that claimed me was to do with the world of animal health and veterinary medicine. Shortly after the announcement of my award, Professor Charles Pilet from the venerable French School of Veterinary Medicine at Alfort, near Paris, contacted me to say that he thought I was the first person with a veterinary qualification to win a Nobel Prize. He proved to be right. Consequently, I've spoken at national and international veterinary meetings, and have also given commencement (graduation) addresses at a number of veterinary colleges. The student body is very different from my day. The sometimes rough-and-ready male-dominated classes have given way to a predominantly female and much more stylish and sophisticated, cohort.

The Grameen Bank (founded by Muhammad Yunus – who is its CEO – in Bangladesh) has shown that one very effective way to alleviate poverty is to make micro-loans based on trust and with no collateral. It has lent more than $US2 billion to 2.3 million people, many of whom are very poor women. What better evidence can there be that the best way to change things for the better is to help people to help themselves? (It would be an interesting experience if this group of ambassadors ever actually got together. This doesn't happen, but each individual's role is to help alleviate the linked problems of starvation, extreme poverty and debilitating infectious dis- eases. I regard writing this book as part of that ambassadorial function though, of course, real ambassadors who answer to their political masters back in their own country often have to be much more circumspect in what they say and do.)

The experiences of my time as Australian of the Year, together with my subsequent exposure to the world of public discourse, have influenced both my thought and my behavior. Research scientists like me live much of our lives in an evidence-based world. We operate by targeting a limited question or set of questions, design experiments to test them or, in a formal sense, to disprove a 'null hypothesis' that there is no difference between our different treatment groups. This may sound a bit odd, but we often don't reach any final proof. We live constantly with uncertainty.

Scientists are not so obtuse that they fail to understand that they can't approach love, beauty or joy in quite the same way they would tackle a laboratory experiment. Although successful scientists tend to be reasonably personable beings who are capable of living normally in society, raising families and so forth, they do often see complex issues through the prism of evidence-based reality. In general, basic scientists are forward-looking, think in terms of underlying moral and ethical principles, tend to be minimally attracted by political cant and react negatively to down-market political and religious populists. Because their world is dominated by ideas that emphasize discovery, development and improvement, they are singularly unimpressed by those who look backwards and espouse reactionary and divisive views. Conversations at, say, a cocktail party where a lot of scientists are together generally provide a robust reflection of such attitudes. In addition, unlike politicians, scientists are allowed to hold two opposing points of view simultaneously in their heads. It's not uncommon to have lunch with a colleague who will argue some deep social issue from one point of view one day and from another the next. Such people are used to rolling complex ideas around in their heads and to looking at them from all possible angles. Those medical scientists who've trained as physicians and did internships, residencies and the like tend to be more balanced and circumspect in their public discourse because they are much more in touch with how the rest of humanity sees things.

It can be quite counter-productive to assume that a clear, evidenced-based view of the world is generally accepted, if the aim is to get a point across to people who have different life experiences and points of view. The first lesson I had to learn is that, for the scientist at least, interacting with and through the media is fundamentally about communication. It's fine to be entertaining and controversial, but the exercise is a failure if you don't get your point across in a way that intrigues or, at least, causes people to question their assumptions.

Thinking in this way has, in turn, induced me to go back and look at many of my own long-held beliefs and prejudices, which is why, for instance, I have a chapter in this book on the interactions between science and religion. In public communications, it's worth bearing in mind the message implicit in the medical Hippocratic oath: 'First, do no harm'. Nothing useful is ever achieved by humiliating people. You offend the poor individual who is crushed and alienate those who witness the performance. It's always better to lose an occasional battle to win a worthy war.

Then there is the question of interaction with politicians. Politicians legitimately look to scientists for specialist advice. According to Winston Churchill, 'experts should be always on tap and never on top'. The 'never' probably refers to that scientific adherence to evidence-based reality. Would Britain have stood as it did in World War II if Churchill had given citizens the evidence, rather than providing the sublime political rhetoric of those great speeches: 'We shall defend our island whatever the cost may be ... We shall never surrender ...'? At times like this, it is an element of fantasy, the leadership of the visionary that's needed.

Politicians have both a public and a private face, depending on their personalities and the way they project their ideas and values. It is death for an Australian politician, for example, to come across as a high-powered intellectual. The former Australian Prime Minister Bob Hawke was a first class intellect and had been a Rhodes Scholar, but he hid behind a studied 'folksiness' and obsession with sport in every shape and form. As Australian argot had it, he was 'ocker Bob'. That other Rhodes Scholar, Bill Clinton, was so quick and confident that this was the political act that was expected of him. George W. Bush, on the other hand, would be in real trouble with his constituency if he suddenly started to come across as a typical product of his Yale, then Harvard, education.

Since the Nobel Prize I've had the opportunity to speak informally with a number of politicians. Whatever their public persona, many are clear thinking, committed people, who often bring that clarity of mind that is associated with a good legal training to the issue at hand. They are generally open to hearing about different ideas and ask good questions, though they won't necessarily accept what you are saying. For instance, my perception is that though Australia is yet to sign the Kyoto protocol on carbon emissions, there is a great deal of interest and concern on the part of the elected representatives themselves with the issue of global warming. The broader Australian public is also, I think, aware of the importance of this issue and of the need for environ-mental protection generally. There are, of course, communities like the timber workers in Tasmania, who feel threatened by measures to promote conservation, but the overall view is that clean air and, say, the preservation of old-growth forests are good things. The level of basic education in Australia is reasonably high, but the culture is such that it is important for anyone who wants to be heard on complex issues to speak with a voice inviting democratic dialogue rather than from the perspective of the

Academyor some kind of Mount Olympus. My life-long experience, from school and university vacation jobs in stores, drivingvans, clearing drains, 'pulling' the rusty pipes that carrywater from windmills, to being on farms and working as aveterinarian, to dealing with everyone from the lab cleanersand glassware-washers to directors of research institutes, tospeaking out as a Nobel laureate on talk-back radio and inpublic lectures, convinces me that the majority of peopleare curious and that each of us forms our own particularworldview based on our education and life history.

Australians will, in the main, resist being told what to think by anyone called an expert, but they will take note ofthoughtfully presented evidence-based opinion. My jobthrough this narrative is to convey my personal under-standing of science and how it works in a way that is, Ihope, useful and informative. I believe it is important forthe population in general, and for politicians and theiradvisers in particular, to approach issues like global warming with some understanding of the science informing thebroad concerns that are being raised. In the end, pussyfooting around reality cannot achieve any useful result. Reality cannot be rationalized or argued away and deception can ultimately be fatal.

The moral and intellectual satisfaction that might come from being an outspoken critic of this or that policy isn't worth much if it doesn't actually achieve anything. Scientists expect a prominent colleague to mediate with politicians, particularly in terms of fostering greater under- standing of the importance of science and technology that will lead ultimately to increased levels of funding for them. Here, I think, the Nobel Prize and my participation on the public stage did help to achieve a doubling of both the medical (NHMRC) and the general science (ARC) re- search budgets in Australia, though many other individuals, organizations and two politically effective ministers of the time, namely Michael Wooldridge in Health and Brendan Nelson in Science/Education, were the prime movers. Providing the individual is articulate, honest and interesting, the Nobel Prize does confer a long-term, public voice.

Taking a very critical public posture is often the rule rather than the exception for those who win Nobel Literature or Peace Prizes. The Peace laureates will almost inevitably be public figures who may or may not be popular with their own and other governments. When you think about it, only a wealthy philanthropist can function as a private humanitarian. Such people can make an enormous contribution, but those who choose to remain anonymous clearly believe that virtue is its own reward. Individuals like the international anti-landmines campaigner Jody Williams (Peace, 1997) or the anti-nuclear advocate Linus Pauling (Peace, 1962) were certainly not putting out a message that was popular with the military/industrial complex (as President Eisenhower had it) of their day. The advocate for women's and children's rights, lawyer Shirin Ebadi (Peace, 2003), seems to be under constant pressure in Iran.

The Literature laureates are expected to be direct in their comments about social and political issues, and it's generally accepted that they can be a bit grumpy at times. Those who do not write in English may be already prominent local figures before the Nobel, while people like V. S. Naipaul (2001) and Saul Bellow (1976) were already well known on the international scene. Some who write inanother language, like Gunther Grass (1999), will havebeen widely read in translation. Great literature is characterized by a critical voice that gives new insights into who we are and how we function in the world. Like science at its best, it explores basic truths. I doubt that any politicianwould ever expect to read a positive statement about him – or herself from a major literary figure, and the popular culture in general may also come in for a heavy caning. Other literature Laureates, like the Irish poet Seamus Heaney(1995), speak in a sympathetic voice that goes to the heartof the human experience and the society that forms them,and are loved rather than treated with a mixture of respectand apprehension.

I have a strong personal sense of being an intellectual child of the European Enlightenment and the age of reason, holding values that increasingly need to be defended in the contemporary world. It's ironic that the UnitedStates, with its extraordinary Declaration of Independence, Constitution and Bill of Rights so grounded in the enlightenment ideas embraced by Thomas Jefferson, James Madison and their colleagues, should be the place where this attack seems most dangerous. The expectation that a Nobel Prize winner can speak with authority on almost any broad issue is, of course, absurd. There are pressures to do this as contemporary Western societies suffer, in general, from a lack of public intellectuals. Of course, the media will derive as much satisfaction from tearing down the pretensions of such people as they will from the initial dissemination of their viewpoints. A public voice should always be used judiciously.

Committing words to paper provides a discipline that forces me to look more critically at my underlying assumptions. In the following chapters I discuss some of the issuesthat have come to preoccupy me. As a scientist, I've seen too many 'intuitively obvious' conclusions overturned bynew evidence to be able to accept even the suggestion of infallibility in anything. Scientists aren't gods or even popes, though a few deluded souls may see themselves as cardinals. It doesn't hurt to retain a sense of perspectiveand your own absurdity on those inevitable occasions when, as the first President Bush so concisely summarizedit, you step in deep doo-doo. It helps to have a sense of humor and, when you're talking the talk and walking thewalk, to look down as well as up.

CHAPTER 6: The Next American Century?

The types of science that are recognized by Nobel Prizes deal with universals that recognize no national or international boundaries. Both the contributions to human knowledge and the resulting technologies are potentially available to all. But the practice of science, its funding and the regard in which it is held differs from one society to another. These differences can influence the careers of individuals and the fate of nations, and can also have profound effects on humanity as a whole, and the survival of our species.

Collectively, we have made huge progress: the population of the world has burgeoned and more of us live goodquality lives. In some crucial aspects, however, the way science is organized now reflects the old world. Modernresearch scientists are a bit like the masons of mediaevalEurope, who moved and worked among cities and states,leaving as their legacies the great cathedrals we marvel at today. Energetic, imaginative people have always migratedto where major resources are being used to create something magnificent, no matter what the tools and materials are – stone, glass, integrated circuitry or molecular genetics. Creative scientists are drawn to well-resourced, supportive centers and to enthusiastic colleagues. In this new century, though, any nation that wants to be economically strong and independent needs to attract and retain such people. The emphasis has to be on openness, education, innovationand knowledge. For those aiming to develop a culture of discovery, novel solutions – and incidentally, winning NobelPrizes in the sciences – the central question is: How is itbest to do this?

For the past fifty years, the United States has been a model of this kind of culture – the entire twentieth century was, in fact, widely regarded as the American century.Relatively open immigration, the broad values of hardwork and individual commitment, along with innovationand the aggressive commercialization of novel technologies have all delivered enormous economic success and power. Underpinning that has been the development of a highquality university sector and the extremely generous federalfunding of basic research. The effect is obvious in the distribution of Nobel awards for the United States, Germany, Britain and France. Less than 30 per cent of the NobelPrizes for science went to US residents in the first half ofthe century, compared with more than 70 per cent in thesecond half. The comparable rankings for Germany, Britainand France were 30 and 10, 15and 11, and 9 and 3. Therelative levels of research support have obviously been a significant factor, though the effects of occupation and theNazi era also played a major part in continental Europe.

We may ask whether the twenty-first century will also be the American century. Other nations have learned fromthe US experience and are ploughing money into researchand building their science base. As standards of living improve globally with the international dissemination ofmanufacturing activities, the lifeblood of the most prosperous economies will be the insight and inventiveness of imaginative, talented people. Even countries like the United States, justly proud of its profile as a center of knowledge generation and innovation, must pay attention to this. Human capital is the most important capital. It's all very well to be bankers and accountants to the world, but that was once the role of city-states like Venice and Florence, which now figure essentially as archives of mediaeval art and tourist centers. Lose the drivers of discovery and technology development and the financial sectors are likely to follow.

There are now many highly competitive research operations in both the physical and biological sciences throughout Europe, as evidenced by the Nobel Prizes for science over the past twenty years, but two factors have been working against European science and they both involve keeping good people. One is that it can still be more difficult than in the United States for a beginning research investigator to establish a fully independent career.

The other problem is that some European countries have excessive regulation and a cultural hostility to the types of genetic engineering approaches that are at the heart of modern biotechnology and biomedical research.

Then there is Asia and the Pacific region. Every Asian country I've visited over the past ten years is emphasizing the central role of science and technology for the future. Singapore has built the Biopolis, a magnificently resourced institute for molecular sciences. The president of the Taiwan Academy of Sciences, Yuan Tseh Lee, who won the Nobel Chemistry Prize in 1986, has played a prominent role in the spectacular expansion of Taiwan's research and technology base. In general, Asian politicians see the capacity of their nationals to win Nobel Prizes in the sciences as an indication they are succeeding in establishing a strong scientific culture. Japan takes pride in the fact that twelve Japanese have been awarded Nobel Prizes, but is ecstatic because three who actually work and live in Japan have been recognized over the past five years. These people are treated as celebrities (which must be tiring for the two who are now in their eighth decade).

Asian countries, however, continue to lose many of their best and brightest to the West. Over the sixteen years or so I've been associated with St Jude Children's Research Hospital in Memphis, we've seen the huge increase in numbers of young graduate students and post-doctoral fellows from Asian countries, particularly China and Korea. Many want to stay, but it looks as if the recruitment process has slowed since more stringent travel and visa restrictions were introduced following the terrorist attacks of September 11, 2001. This may adjust naturally, but if it doesn't, the United States could find it difficult to maintain its leadership of the sciences in a competitive global scene. Bright young Asians may go elsewhere.

Australia has also benefited from the same migration of Asian talent, though on a much smaller scale. The process began somewhat earlier because of the Colombo Plan, which, like the Marshall Plan in Europe, was designed to help build modern economies in the Southeast Asia-Pacific region in the post-war period. Australia makes it relatively easy for high performers to stay in the country, and the face of academia is increasingly less European. The country, however, has its own brain drain, with almost 1 million of its 20 million or so people now living in Europe, the United States and other places. Yet by far the most substantial research and academic culture in the South-East Asia region is still to be found in Australia where, since white settlement in 1788, exploration and development have proceeded in step with the scientific revolution in the northern hemisphere. Most early Australian scientists concentrated on the unique flora, fauna and landscape, a focus that continues with initiatives like sequencing the Tamar wallaby genome and the research that seeks to conserve the Great Barrier Reef. Since political federation in 1901, the nation has built strong universities and high-profile science in a number of areas, including agriculture and mining, radio and optical astronomy, medical research and molecular biology.

The PhD research degree was not offered by any Australian university until 1950 when, partly as a consequence of advice given by the Oxford-based Australian scientist Howard

Florey who won the 1945 Medicine Prize for bringing penicillin to the world, the federal government set up the Australian National University in Canberra. The ANU was lavishly funded for its time, andcomprised a number of separate Research Schools dedicated to training PhD students and to pursuing research atan internationally competitive level. Rolf Zinkernagel and I did our Nobel Prize-winning work at the John CurtinSchool of Medical Research, as did the neurophysiologist Sir John Eccles (Medicine, 1963).

Money is, of course, central to the development of a dynamic research culture. Nations serious about R&D aim to boost spending to at least 2.5 per cent of gross domestic product. When it comes to translating the benefits of science for human well-being, the model for the future rests in tacit, not necessarily formal, partnerships between government and the private sector. Again, the United States is the prime contemporary example: discoveries made in university laboratories or research institutes are translated quickly to the private sector. This can happen when the scientists themselves initiate the development of a new biotechnology start-up, or when BigPharma becomes immediately involved in developing a novel discovery to the point where it may emerge as a possible therapeutic. This is exactly how the first AIDS drugs came about.

How well this works in other nations depends on two things: the level of government funding for basic science and the sophistication of investors and the business sector. The United States provides massive federal support for biomedical research in particular. Americans focus very much on the stock market when they think in terms of wealth generation and they are accustomed to the idea that there may be some risk involved. There is a whole sub- culture of venture capitalists and technology analysts that is totally absent from simpler societies. Well-motivated individuals who have made large amounts of money are happy with the thought of supporting high-risk start-ups as 'angel investors'.

Australia's own internal market is small, but we've already seen one of the few major science-oriented companies, the Commonwealth Serum Laboratories (CSL), establish a substantial presence in the northern hemisphere. Increasingly, both federal and state governments in Australia have recognized that the lack of innovative privatesector involvement is dangerous, and have tried to do something about it. The point is nevertheless that while enlightened politicians and bureaucrats can put in place the necessary tax and investment policy reforms that promote investment and innovation, governments are by their nature unsuited to driving such activities. Dollars always help, but when those in the public sector try to initiate and direct commercial development the result is often a great deal of hype and little real achievement. Bureaucracies can facilitate, but they must also understand how to get out of the way. Unlike politics, industry has to deliver a real, not a notional, product. The bottom line is a continuing income stream, not votes on one day every three or four years.

Contributions from the public and private sectors across several countries have come together for great human benefit in the evolving story of the human papillomavirus (HPV) vaccine. A number of first class scientists, including Harald Zur Hausen at the German National Cancer

Institute in Heidelberg, Margaret Stanley at Cambridge University and many others have progressively made the case that some variants of HPV cause cervical cancer in women. The idea of developing a vaccine against HPV was taken up in the early 1990s by Ian Fraser, a Scots-trained medical doctor who learned immunology while working at the WEHI, then moved to the Princess Alexandra Hospital and the University of Queensland in Brisbane.

The grant reviewers are usually established, specialized, mid-career researchers and scholars who give a month or more each year to study section service over four to eight years. This prevents any tendency for the funds to be controlled by a few powerful senior people. The US National Science Foundation (NSF) that supports research in physics, chemistry, mathematics and linguistics, among other things, operates in a similar way. In both cases, I doubt that any federal money is distributed on a better-evaluated or more ethical basis. The processes that decide on the 'big ticket' items, such as optical and space telescopes, however, are inevitably more political.

The net result of the peer-reviewed 'small science' mechanisms used by the NIH and the NSF is that the best and brightest young US scientists become completely independent early in their careers, and can rapidly build research groups limited only by their capacity to do innovative science. It isn't just the individuals who win: each grant comes with an amount for overhead expenses which goes directly to the host institution. With a typical overhead rate of 40 per cent, this means $400,000 for the university administration when an investigator receives a grant of $1 million. Not surprisingly, university deans and presidents love the competitive medical scientists who, in turn, enjoy a very active job market and relatively good incomes, as much of the salary costs are paid through the research grants.

Working in the United States, I had the sense of being a marketable commodity. Anyone seen as a potential Nobel Prize winner is hot property. As in all countries, the universities vary enormously in standards. Those at the top of the pile retain their position by attracting very talented people who, incidentally, are likely to generate the most research dollars. The US system is very effective in bringing forward Nobel laureates, though the model can at times seem too goal-driven and 'busy'.

Though the university cultures are somewhat different, research in Britain and Australia has tended to operate along the lines of the US peer-review model. The total dollar amounts allocated to discovery science per head of population are smaller, and the lower indirect cost rates may not be tied so directly to the individual scientist's performance. The result is that the interaction between scientists and administrators assumes a different and more stable dynamic in the countries of the old British Commonwealth. People often do remarkably well with less funding than they would have had in a comparable US institution. Other countries, particularly Japan and Germany, provide relatively good levels of science funding, but have suffered from a traditional institutional bias towards a much more hierarchical – and sometimes stultifying – university structure. Fairly recently, at least, a number of young Japanese and German scientists have first established their research careers in the United States and then returned at senior level to major positions at home. Leading Japanese and German academics are aware that many of them aren't comfortable with the old system after their experience in the States and are making efforts to change their university systems.

Part of the problem is that there has been a greater tendency in some countries to favor core-funded researchoperations. In a core-funded operation, the dollars are given to the institution and are then distributed by an all- powerful director who parcels out the resources to the individual research groups. The core-funding practice is pretty much restricted to independent research institutes. Unlike the situation in a teaching university where there are other jobs for staff whose interests have changed, there aren't many alternative roles in dedicated research operations for full-time scientists who have lost their edge. That's why the question of tenure inresearch institutes and research universities is such a difficult problem.

Among the more successful examples of a core-funded research operation is the massive NIH 'intramural' laboratory complex in Bethesda, Maryland. Scientists working inthese laboratories have been awarded five Nobel Prizes. Taken together, the intramural core-funding mechanism at Bethesda and the peer-reviewed extramural NIH grantsthat fund biomedical scientists throughout the United States via competitive grant applications have supported more than eighty Nobel laureates, including me. Another example of a stellar core-funded operation is the British Medical Research Council Laboratory of Molecular Bio- logy, the iconic LMB. This is a centrally funded institute led by extraordinarily talented people who stay close to the actual practice of science. Together with its precursor, the LMB has provided the Cambridge working environment for twelve Nobel laureates.

Can high quality basic research ever flourish in repressive, centrally organized societies? The answer is clearly ‘yes’ for applied military science and technology: Nazi scientists developed jet fighter planes and other effective killing machines. Apart from the fact that the Nazis drove out many of their most established scientists like Albert Einstein, and future scientists like Max Perutz, because of their Jewish heritage, the cultural values and propaganda of these ersatz Aryans made the honest pursuit of new knowledge in areas like medical genetics and even hematology impossible. Science cannot be built on human degradation and lies.

Something similar happened with genetics in the USSR. Stalin embraced the arguments of the plant breeder T. D. Lysenko, which claimed that acquired characteristics are inherited, an idea attributed to the eighteenth-century French scientist, Jean-Baptiste Lamarck. It suited that totalitarian ideal that people could be 'improved' in some heritable way by social conditioning, and also suggested a rapid route to enhanced agricultural production. Lysenko was appointed director of the Institute of Genetics in the USSR Academy of Sciences while his predecessor N. I.Vavilov, was exiled to Siberia. This effectively destroyed research in genetics for twenty years and contributed to thelater inefficiencies in food production that proved a major embarrassment for Russian communism.

The only Russians ever to win Nobel Prizes for Medicine are Ivan Pavlov, of the Military Medical Academy of St Petersburg in 1904, and Ilya Mechnikov, who worked at the Institut Pasteur in Paris, in 1908. Pavlov survived the 1918 revolution and, though he was for a time highly critical of both the communist regime and Stalin, lived to the age of 87 and died of natural causes. His experiments on conditioned behavior in dogs evidently appealed to the 'man of steel'. Though some of the techniques and ideas that Pavlov developed were later used in the treatment of psychologically disturbed humans, he himself was a decent and courageous man and can in no sense be blamed forthe notorious abuses of psychiatry that were to develop in the Soviet system.

Russian medical scientists did a good job in developing influenza vaccines and in working out the epidemiology of the tick-borne infections that cause problems in spring and summer. Of course, they also developed a sophisticated capacity to make bio-terror weapons. Although these programs have been closed down, there is still concern about the fate of Russian stocks of lethal, genetically modified smallpox viruses. All this type of work is now focused on protecting human populations, not the opposite, and the Biological Weapons Convention of 2002, endorsed by 147 countries, was created to ensure that this situation continues. As with all leading nations, the United States has long abandoned biological warfare as a strategy and turned the supporting military facilities, like the Fort Detrick complex in Frederick, Maryland, over to the study of dangerous, so- called emerging, diseases like Marburg and Ebola virus infections. These bio-security laboratories are also being used to develop strategies and reagents for countering possible bio-terrorism; but the perception is that any such attack would come from groups of isolated zealots rather than from the agencies of an established government or nation-state. Overall, biological agents are not perceived as being particularly efficient military weapons but, as the anthrax episode in the United States that followed shortly after the September 11catastrophe showed, they are effective at promoting disruption (of the postal service in that case) and general fear.

Based in Lyon, the for-profit Institut Merieux did extremely valuable research at the more practical end of the spectrum. This 'translational' aspect of science is enormously important and is sometimes recognized by Nobel Prizes: the 1991 Medicine Prize, for example, went to two Americans, Joe Murray and Don Thomas, for pioneering the techniques of organ and bone marrow transplantation. The only Nobel Prize for Medicine ever given directly for the development of a viral vaccine went to Max Theiler of the Rockefeller Institute of Medical Research – now the Rockefeller University – in 1951 for the 17D yellow fevervaccine that is still in use today.

The Institut Merieux is now part of the world's largest vaccine manufacturer, the commercial Aventis Pasteur operation, which also incorporates the north American Connaught vaccine development and production facilities. Over the past ten years, amalgamations have been the rulein what is known as BigPharma. This extensive restructuring of the drug industry, with the reduction in staffnumbers that results inevitably from mergers has changedsome of the realities for scientists working in areas like pharmacology. Some big companies have essentially dismantled a substantial proportion of the ‘R’ component of their R&D operations, and are now relying a great deal on the innovation and discovery that comes from the public sector, or from small high-technology start-ups that they then absorb.

The Basle Institute was unique in that, apart from the position of the founding director Nils Jerne, who had turned his mind to theory and no longer led an active laboratory program, there was no hierarchical structure. All the scientists, whatever their age or eminence, were identified by the title 'member' and were theoretically equivalent in stature. I like this idea a great deal but, in practice, although all the members were equal, some (like the animals in Orwell's *Animal Farm)* were inevitably more equal than others.

The other great example of a research support organization developed from the bequest of an industrialist is the Howard Hughes Medical Institute, funded from the estate of the eccentric and reclusive billionaire. Operating as a 'virtual' institute, it pumps more than *$500* million a year into basic biomedical research. The administrative headquarters are in Maryland, and its scientists are scattered through the country's leading universities and research institutes. Though most Hughes funding goes to US residents, they have also provided some support for international programs in infectious disease and cancer led by scientists in Australia, Eastern Europe and so forth.

The Hughes Institute is an unashamedly elitist organization. The central idea is that the very best scientists should be free to concentrate on their research, and should not have to be constantly writing research grant applications. Leading scientists and younger research investigators who show evidence of exceptional promise are invited to join, and are then provided with very substantial funds. After they have come through the up-or-out process, their performance is reviewed at regular intervals. To date, thirteen Howard Hughes scientists have been awarded Nobel Prizes, including Linda Buck and Richard Axel who shared the 2004 Medicine award for working out the neurological basis of olfaction, the sense of smell.

The most recent US Nobel Prizes for research done in the for-profit commercial sector went to William Knowles of the Monsanto Chemical Company for Chemistry in 2001 and Jack Philby of Texas Instruments for Physics in 2000. Both had retired by the end of the 1980s. The latest award to a scientist still working in the chemistry/pharmacology industry was the 2002 Chemistry Prize to Koichi Tanaka of the Shimadzu Corporation in Japan.

This could be a sign for the future. The large US drug companies are, for the reasons discussed earlier, much less likely to be supporting innovative, in-house research. By concentrating on the development part of R&D (clinical trials and so forth), they are in effect reacting to the reality that, with the application of contemporary molecular approaches, major new discoveries can emerge anywhere – and sometimes from the most unexpected places. The involvement of BigPharma and the profit motive is, however, absolutely essential if any such findings are to be exploited for eventual human benefit.

Since the 1970s, one of the major areas of excitement has been the new biotechnology industry. It blossomed in the wake of Watson and Crick's 1953 model of the DNA double helix and progressed through the development of restriction enzymes to cut DNA to the development of recombinant DNA technology. The scientific founders were generally university scientists, though those who succeeded also had the good sense to involve leaders with business skills from the outset. Some of the early players, like Genentech, DNAX and Immunex, have been tremendously innovative and it would not be surprising to see Nobel Prizes going to researchers who did their best work in such operations.
Every city from Cambridge, Massachusetts, to Brisbane, to New Delhi, to Cambridge, UK, that hosts major research universities now has an associated 'biotechnology cluster' that can number hundreds of small start-ups and larger companies. Many of these operations develop their intellectual property to the point that it is eitherattractive for the drug companies to buy them *in toto* or topurchase the technology they have developed. A number ofscientists who began as modestly paid but intellectuallydriven research workers have become wealthy through thisprocess, proving that a Nobel Prize is neither the sole northe most lucrative reward for a research scientist.

The small biotechnology operations that take one or a few discoveries part-way down the track to commercialization have emerged naturally in those nations that have amajor publicly funded science base. Many smaller countries are also hoping to stimulate economic growth bydirecting their more limited resources towards biotechnology. In Cuba, for instance, such developments are beingdriven from the public sector to provide opportunities forbright young scientists.

As with the wealth of nations, there tends to be a north-south divide in science. Very expensive facilities, like the billion dollar accelerators used in high-energy physics, are generally found in the prosperous countries of the northern hemisphere. For instance, the Tesla accelerator that is currently being constructed in Hamburg is costed at 684 million euros. The exception is the Brazil synchrotron, a smaller scale accelerator that, among other applications, is used by the contemporary equivalents of Max Perutz and Rosalind Franklin to determine protein structure. Australia has started to build a synchrotron, but for now Australian structural biologists see themselves as 'suitcase scientists' who travel to Narita, Hamburg or Chicago to do their key experiments. Apart from the inconvenience and loss of time, transporting even the types of non-living materialsthey study has become more cumbersome with the increasingly stringent regulatory requirements spurred by concerns about bio-terrorism.

Obvious exceptions to the north-south rule are the big optical telescopes, where the ideal site may be in the high,clear air of the South American Andes. The twin 8-metretelescopes of the Gemini Observatory are located onManua Kea in Hawaii and on Cerro Pachon in Chile. These instruments are supported by international partnerships involving many nations. Some of the Associated Universities for Research in Astronomy telescopes are to be found near the city of La Serena in Chile, which seemsa very appropriate place, as optical astronomers tend to be calm types who enjoy sitting on top of mountains.The southern sky has obviously been the focus of thevarious Australian observatories, with radio and opticalastronomy traditionally being very strong on the Australianscience scene.

International consortia are, of course, enormously important when it comes to seeking scientific solutions to theinfectious diseases, like malaria, which continue to kill so many in the poorer countries. The efforts to deal with the AIDS catastrophe, where some 3 million people, including 1.2 million women and 600,000 children, died in 2002 alone, constitute a massive global enterprise. Candidate AIDS vaccines must ultimately be tested in high-incidence areas, so we see the development of interactive networks that bring together scientists, ethicists, health care delivery personnel, administrators and a new breed of specialists who interact with regulatory authorities. A potential vaccine developed in the United States will have to be approved by the FDA and by the comparable regulatory body in thecountry where it is to be tested. The design of the trial willbe subject to the requirements of the human subject experimentation committee at the institution where the product is developed and by the authorities in the recipient nation.

In developing countries, where catastrophic infectious diseases like tuberculosis and malaria are still rampant, international collaborations and funding are having a dual outcome. A major advantage of involving both altruistic foundations and government-supported Aid agencies is that they can sometimes set up substantial research operations that train young local scientists and provide opportunities for them. As I mentioned earlier, I was for six years a board member of the internationally resourced and directed ILRAD/ILRI research institute in Nairobi thathad the job of trying to deal with African trypanosomiasis (sleeping sickness) and theileriosis, a fascinating disease caused by a malaria-like parasite that infects white rather than red blood cells and makes them essentially cancerous. In the process of trying to solve these very difficult disease problems with relatively limited (compared to TB and malaria) resources, ILRAD/ILRI trained a number of first-class young African molecular biologists and epidemiologists who now work in all types of related areas.

Generally, however, there is no global, level playing field for young scientists who want to seize available opportunities and develop their own potential. The answers to the important questions – Where can I best train andwhere should I ultimately aim to develop my own independent research program? – are not at all simple for thoseborn outside the large open economies of the United States or Europe. Many scientists from the developing world who work for a time in the universities and research institutes of the advanced countries find it difficult to return home. The resources to pursue their particular passion may simply be unavailable.

Science at its best is a universal activity that benefits everyone. Positive international change is more likely to be achieved if scientific discoveries and advances are seen as broadly 'owned' by all members of the human family. There is no simple answer to the global inequities in wealth and the spread of resources for national research enterprises.

Nevertheless, approaching science in a targeted and thoughtful way that emphasizes local, selective advantage and altruistic international partnerships has real potential for building one or more areas of national research excellence. A major breakthrough with malaria, AIDS or starvation could well result in a Nobel Medicine or Peace Prize to a scientist working in a developing nation. I can't think of anything that would be more likely to delight the Swedish and Norwegian Nobel committees than being able to make such an award, especially in the sciences.

Meanwhile, advanced nations like the United States and Australia need to do more to keep ahead of the game. The United States is currently suffering from a rise in anti-science and anti-intellectual attitudes fuelled by parochialism and political and media pandering to narrow religious fundamentalism and the perceived interests of large corporations. Australia has fulfilled the prediction of Arnold Toynbee's theory of history that the creative minds that drive innovation come to the fore under conditions of crisis and extreme difficulty. The penalty has been that resultant prosperity has been sufficient to marginalize the sense that the nation must build a much broader, and more dynamic, culture of innovation and development if it is to remain prosperous and be a significant international player in the long term. This book is aimed at generating greater awareness around this issue. As Prime Minister John Howard said to me: if you want to influence the political process, get the voting public interested and involved.

CHAPTER 7: Through Different Prisms: Science and Religion

Is a faith-based view of the world in irrevocable conflict with science and with developing new knowledge? Does adherence to religious tradition and practice limit the willingness of a nation or an individual to embrace new ideas and ways of looking at the world? Is the tolerance of social diversity that accompanies a dynamic science culturea threat to religion? Can scientific discovery and theorybe reconciled with religious belief, or is useful dialogue between these value systems impossible?

Science is an activity that suits people who question, test ideas and then embrace the intellectual and philosophical consequences of their findings. There are no absolute or revealed truths in science: any belief or theory will soon be discarded and forgotten if it no longer fits the available evidence. The differences in scientific and religious cultures mean that people who hold to literal, faith-based views can find this difficult to understand. The theory of evolution is attacked because 'it's only a theory', but the fact is that evolutionary theory has been the single most important explanatory model in biology for more than a century and it underpins many of the key breakthroughs in medical science recognized by Nobel Prizes over the past fifty years.

In the media, the public debate between science and religion is often posed at the extremes, creating a superficial perception that adherence to the one means automatic hostility to the values and practices of the other. In fact,though there are obviously situations where no intellectualcompromise can be reached, this rarely spills over in a way that limits the useful application of science for the generalgood. These two cultures can and generally do live side by side in reasonable harmony and, given the massive problems that humanity will face over the next century, they must be able to talk to each other.

University was my first introduction to real people who live by ideas and experiments, though I already had someinsights into that world from reading. These years alsobegan my life-long intellectual adventure with biology,and biology makes no sense whatsoever in the absence of Darwinian evolution. This is particularly obvious for the late-evolving adaptive immune system that I have described earlier, which operates more like a street person dressed in cobbled-together hand-me-downs (the molecular mechanisms used by 'older' systems like the brain) than a perfectly arrayed socialite in an elegantly accessorized Armani or Versace outfit. Immunity does not look to me like some- thing that is 'intelligently designed'.

Once I had made the transition in thinking to evidence-based enquiry, there was no going back to assertion and dogma. The consequence is being eternally condemned to an intellectual view dominated by verifiable data, reason and, so far as any human being can achieve that, self-knowledge. That doesn't mean that I've set aside early positive influences that came from the non-conformist Protestant tradition. I also realize that, to some religious people, my reality-oriented view of the world must seem like a vision of hell.

My childhood left me with a reasonably good, if superficial, knowledge of the four gospels in the magnificent King James Bible. I dip into them from time to time, andtend to quote religious texts, probably incorrectly, at some of my more religious friends in the American south. Tome, the Bible represents the collective wisdom and stories of the Jewish and early Christian people. The oldest of thegospels, St Mark's, was not written until forty years after what is generally accepted as the time of Christ's death. Iam clearly more impressed with statements like 'It is easierfor a camel to go through the eye of a needle than for a richman to enter the kingdom of God' (Matthew 19:24), 'Sellwhatsoever thou hast and give to the poor' (Mark 10:24), or 'Judge not, that ye be not judged' (Matthew 7:1) than many religious Americans. Like everyone else who has some religious background, I quote selectively from the bits that suit my particular experience and consequent view of life and the world. Many of us, when it comes to thinking about religion, relate to an early childlike experience of church-going that is fairly narrow and unsophisticated, and in total ignorance of the vast mass of religious scholar- ship and theology.

The Methodists also have a great dedication to hymn singing, which I sometimes inflict on those who are unfortunate enough to be in my immediate vicinity at the time. Entering the great European cathedrals leaves me with a profound sense of immanence and inner peace, which is exactly what they were designed to do. One of my most vivid memories is of being at the deathbed of my religious grandmother as a 10-year-old child. While she was dying, she recited the 23rd Psalm, 'The Lord is my Shepherd; I shall not want ...' This calming mantra goes through my head when I am deeply troubled about something and can't sleep. Saying 'om' over and over does nothing for me and I don't count sheep, but I have an olivewood carving of the Good Shepherd carrying a lamb that I bought in a Bethlehem tourist gift shop many years ago. The shepherd, with his humble status and simple dedication to protecting the vulnerable, seems to me to symbolize the very best of the Christian tradition. The Bethlehem shepherd stands on my bedside table.

The point I would make here is that for anyone thinking about a career as a research scientist, a religious upbringing should not be a problem. At some stage, the individual concerned will be forced to confront, and deal intellectually with, the mass of evidence for evolution and natural selection. The need to discuss religion in a book about science would have been considerably less obvious twenty or thirty years ago. Much of Western Europe had moved towards what is now often described as a post-Christian civilization, with even those who had some religious affiliation practicing 'cafeteria Catholicism' and the like. The German philosopher Friedrich Nietzsche had long since declared 'God is Dead', a view that resonated in the influential book *Honest to God by* the Anglican bishop John Robinson, published in 1963. The fact that many US intellectuals were in denial about the lives of those who inhabit 'middle America' had pushed any consideration of religious fundamentalism into the deep background. After Sinclair Lewis, the 1930 Nobel Literature Prize winner, created the despicable evangelist Elmer Gantry, I can't think of a major US novelist who has addressed the outer limits of Christian practices in the American heartland. Maybe it would have been impossible to invent characters who were more extraordinary than Jimmy Swaggert, or Tammy Fae and Jim Bakker.

Beginning in the 1990s, however, substantial new books that look analytically at religious fundamentalism have been emerging with increasing frequency. The most helpful account that I've read is Karen Armstrong's *The Battle for God,* which provides thoughtful, and even sympathetic, insights into the extremes of the three Abrahamic religions, Judaism, Christianity and Islam. John Krakauer's *Under the Banner of Heaven: A Story of Violent Faith* is particularly intriguing because it relates the very recent and well-documented origins of Mormonism, while at the same time focusing on the more regressive fringes of that belief system. Krakauer also documents the way in which American fundamentalism can be tied to the libertarian philosophy which holds that the individual has no social obligation to pay taxes or to obtain a driver's license. Combining the fundamentalist and libertarian themes with the US gun culture gives the lethal mix that led to the 1993 tragedy in Waco, Texas, where seventy-six members of an extreme cult died in a confrontation with the secular authorities.

The reality that religious fundamentalism is a major political force was made clear during the 2004 US presidential election, and in a way that was almost incomprehensible to observers elsewhere. The United States is the most conventionally religious country in what we traditionally think of as the Judeo-Christian world. The presidency of George W. Bush has left us in no doubt that a substantial percentage of US citizens think of themselves as 'born again' Christians.

The big area of conflict between science and religion is, of course, to do with the belief system known as 'creation science'. Some religious people find the idea that humans have evolved from simpler life forms to be unacceptable. Others go further and accept that every word in their particular translation of the Bible is literally true, which means that, when the dates are calculated, the world can be only about 6,000 years old. At this extreme, the creationist argument has to rationalize the biological and geological record as either some sort of theistic trick, or a test of faith. At the other end of the spectrum is the idea of 'intelligent design', which accepts evolution but argues that the process is not random, but God-directed. Biologists and 'intelligent design' people can at least talk to each other, though I doubt they will ever agree.

Why should science be unduly bothered by creationist arguments? The debate has been going on for almost 150 years and it is clearly not going to be resolved by reasoned discussion. The democracies where science flourishes are equally dedicated to the idea of religious freedom provided the particular belief system doesn't lead to practices that involve the abuse of women or children, or are otherwise dangerous and illegal. Surely, if some people want to believe that there is something called 'creation science', that's their business? In any case, my personal perception, from conversations with religious fundamentalists, is that most of them are much more attached to the value they place on traditional moral, ethical and behavioral models than with the creationism. In fact, some of the better educated are clearly embarrassed by the creationist obsession. Is signing on to creationism perhaps a test of faith, a requirement to abandon reason?

The magnificent US Constitution, which was drafted in the spirit of the European Enlightenment, mandates a division between church and state that has been interpreted by the US Supreme Court as requiring a 'wall of separation'. As with many aspects of American law, this is enforced with great rigidity. A country that is based in both a strong Christian tradition and the philosophy of the founding Pilgrim Fathers forbids the singing of Christmas carols, the display of Christmas trees and any form of religious observance in public schools or other state-owned facilities. The denial of what they see as their heritage acts as a point of friction that irritates many rather normal and decent Americans.

Religion is an enormously important part of the human story. Every school child in the Western democracies should be taught comparative religion and the role that belief systems and practices have played in the evolution of their particular national culture. It is pretty obvious that teaching 'creation science' alongside molecular genetics, evolutionary biology, geology, chemistry and physics in schools will only cause bright kids to ask, 'Who are these people, and what are they talking about?' Fundamentalists are not stupid, and that, of course, is why they encourage home schooling and set up their own schools and 'universities'. Intelligent young people, no matter what their beliefs, owe it to their development as human beings to expose themselves to the openness and excitement of a good university. Their parents also owe them a level of respect that frees them to make their own judgments. Knowledge enriches. If beliefs are valid, they will survive.

Religion certainly has much less traction in Australia than it does in the United States. Though there are still very committed groups of believers and fundamentalism is gaining some ground, the majority show little deep adherence to religious beliefs – though they embrace ethical and moral values that are broadly Christian, or perhaps more correctly based in Athenian democracy and Aristotle's ideas of more than 2,300 years ago. Many describe themselves as 'Catholic' or 'Orthodox', but often these are as much ethnic and cultural as they are religious identifications. Melbourne, for instance, is the third biggest Greek city in the world. The Greek Orthodox church supplies a connection and a tradition that is life-enhancing for members of this community, but, like most of the long-established Christian denominations, they are losing their young people when it comes to regular church attendance.

The point of contention was Charles Darwin's ideas about natural selection and evolution, published in his 1859 account *On the Origin of Species.* Darwin himself had been studying for the Anglican priesthood when he accepted the invitation to sail as naturalist on the 1831–36 voyage of the *Beagle.* The scientific conclusions that he reached concerning life forms on the isolated Galapagos Islands led him to formulate the theory of evolution, which, as I've discussed earlier, is the basis of modern biology. Bishop Wilberforce was known as 'Soapy Sam' because of his skills as an ecclesiastical debater. Speaking with great eloquence at the British Association for Science meeting at Oxford in June 1860, the good bishop is reputed to have smiled as he concluded his remarks by asking Huxley if it was through his grandfather or his grandmother that he claimed descent from a monkey. Huxley evidently turned to Sir Benjamin Brodie who was sitting next to him and exclaimed, 'The Lord hath delivered him into my hands'-a little irreverent, since Huxley did not subscribe to a theistic view of the world. His response to Wilberforce was:

I asserted-and I repeat-that a man has no reason to be ashamed of having an ape for his grandfather. If there were an ancestor whom I should feel shame in recalling it would rather be a man-a man of restless and versatile intellect-who, not content with an equivocal success in his own sphere of activity, plunges into scientific questions with which he has no real acquaintance, only to obscure them by an aimless rhetoric, and distract the attention of his hearers from the real point at issue by eloquent digressions and skilled appeals to religious prejudice. Huxley is considered to have won the debate.

The consequence of Huxley's advocacy was that over the ensuing years enlightened Anglicans, like their Catholic counterparts, progressively gave up the idea that the biblical account provides anything more than a symbolic explanation for the origin and development of life forms and the natural world. As I discussed earlier, this built on the earlier rise of science that resulted from the Renaissance, the Protestant Reformation, then the seventeenth-century philosophical writings of Francis Bacon and the Enlightenment. Thus, while many English scientists were essentially agnostic, others did not have a particular problem reconciling their science and relatively open forms of religious belief.

Like the United States, Australia has been greatly influenced by the waves of Irish, then Italian, Catholics who settled there. My understanding is that the Catholic hierarchy has no particular problem with evolution or with modern science in general, providing the activity does not cut across the 'sanctity of life' issue that is a central article of faith and forms the basis of the implacable opposition of the church hierarchy to abortion and research that uses embryonic stem cells. If this is a personal moral and ethical concern for someone considering a career in biomedical research, it is important to realize that the great majority of such science does not require any interaction whatsoever with human embryonic material. Apart from that, even those involved in stem cell research who don't have the same moral reservations are working towards strategies, like using post-partum umbilical-cord blood, that will obviate any need to rely on human fetal tissues for future therapeutic applications.

For a long time, the Catholic church held onto the notion that religious doctrine can explain the physical nature of the world. In 1633, Galileo Galilei was forced to recant his belief that the Earth circled the sun, and was not granted a papal pardon until more than 350 years later. Nevertheless, the Catholic Church is justly proud of its intellectual and scientific history. Even in the seventeenth century, the move against Galileo may have had more to do with Church politics than with suppressing his discoveries. Many of the great European universities – Oxford, Cambridge, the Sorbonne, Glasgow, for example – find at least some of their origins in ecclesiastical institutions, and the Catholic Church maintains some substantial US academic institutions to this day – Notre Dame at South Bend, Indiana, St Louis University in Missouri and Loyola University in Chicago. In Australia, there is a network of teaching universities known as the Australian Catholic University.

I was reminded of the scholarly face of the Catholic tradition when I was awarded the 2000 Mendel Medal by Villanova University, a prominent Philadelphia institution run by the Augustinian Order. Gregor Mendel was an Augustinian monk credited with founding the modern science of genetics. His seminal breeding experiments with sweet peas were done at the monastery in Brno, Austria, published somewhat obscurely in 1866, and rediscovered in 1900, with full credit to him, by a trio of European botanists. The citation for the Mendel Medal reads: 'The Mendel Medal is awarded to outstanding scientists who have done much by their painstaking work to advance the cause of science, and, by their lives and their standing before the world as scientists, have demonstrated that between true science and true religion there is no intrinsic conflict'. Aside from feeling more than a little inadequate as a recipient, I had no quarrel with the high sentiments expressed. The problem is that although it is easy to agree on the universal characteristics of 'true science', as I discuss throughout this book, many of those who are religious have great difficulty reaching any globally inclusive definition of 'true religion'. The degree of flexibility within a particular belief system is clearly a key issue for anyone with deep religious convictions who is contemplating a career in science.

Fundamentalism has been part of the Australian experience for many of the same reasons that it became established in North America. Fundamentalism is increasing its influence in Australia as, in these very uncertain times, some seek a worldview that is more stable and enclosed. However, fundamentalism does not play out politically in anything like the same way as in the United States. The fundamentalist, Family First Party is small and gained a seat in the Australian Senate only because of peculiarities in the preferential-plus-proportional representation voting system. From what I've read, Family First seems genuinely concerned about families, including poor families. They are also focused on helping the homeless, drug rehabilitation, child protection and valuing the elderly. I couldn't find a single word about science or creation science in their published manifesto, and Family First seems to be broadly pro-environment. Recently, it has also been encouraging to see the Evangelicals of the US Southern Baptist convention embracing the idea that they have a responsibility for the natural world as the "Stewards of God's Creation".

There are two likely reasons why a well-organized, extremist fundamentalist view has relatively little political sway in Australia. One is that the majority of Australians disagree with the hard-line 'right-to-life' position of fundamentalist Christians. Although many Australians are uncomfortable about abortion, when it comes to the rightto choice, the majority are definitely in favor of this. When more than 4,000 Australians were asked to respondto the statement, 'A woman should have the right to choose whether or not she has an abortion', the answer wasin the affirmative for 93 per cent of non-believers, 77 per cent of those with some religious affiliation, 70 per cent of Catholics and *53* per cent of evangelicals (Baptist, Lutheran, Pentecostals). The other factor is Australia's compulsory voting system. Unless they register for exemption on the grounds of religious belief, every adult Australian who is living in the country must turn up at a polling booth on election day and collect their voting paper. They can spoil the ballot paper if they don't wish to register a vote, but they must participate in the process. Compulsory voting was introduced in 1922 when the voter turnout was only *59.2* per cent – which would be regardedas a pretty good figure in a contemporary US election – and has been around the 91 per cent level ever since. This means that it is much more difficult for a well-organized, minority group to gain political traction in the governing house, the House of Representatives, though minority political parties have often held the balance of power in the upper house, the Senate, which is the house of review. Australians should, I believe, protect compulsory voting at all cost. Surely nothing serves democracy better than a high voter turnout?

Other religions also seem able to live in reasonable accord with science, despite popular stereotypes that prevail in Western thinking. Religion is a major force in nations where Islam is the dominant belief system. The events since September 11, 2001, including the invasion of Afghanistan and the ongoing struggle in Iraq, have had the perverse effect of educating those in the West about the depth and power of religious tradition and religious leaders in such communities. Some of the television pictures and stories that many have seen originating from Afghanistan and northwestern Pakistan describe both towns and social structures that seem essentially mediaeval. Guns are everywhere. Unlike the situation in a Western country, the focus of power is still very much the family, with family rivalries assuming the same attributes we recognize from the Montagus and the Capulets of Shakespeare's *Romeo and Juliet.* Of course, this describes only the outer fringes of the Islamic world. A visit to a modern Islamic nation, like Malaysia, quickly leads to the realization that Malaysians see no conflict in simultaneously embracing religion, science, technology and innovation.

Educated and thinking people in Islamic societies are rightly proud of the open and ecumenical spirit that led to the intellectual, scientific and literary leadership provided by Islam when Christian Europe was in the dark ages. Arabic scholars preserved many of the ancient Greek texts, made useful inventions like the portable astrolabe, and introduced the numerals we all use today. Sometimes it is possible to find a way back to an earlier positive tradition. A hopeful example of this happening is the recent magnificent reconstruction of the Bibliotheca Alexandrina; the Great Library of Alexandria that most believe was destroyed by fire more than 1,500 years ago. The funds to build the Bibliotheca Alexandrina have largely been provided by the governments of Egypt and the neighboring Arab nations.

Buddhism doesn't create obvious problems for someone who wants to be a scientist. In an opinion piece for the *New York Times* in April 2003, Tenzin Gyatso, the 14th Dalai Lama, writes about his long-term discussions with scientists in fields as diverse as cosmology and neuroscience: 'It may seem odd that a religious leader is involved with science, but Buddhist teachings stress the importance of understanding reality, and so we should pay attention to what scientists have learned about our world through attention and measurement'. He has encouraged scientists to study the physiological basis of the meditation techniques that promote happiness and 'inner balance'. His point is that understanding how meditation works in the scientific sense could help to promote therapeutic approaches that emphasize behavioral change rather than drugs in combating depression and anger. The idea that insights drawn from religion and science can come together to achieve harmony is one that any sane society should be happy to embrace.

The Judaic heritage that has nurtured the early lives of many Nobel laureates, particularly in medicine, is also quite open to the scientific traditions of speculation, experiment and conclusions based in verifiable evidence. The complete list of Jewish laureates includes more than 120 people, though many of these would, I suspect, be essentially secular in outlook. As I understand it, a central idea in Judaism is that, though the words in their holy text (the Torah) stand at the center of belief, they are not to be taken literally in a changing world, but require constant thought, interpretation and commentary. The result is an intense rabbinic dialogue that depends on questioning and argument, both of which are central to modern science. Claude Cohen-Tannouiidji, the 1993 Physics laureate who grew up in a devout Jewish family in Algiers, summarizes this tradition as an emphasis on studying, learning and sharing knowledge with others. Perhaps he could also have added questioning.

What if the question is turned around, though, and we ask how scientists approach religion? In a widely quoted 1998 study, published in *Nature,* Edward Larson of the University of Georgia surveyed the religious beliefs of those who may generally be regarded as the great, living US scientists, the members of the National Academy of Sciences (NAS). Larson concluded that only 5.5 per cent of the biologists, 7.5 per cent of the physicists and astronomers and 14.3 per cent of the mathematicians believed in a personal god. (Interestingly, mathematicians tend to deal with abstractions, and are often not much interested in data.) Among the broader scientific community in the United States, 60.7 per cent are said to be 'doubters'.

This is not to say that a lack of religious belief is the mark of all successful scientists. Bill Phillips wrote about both his religious upbringing and his commitment to an ecumenical Methodist communion in the biographical account that he provided as a co-recipient of the 1997 Nobel Physics Prize for laser cooling. Francis Collins has been directly responsible for identifying a number of genetic abnormalities associated with humandisease and is a prototype for the concerned research investigator. His viewpoint is: Who are we to criticize a god whohas chosen to work his miracles through natural selectionand evolution? This is a perspective acceptable to manyChristians, though is unlikely to appeal to those whobelieve that the words of the Bible are God's literal truth.

I know a number of first-class scientists who are, at least occasional, church-going Catholics. One NAS foreignmember, the Australian neurophysiologist and 1963 Medicine laureate Jack Eccles was, among many other distinctions, a Papal Knight. He ended his speech at the Nobelbanquet with 'May God bless you'. Eccles was a goodfriend of the philosopher of science Karl Popper. They published a book together *(The Self and its Brain),* which I found to be hard going. Popper's own book, *Conjectures and Refutations: The Growth of Scientific Knowledge,* on the other hand, is much more accessible, but there are no Nobel Prizes for philosophy. In his more speculative writings,Eccles explored an idea he called 'dualist interactionism'. As I understand his position, he believed that the 'self- conscious mind' draws on the physical brain rather than, as most biologists would think, the mind being a product of the brain. Speaking with people who knew him, I gainedthe impression that Eccles moved away from this idea in later life. He lived to the age of 94, spending his latter yearsin Switzerland.

One analysis of the revival of fundamentalism is that the scientific case is so strong that the more dogmatic religious communities fear for the survival of their belief system and in response retreat into a narrow literalism that emphasizes the denial of evidence and open higher education. Considering what has happened to institutional religion in Western Europe, there can be no doubt that they have a point.

Sometimes belief systems can go in directions that seem both dangerous and irresponsible. When it comes to preventing HIV/AIDS, the mantra that works is the ABC protocol: Abstinence, Be faithful and, failing that, use a Condom. The churches have no problem with 'A and 'B', but some are directly opposed to 'C'. My friends in the behavioral sciences, who pursue what are termed harm-reduction policies to try to minimize the impact of AIDS in Africa, tell me that the most important thing to do in such situations is to maintain an open dialogue. Perhaps the religious leaders can be persuaded to minimize the extent to which their opposition to 'C' is stated from the pulpit; if that is not possible, maybe they will agree to limit their proselytizing to their own community and refrain from promoting a more public stance that will only serve to confuse people generally. The important thing in such a situation is that medical professionals and religious leaders are able to talk to each other in an atmosphere of mutual respect. This proved to be very important in reversing the recent break-down of both the poliomyelitis and the measles vaccination programs in Nigeria.

Scientists who choose to be involved in the public arena must be prepared to work towards building consensus concerning the issue that they want to promote. This isn't done by being some sort of secular pope or Oliver Cromwell, but requires dialogue, insight and discussion.

Certain religious communities will see some issues related to science as important, or dangerous, but others will be welcomed or get an essentially neutral reception. No medical missionary, for example, is going to be upset by the sudden availability of a new and effective AIDS or influenza vaccine, even though the underlying science will be oriented towards defeating the consequences of the rapid natural selection that features so prominently in these infections. If religious groups can be convinced to come in on the right side, they can be powerful allies. We shouldn't automatically assume that even those in the most fundamentalist communities will be firmly in the camp of the evidence-deniers on all issues.

Surely people of good sense who approach the world from a more faith-based religious perspective should be able to agree with those who hold firmly to ideas based in scientific discovery and verifiable reality that the survival of our species, along with the animals and plants in the green and pleasant world that supports our physical and spiritual existence, is of great importance. Whether or not we accept that the responsibility derives from a divine mandate or from the evolutionary need to ensure continuity, it is essential that we all come together to accept that the stewardship of the planet is in the hands and minds of human beings. Though the underlying convictions may be different, it is incumbent on all of us to work towards positive results. What greater betrayal can there be of God's good grace, or the continuity of our species and all life, than to embrace polarized attitudes of mind and practices that compromise the lives and opportunities of the generations that are to come? If I could ask one thing of my religious friends, it would be that they look hard at political parties and their policies from the viewpoint of global sustain- ability when they vote, particularly in national elections.

CHAPTER 8: Discovering the Future

Nanotechnology deals with building minute molecular machines at dimensions smaller than those of a human hair, and micro-machines might be more like a tiny chip and associated 'wiring' that could, for instance, be implanted to help to re-establish the connection between brain and muscle after a nerve is severed. We are all familiar with larger, plumbed-in gadgets like heart pacemakers and the 'bionic ear', so this will, in a sense, be a continuation of an established theme. Nanotechnology is new and at a much more speculative stage. Scientists are working on ideas like building tiny molecular devices that could be injected into the blood to cut away the accumulated cholesterol plaque on arterial walls, or would go directly to disseminated (metastatic) tumor cells and kill them. Think of a scenario similar to the miniaturized submarine and crew in the movie *Fantastic Voyage,* then think millions of times smaller. Though there are these exciting advances like nano-technology that are just beginning to happen now, scientists are really no better at guessing the future than anyone else. Most specialists can speculate about the long-term consequences of established trends, but novelty and radical change can take everybody by surprise. Humanity has had to deal repeatedly over the past 500 years with revolutionary advances that were both sudden and transforming - just forty years ago, for instance, nobody predicted the Internet, or suggested that many businesses would now be using a globalized, electronically linked workforce. Some of the challenges for the health and longevity of both individuals and the planet are, however, already obvious and ominous.

Like everyone else, when it comes to sooth-saying, anything useful that I have to say is likely to be in the areaof my own broad interests: biology and medicine. Myfellow 1996 laureates were right: there is potential forimmense human benefit from the work being done in biology, particularly genetics and molecular medicine. Infact, when people look back on the science of the twenty-first century my guess is that they will talk of it as the century of biology and the chemistry and physics associatedwith biological processes. Looking forward in biology, it is hard to see the excitement diminishing for many years to come. The challenges are enormous because we now have the potential to go from the detailed observation of biological processes to broad landscapes that encompass the chemistry and interdependence of all life. On the one hand, we can progressively see unfolding the nature of precise molecular events that can lead to the development of much better and more specific chemotherapeutic agents (drugs). On the other, it has also become possible to tackle the complexities that are central to the operation of immunity, the brain, human connectivity, and the interaction between all life forms (the biota) and the air, water and earth of our planet.

There is great excitement in all areas relating to genetics, and I don't see that diminishing over the next hundred years. Here is an example as to why: recent research byJim Downing, Bill Evans, Mary Reiling and colleaguesat St Jude Children's Research Hospital used genomicapproaches to develop a new analysis of acute lympho-blastic leukemia (ALL). This is a bad cancer of the whiteblood cells that was a death sentence for more than 90 percent of the kids who were diagnosed. Progressive advancesin chemotherapy and radiation therapy that were pioneeredat St Jude brought the survival rate to more than 80 percent, but there is still a very distressing tail. The mission ofSt Jude Hospital is 'No child should die before its time', sothere is a way to go with this disease. The scientists and physicians who started St Jude in the 1960s thought ahead. The basement is full of rows androws of deep freezes containing blood and cancer tissue from every child who has been treated there over the past forty years. The hospital also monitors patients from thetime of treatment through to a 15-25-year survival period,so there are very comprehensive clinical records. Our genetics research team went back to these samples and their associated histories.

My expectation is that within ten to twenty years, a first step for everyone who is treated in a world-class, comprehensive cancer center will be to have a blood or biopsy sample taken before the commencement of therapy so thattreatment can be individualized to the genetic profile ofboth the patient and the particular cancer. Though everytumor may differ in specifics, the ALL study suggests thatthere will be common genetic themes that link different 'families' of cancers that can be treated in different ways.Also, knowing the individual's own genetic make-up will tell the doctors which drugs can both be tolerated and are likely tobe effective, and atwhat level. Researchers through- out the world are currently gathering similar genomic information for all the major tumors of the brain, breast, gastrointestinal tract, reproductive system and so forth. Unlike pediatric ALL, these are high volume tumors that don't require an interval of forty years to accumulate enough samples and clinical histories.

The gene chip referred to above for the ALL study is a direct product of genomics, the science that really got under way with the sequencing of the complete human genome, the major milestone achieved right at the end of the twentieth century. The Affymetrix company, for example, sells two small chips (looking much like those in the back of a digital camera) that express the 30,000-plus genes that provide the necessary code to make a human being. We have, of course, no idea how to do that other than by the traditional way of having a sperm fertilize an ovum. Most sane human beings would not want to see that particular situation change. Think, all the same, how great it would be for transplantation if we could take some stem cells from an individual's own bone marrow and use our understanding of the particular sequence of molecular interactions that determine organ development to make a new kidney or pancreas in the laboratory. We are decades, perhaps centuries, away from being able to do anything remotely like this.

What will undoubtedly happen over the next twenty years or so is that the application of molecular genetic and genomic approaches will lead to the development of novel anti-cancer drugs that are less toxic and have fewer side effects.

The structural guys traditionally used X-ray crystallography, the technology that was first developed by Williamand Lawrence Bragg (Chemistry, 1915). The 'new' structural biologists, like Rod MacKinnon, who won the Nobel for Chemistry in 2003,use the smaller linear accelerators, the synchrotrons (which I referred to earlier in the book), for the same purpose, a change that enables the analysis of more complex interactions and infinitely speeds up progress of this area of science. Many structures are now solved with a rapidity that would have looked impossible to Rosalind Franklin; she took the key X-rays of DNA that allowed Watson and Crick to sort out the double helix structure, but died of cancer soon after that, in 1958.

Knowing the topography of the molecular interface then allows various types of chemists to design and test small molecules (drugs) that might fit into the binding site of one or other molecule to block the interaction. This complex and difficult chemistry is very much helped by modern computer simulation techniques. The first anti-tumor agent to become available as a result of the rational drug design approach that I've described above is Gleevec, an inhibitor that binds to a particular molecular target (a tyrosine kinase enzyme) and blocks the uncontrolled cell proliferation that is characteristic of cancer. Until now, cancer chemotherapy has essentially depended on the use of poisons to kill the dividing cells. The result is hair loss and destruction of the immune system, which makes patients very susceptible to infection. A much more specific therapeutic like Gleevec lacks these side effects.

The problem that is emerging with Gleevec is the same as with any cancer therapy: the development of resistance. Before discussing that, it is necessary to say a little about the nature of cancer. The following discussion is very simplistic, as there are many types of cancers that can develop for different reasons, but it should be sufficient to provide some understanding of how tumors escape from drug control.

With the exception of a few cancers that are caused by viruses, tumors develop as a consequence of genetic mutation(s). A mutation is simply an error within a gene that occurs at the time of cell division and, providing it isn't lethal, will then be passed on to 'daughter cells' with, in most cases, no undue consequences. This process, called 'background, somatic mutation', is occurring all the time in every one of us, but there is generally no reason to select for the particular clone of cells that carries the altered gene. Cancer develops when the mutation disrupts the signals responsible for the normal process of growth control, the progeny cells continue to divide and, depending on how fast and where this growth proceeds; the characteristic lump is eventually detected. Often one or more sequential mutations are required to trigger the process. This is where ultraviolet light (skin cancer) or the coal tars in cigarette smoke (lung cancer) play a role as 'co-carcinogens' by inducing DNA damage and mutations.

In genetic terms, tumors are both selfish and dumb. The tumor genome is 'selfish' in the sense that it takes no account of the needs of the tissues, the organ or the sensate being that surround it. Due to genetic changes, it has broken free of the normal 'social controls' of the body, like contact inhibition. It is, in a sense, a cellular entrepreneur gone mad. The tumor genome is 'dumb' because it cannot ‘know’ that by killing the individual that provides the nutrients to support its own survival; it is also committing suicide.

Because the tumor genome is completely selfish, it will mutate and try to defeat any type of inhibitory mechanism. Gleevec, or any therapeutic agent, supplies an additional evolutionary 'pressure', favoring the selection of mutant clones that have managed to engineer a further escape from the drug. The solution in conventional cancer treatment is to use multi-drug chemotherapy, where each chemical targets a different molecular mechanism within the cell. This is the high-wall, prison-cell, ball-and-chain approach to containment. It is much less likely that the cancer will be able to develop mutational changes that defeat two or more different control pathways. This diversity of possible treatments will also need to emerge for the 'designer' drugs, like Gleevec, if we are to develop non-toxic, specific cancer therapies that are effective in the long term. Given the rate of progress and the science strategies that are already available, we can expect to see significant advances in this field of rational drug design over the coming decades.

Many infectious agents will also be on the 'designer' drug hit-list for this new century. Such compounds are already being used to counter influenza and HIV/AIDS, though there is always the danger that mutant viruses will escape and no longer bind the particular chemical inhibitor. Apart from the selective pressure applied by the drug, mutant HIV and influenza viruses are constantly emerging as a consequence of the need to defeat immune control. When it comes to viruses, we are dealing with biological entities that cannot be either totally selfish or dumb.

Viruses, unlike tumors, are not 'dead end' in nature. In order to grow and survive, they must be able to exit the body and transmit to other hosts. This requires the operation of many different molecular mechanisms, any of which might be damaged by a mutation that would simply allow the virus to escape drug or immune control within a particular individual. The 'designer' drugs Relenza and Tamiflu, for instance, specifically inhibit influenza virus growth by binding to a viral surface protein, the neuraminidase, which normally functions to allow escape from the cell it infects. Both these chemical inhibitors have now been in use for some years, and there are no signs that highly infectious, resistant mutants are emerging. If the lethal H5N1 avian 'bird flu' adapts to transfer from human to human, Tamiflu should provide an immediate first line of defence (see chapter 4).

The AIDS challenge for medical scientists is to develop affordable, effective preventive measures. All types of approaches are being tried, from the topical application of lemon juice and more sophisticated formulations that can be used by women to prevent transmission, to the development of very complex vaccines. As I discussed earlier in the book, the results with experimental vaccines have so far been extremely depressing, and it is likely that some major, new conceptual breakthrough will have to occur before we see even the possibility of a solution. I am personally involved at one level or another in three different programs, two in Australia and one in the United States, and there is nothing that looks even remotely like a certainty.

One problem is that, unlike the influenza virus that is completely eliminated within one to two weeks of exposure, HIV both persists and mutates to avoid immune control. Another is that there is no mouse model of AIDSthat we can use quickly and cheaply to try new immunization strategies, while the HIV-like viruses that infect non-human primates seem not to provide a perfect mimic ofthe human disease. Even so, this is the best we have and itis unlikely that a candidate vaccine showing little protective effect in preliminary monkey studies will be of muchvalue for people. The result is that the only true test of anovel AIDS vaccine is to do human trials in endemic areaswhere the disease is currently spreading. Such studies arepolitically and strategically complex, and very expensive.

This is where I will spend the remainder of my scientific career, trying to develop a better understanding ofwhat is going on during the course of immune responses toboth influenza and HIV infections. I referred earlier to a recent WHO estimate concerning a potential pandemic: it suggests that even with modern drugs and improved vaccine technologies, there could be in the order of 72 million deaths if an influenza virus as severe as the current H5N1 infection in birds breaks across into the human population and causes a global pandemic. At the 2002 mortality rates, which are increasing, that would equate to twenty-four years of AIDS deaths. These are sufficiently important problems to keep me going, as I said before, as long as col- leagues think I am still contributing to innovative science.

Another infectious disease problem that is ofimmediate concern is the rapid development of antibiotic resistance, leading to the emergence of conditions like refractory tuberculosis, 'golden staph' and necrotizing fasciilitis, the latter caused by 'flesh-eating' variants of the ubiquitous type A streptococci. Here there is cause for considerable optimism. All the antibiotics in common use are, in fact, natural defence molecules used by a few species of bacteria and fungi. There are millions of different micro-organisms that could potentially provide novel products that operate in quite different ways. Apart from that, a combination of more traditional 'reductionist science' and genomics approaches is allowing us to identify a whole spectrum of new defence mechanisms used by species as diverse as termites and trees. Using modern techniques, the genes coding such a molecule can be cloned, then made to express the protein of interest in bacteria so that it can be screened for possible effects on the various bugs that plague us and our domestic plants and animals.

Craig Venter, the scientific visionary who contributed enormously to solving the human genome in record time, is currently sailing around the world on a yacht sampling all the life forms in the top two meters or so of the sea at various locations. His team negotiates questions of 'owner- ship' with the various governments that lay claim to the different sampling locations, then uses genomic approaches to probe the total genetic spectrum for the different plankton and so forth that are retained on filters of diminishing pore sizes.

Even at this early stage, they have identified what could be the basis of novel photosynthetic mechanisms, raising the possibility that there may be revolutionary, non-polluting ways of solving the sunlight to energy equation.Perhaps a team of innovative molecular biologists could use one of these new plankton genes to make bacteria that convert the energy of sunlight to hydrogen in some noveltype of fuel cell. On a more mundane level, what the Venter team is also doing is providing extraordinarily valuable 'biota' baselines against which the effects of global warming in the oceans can be sequentially measured over this coming century.

Not all advances in medicine and so forth will necessarily depend on the use of modern molecular genetics and genomics. China, in particular, has gone back to look very closely at the active principles in their traditional natural medicines. A recent development is the very effective anti-malarial artemisinin, which is currently in short supply because it has to be made from plants growing on Chinese and Vietnamese farms. As related in *Science* (7 January, 2005), the Bill and Melinda Gates Foundation recently committed $40 million to developing genetically modified bacteria that will churn out a precursor of the drug. In addition, knowing the nature of artemisinin has allowed the chemists to make variants that work even better. A former colleague from Canberra days, Graham Johnston at the University of Sydney, is also in the business of identifying the key ingredients in natural herbal medicines. As he pointed out to me, these 'natural medicines' tend to be fairly weak drugs. If this were not so, the variations in growing conditions, life cycle and so forth could lead to differences in the concentrations of the active chemicals in the plant that might result in overdose and toxicity.

The challenge with these drugs of plant origin can be that, even when the elements are identified, the chemistry required to make synthetic analogues may still be too difficult. Again, this situation is likely to improve through the years to come, and is a challenge for aspiring young chemists.

Dealing with complexity may be the major challenge for science in the twenty-first century. Understanding and manipulating the complexities of infection and immunity, or of cancer immunity, provides a continuing, major research focus for those interested in vaccines and therapy. Genomics and the array techniques of 'discovery science' have opened the way to scan the totality of the complex genetic 'read-out' in a cancer cell or an activated T lymphocyte. Through the latter part of the twentieth century we had great success in the type of reductionist science that looks at the different parts of various molecular pathways. This will continue, with the discovery of novel genes and molecular interactions forming the base of many new scientific careers. The big questions may be concerned, however, with putting the whole molecular machine together to explain function at the level of the cell, the organ and the organism. As yet, though the triumphs of medical science have been extraordinary, we haven't even answered such simple questions as what makes a liver grow to the shape and size of a liver.

The great complex and mysterious system that defines all of us is, of course, the human brain. Here we can expectenormous advances in understanding over the next hundred years. New insights will undoubtedly come frommolecular biology and genomics, where individual genes and/or predictable profiles of multi-gene read-out will be associated with both physiological abnormalities andpsychosomatic disorders, or mental illness. Deciding whatto

do with such information may not always be straight- forward. Applying new targeted therapies that alleviate debilitating conditions like schizophrenia or epilepsy mightseem to raise no obvious problems, but how does society handle a situation where an individual's DNA pattern isassociated with, for example, a tendency to extreme violence and criminality?
The question has already been raised by the genetic correlation between monoamine oxidase A promotor(MAO-A) polymorphism (genetic variability) and a tendency to violent, antisocial behavior for people with a particular MAO-A genotype. We can't lock people up on thebasis of a tendency. If possible candidates (or their parents) who have committed no crime refuse to be tested, how isthis to be handled both legally and ethically? Perhaps sometypes of severe crimes could be totally prevented byidentifying potential offenders as children then providing appropriate counseling or drug therapy; but does society have aright to insist on such intervention in those who constitutea clear risk? On the other hand, if such a genetic predisposition is first identified after the event, is it legitimate touse severe punishments against people who could be saidto be trapped by their underlying biology?

Even the schizophrenia and the epilepsy examples are not as simple as they may seem. Though individuals and their families would clearly benefit, effective treatment may also eliminate certain elements of the cultural dynamics that have shaped human society. Most would agree that we can do without either of these debilitating conditions, just as we have no reason to miss diseases like smallpox. How- ever, though treatment with the appropriate psychoactive drugs might indeed have saved Vincent Van Gogh's ear, would this have been at the expense of his artistic vision and creativity? There is little doubt, I think, that most schizophrenia sufferers would gladly accept any such loss if the medication allowed them to function normally in society.

Temporal lobe epilepsy is frequently associated with episodes of profound spiritual experience. Neurologists have argued that the account of St Paul's revelation on the road to Damascus is, in fact, a classical description of such an epileptic seizure. How different would the history of Western civilization be if we could time-travel back to the beginnings of the Christian era and give St Paul the twenty-first-century epilepsy therapy that may be just around the corner? What do we lose if a more sophisticated understanding of brain function leads to the implantation of electronic chips, or to an extensive pharmacopeia, that modulates the more distressing and debilitating extremes of the human experience? Again, I believe the majority of those who are subject to epileptic episodes would opt to give up the possibility of a spiritual revelation for well-being and the right to hold a driving license.
Many, if not all, forms of drug addiction are likely to have a basis in how a particular individual's nerve cells respond to the various neurotransmitters. These are the chemical signals that pass from one nerve cell to another to stimulate the electrical activity that allows the brain to function. A key neurotransmitter is dopamine. Parkinson's disease, which is classically characterized by tremor, a stooping gait and slowness to initiate and maintain movement, is due to the loss of many of the dopamine-producing nerve cells in one particular region of the brain, called the substantia nigra. These patients are treated with a drug that substitutes for dopamine, L-dopa. On the other hand, people suffering from schizophrenia may have toomuch dopamine and benefit from being given

dopamineantagonists that block neurotransmission and thus over-stimulation. Cocaine can inhibit dopamine removal, leavingmore around to give continued stimulation. The mono-amine oxidase inhibitor that we met earlier, when talkingabout the genetics of violent behavior, normally functionsto break down dopamine.

It would not be surprising if the application of modern genomic screening, the gene chips that we discussed in relation to cancer, reveals genetic profiles associated with neurotransmitter levels, sensitivity, and so forth that deter- mine the susceptibility of any given individual to drug or alcohol addiction. Many of these conditions are likely to reflect the interaction of multiple genetic effects or, as they're known in the genetics trade, complex traits. Knowing that someone is born with a genetic predisposition should lead to more focused education and prevention programs, while understanding the nature of the molecular targets is likely to result in the development of better therapeutic agents.

The nature of drug delivery systems should also improve. Nowadays, if we take a tranquilizer or a sleeping pill, the active chemical is distributed through the blood and binds to the appropriate receptors wherever they may be. Perhaps the application of nanotechnology approaches will lead to the development of drugs that are molecular machines destined to go only to where they are needed. It's the difference between using police to find an offender in a big crowd at a football game, or sending a couple of detectives to a house the guy was seen entering half an hour earlier. The process is both more economical and less likely to result in unhappy side effects.

The other big challenge when it comes to brain function is posed by degenerative neurological conditions like the pre-senile dementias, Alzheimers disease and so forth that are an increasingly serious plague in the elderly. The dementia epidemic reflects that human beings-in the developed countries, at least-are living longer than they did even thirty years ago. A lot of this is a direct result of improved preventive treatments for cardiovascular disease. What happens in a condition like Alzheimers is that wrongly folded proteins accumulate in, or around, the irreplaceable nerve cells and eventually poison them: think of the tarry gunk from an oil spill at sea that is washed ashore and chokes the plant and animal life.

One approach is to immunize with one of the offending gunk proteins, called amyloid, so that it can then beremoved by the resultant immune response (discussed in chapter 4). However, this has so far proven to be too dangerous. It worked well in mice that were geneticallymodified to express human amyloid protein in the brainbut, for obvious reasons, the initial human trial focused on people with advanced disease. At that stage, there is so much amyloid around that the immune cells that invadefrom the blood cause severe symptoms as they try to get ridof it. The best solution is likely to be the development of a small molecule (a drug) that will block the folding process.Even if this only served to delay the onset of symptoms,the benefits not only in terms of alleviating human suffering but also in health economics would be enormous.

One certain development through the twenty-first century is that the different scientific disciplines will workmore closely together. This is hardly a new trend, but whatis new is that major institutions are taking active steps tofacilitate interactions between those who come from different science cultures. The history of Nobel Prizes showshow significant this interaction can be: the first NobelPrize in Physics was awarded to Wilhelm Roentgen for discovering X-rays and the invention of X-ray crystallography by William and Lawrence Bragg led to structuralbiology, which has been recognized by a number of NobelPrizes and continues to contribute massively to biology andmedicine. The 2003 Medicine Prize went to the chemistPaul Lauterbur and the physicist Peter Mansfield for thedevelopment of magnetic resonance imaging (MRI). NobelPrizes for Chemistry are frequently given for discoveriesand technological developments that have their majorapplication in biology, the two awards to Fred Sanger forprotein and DNA sequencing being a case in point. Breakthroughs often result from bringing fresh minds trained in different fields together for some common purpose. Rolf Zinkernagel had taken a course that emphasizedcurrent thinking in immunology, but I had worked previously in virology and pathology and we were both ingénus at the time we did the key experiments and thought 'outsidethe box' about immune recognition. Established theoreticalphysicists like Erwin Schrodinger (Physics, 1933) and Max Delbruck (Medicine, 1969) made substantial contributionswhen they switched their interests to biology.

Max Delbruck worked at Caltech after he fled the Nazis, but in 1945 he also started a summer course on the genetics of bacteriophages (viruses that infect bacteria) at the Cold Spring Harbor Laboratory (CSHL) on LongIsland Sound, New York. The bacteriophages were the initial research tools that led to the current era of biotechnology and molecular medicine. The summer courses at CSHL continue and-still an intellectual powerhouse – it is legitimately regarded as the ancestral home of molecular biology. A picture on a wall at CSHL shows a very young Jim Watson, of Watson and Crick fame, working there in a summer job as a waiter, while he was a course participant. Jim later served as CSHL director for more than twenty- five years and was also the first director of the US federal human genome project. He continues in a senior role as CSHL President, and was succeeded as director by the JCSMR-trained Australian virologist, Bruce Stillman. Max Delbruck, Al Hershey and Salvador Luria shared the 1969 Nobel Prize for Medicine, for their 'discoveries concerning the replication mechanisms and the genetic structure of viruses'. Al Hershey worked at CSHL, and Salvador Luria was Jim Watson's PhD supervisor at the University of Indiana.

There will be similar science stories through the twenty-first century, though only a science fiction writer could guess at the fields of interest, who the characters might be and how the stories may unfold. Apart from improving the human condition, science has a job to do in protecting humanity and the world we live in. What could be the ultimate threat? We have to hope that no person or group is crazy enough to start a nuclear war. One theory to explain the extinction of the dinosaurs is that there may have been a massive asteroid hit, creating such a storm of atmospheric debris that the life-giving rays of the sun were blocked out. No doubt the probability is low, but what could, or would, scientists do to prevent a recurrence? Perhaps we couldn't stop the hit, but might it be possible to work out how to be independent of solar energy until the dust cleared? We must continue to stretch both our imaginations and our understanding to the utmost. If we want our species to survive in the long term, human beings cannot afford to stop reaching for the stars.

CHAPTER 9: How to Win a Nobel Prize

So you want to win a Nobel Prize: to become famous, powerful and maybe even very wealthy? If that's your ambition I can't help you. There is no instruction manual or course that can guide you to a Nobel Prize and, numerically speaking, most of us have more chance of winning an Olympic gold medal. There's also another difference: an Olympic medalist might go on to win a Nobel, but can you imagine Albert Einstein or Bertrand Russell competing in the decathlon? I was brutally reminded of this when I had to present a large cheque to Michael Chang for winning the St Jude Tennis Classic in Memphis. We were both winners in one sense or another but, though Michael might conceivably change his life at some stage to become a great scientist or writer, there is no way that I could ever beat even an 85-year-old Chang or Sampras on the court.

Now that I've had your attention and you have read this far, I hope you will recognize something of what it takes to make an outstanding research scientist. It involves a personal recognition that humanity advances by insight, discovery and a capacity for serious effort and commitment. So, following what I've written here won't guarantee a trip to Stockholm or Oslo, but, with a little luck, it could lead to something worthwhile.

Try to solve major problems and make really big discoveries

The individual who is well educated, works enormously hard and has inherited extraordinary ability and intellectual capacity might just conceivably be able to identify a major problem at the Nobel level of achievement, then move ahead to solve it. From my experience such people are pretty rare, and may well be either alien life forms or the next stage in human evolution. Discovery is different. Nobody can decide to discover something, but there are ways of making a discovery more likely. Focus on generating new information and insights and look for unexpected outcomes and results. Accept nothing at face value and get in the habit of thinking unconventionally. Work hard, work smart and, with a bit of luck, serendipity will play its part.

Be realistic and play to your strengths

A trained veterinary surgeon like me knows, like all punters, that there are horses for courses. Everyone has to find out what sort of horse they are. Anyone with a brain that does best at ploughing long, straight furrows should give up on the idea of being an intellectual polo pony or steeplechaser. Perhaps a molecular biologist or organic chemist can also be a poet, but it's likely that most will do a lot better at one than the other. Science at its best is for people who love to ask questions and are delighted by discoveries that over- turn established ideas and prejudices. If they have to choose between authority and evidence, basic scientists will always go with the evidence. Most scientists are notoriously contemptuous of authoritarian politics, for example. Any love affair between science and politics is always fraught with potential conflict, though the passion and betrayal that characterizes tempestuous affairs often makes the best theatre, or press-as is usually the case.

Acquire basic skills and work with the right people

The elements that make an exceptional humanitarian or writer can be as varied as the individuals themselves – apart from the obvious ones, like a keen intellect and a serious sense of commitment. On the other hand, scientists have an absolute need for in-depth, specialist training at the university undergraduate level and beyond. Though it's not essential, it helps to be born into an intellectual and supportive family, grow up in the United States, Europe, Japan, Canada or Australia, attend an academic school and a great university, and train with a top person. Some aspirants try very hard to work with a Nobel laureate, as they have the right to nominate people for Nobel Prizes – and only those who are nominated are considered. Senior scientists like to think that they create enduring 'schools', so it can help to be part of such a lineage. None of these factors, however, will guarantee a Nobel. Sometimes the idiosyncratic outsider will rise to the top over those within the big tent of mutual reinforcement, where it can be too warm and too comfortable. Thank goodness for that. Otherwise science would be a stuffy and obsequious business.

Learn to write clearly and concisely

Many people who are very good at science are great doers, but uninspired writers. It isn't necessary to be a Shakespeare or a Michael Ondaatje, but anyone who wants to be recognized as a top scientist must be able to write clear, concise English. English is the language of science and manycountries, among them Malaysia and Singapore, that are building their science profiles teach in English at school and university level. Science is about telling good, readable,memorable stories.

Work in an appropriate field

Nobel Prizes recognizes some, but by no means every, aspect of what we may think of as the high culture of humanity.There are no Nobel Prizes for the visual arts, for music orfor dance, so these might be fields you would want toavoid. The performing arts have been recognized onlytwice, to my knowledge, by the 1997 Literature award tothe Italian playwright Dario Fo and the 1953 LiteraturePrize to the British leader Winston Churchill, who was, of course, a noted orator as well as a writer-although thepublic advocacy required of many Peace laureates as they seek to promote their particular interests might be considered partly under the head of 'performance'. For scientists, speaking about their work to both specialist andbroader groups is an essential component of receiving creditand building a reputation. You and your work will remain anonymous if you just stay home.

You will also need to exercise caution in the area of science you work in. While some areas of research are notspecifically identified as targets for Nobel Prizes, they may slip under the wire in another category. Though puremathematics may have been excluded, theory based inmathematics is clearly central to physics and economics, asexemplified in the Economics awards to John Nash in 1994 and James Mirlees in 1996. Geology, for instance, is not specifically identified, but it is possible that someone who trained primarily as a geologist might be honoured for contributions to physics or chemistry.

There is no agriculture prize, but plant scientists who have been recognized include the wheat breeder Norman Borlaug referred to earlier, who won the Peace Prize in 1970 for the part he played in what has become known as the green revolution; the agricultural scientist and research administrator John Boyd Orr was awarded the Peace Prize in 1949 for establishing the FAO; and the plant geneticist Barbara McClintock the Prize for Medicine in 1983 for jumping genes in corn. Still, anyone who is set on the idea of a Nobel Prize would probably leave the plants to some- one else. Otherwise, there is a world food prize.

Find and cultivate your true passion

Despite everything I've just said in the above, one of the best things that can happen in life is to discover a line of enquiry that really grabs your interest. Someone who hasfound a passion that doesn't fit the Nobel, or any other mould that conventionally leads to the 'glittering prizes',should forget the award and go for the satisfaction and theexcitement of what they love doing, whether it's philosophyor building surf boards. That's where the prizes that really matter are to be found. According to the poet Ezra Pound,who would certainly have been ruled out of considerationfor a Nobel Prize because of his fascination with Mussolini's fascism, 'What thou lovest well remains, the rest is dross'.Preoccupation with dross and irrelevance is a sure-fire way to avoid the Nobel Prize. Most of those who do win have not only achieved over a long period, but are likely to have given their full attention, energy and enthusiasm to what they do. On the other hand, a passion for working out mechanisms for usefully recycling the dross of packaging, junked cars and so forth that we produce in our daily lives could lead to one of the numerous environment prizes that can be identified by searching the web.

Focus and don’t be a dilettante

Most scientists and economists are identified with a particular sub-field of investigation for much of their lives. Sometimes the best scientists will take on new challenges, but the majority-and particularly the prize winners- tend to remain within the same broad field, like cancer biology, neurobiology or immunology, where they are well known and regarded. Bright people who hop around from one topic to another often achieve very little.

The exception may be the Nobel Peace Prizes. Concentration of effort may be required only in the relative short term for the humanitarian who wins a Peace Prize – thesuccessful resolution of a major confrontation, for example, can depend on an individual's political power or stature as a negotiator. These credentials are likely to have been achieved in a completely different context, such as being US Secretary of State: Cordell Hull, Peace Prize, 1945; Henry Kissinger, Peace Prize, 1973. Other causes, like the elimination of landmines, gain traction only because someone like the 1997 Peace laureate, Jody Williams, is totally dedicated to finding a solution. The novelist or the poet may contribute in a variety of forms, though their style and approach may be consistent. Writing itself is the most intense of human activities. Again, it's all about intensity and commitment.

Be selective about where you work

As a scientist, your chances of achieving anything can be greatly diminished by working in an institution that isunder-resourced financially, does not value creativity or demoralizes even the bright people that it manages torecruit. The places that nurture winners don't all look thesame, and can vary from small private institutions like Caltech, to massive Ivy League conglomerates like Harvard University, to state institutions like Southwestern MedicalSchool in Dallas. Every one is different, so find an environment that suits your personality and work habits. Being inthe regular company of colleagues who are stimulating to talk to and living in a culture that values creativity and insight contribute mightily to a satisfying life, even if the big prize doesn't come your way.

Value evidence and learn to see what's in front of your nose

In the end, science is about data and being able to 'read' the real meaning of what you find. Keep an open mind, be pre-pared to think laterally, and be instructed by nature and observation. Great literature and visionary science share a characteristic: the reader recognizes that there is a sense of truth. The resolution of conflict or the navigation of animpasse that has been achieved by a Nobel Peace laureate also reflects a capacity to recognize, then act on the under- lying reality. Such people bring to the task not only a substantial intellect, but also a clear perception of what can be achieved.

Think outside the box

Following the obvious path is not likely to lead to a novel question, interpretation or solution. If the way is both straight and narrow, the odds are that somebody else will have gone down that road. The mind works in strange ways, and it can help to short-circuit, or bypass normal thought processes. Edward de Bono formalized one such technique when he identified the 'lateral thinking approach. When struggling with a scientific problem, it often helps to 'draw' the possibilities, either in your mind or on a piece of paper. Human beings think in both words and pictures. Illuminating ideas come at odd times, In the shower, for instance, or on the top of a mountain. Ilya Mechnikov, who won the Medicine Prize in 1908 discovered phagocytosis when, bored and at the beach, he poked small thorns into starfish larvae and watched the inflammatory cells congregate at the site of injury. Get rid of the clutter, and let the mind roam.

Physical activity, even if it's only walking, work to free the thought-processes. New ideas often seem to pop up when the mind is idling or half-concentrating on some more mechanistic activity, like gardening or building a bicycle shed. The 1993 Chemistry Prize wino Mullis, describes in his autobiography *Dancing Naked in the Mind Field* how the idea of the polymerase chain reaction came suddenly when he was tired and driving alone at night. This won't happen to you if your brain isn't grinding away at the problem in the background, which only happens if you are very attached to the particular question – obsessed even. Ask anyone who is married to a serious scientist, and you're likely to get into a discussion on the nature of obsession.

Talk about the problem

Don't be a lone wolf. Two heads are often better than one. The most obvious way to develop novel insights is to talk with others, particularly those who come at the issue fromdifferent backgrounds. Jim Watson's little book *The Double Helix* gives a strong sense of the intense interaction atCambridge's Cavendish laboratory between the biologist(Watson) and the physicist Francis Crick (Medicine, 1962) as they tried to build their DNA model. The essential information that they had been using the wrong tautomericform of the DNA bases came from Watson's chance conversation with a visiting American, the crystallographerJerry Donohue. Without knowing this they were stuck.Though Rosalind Franklin took the key X-ray pictures thatprovided the solution for Watson and Crick, she and herKing's College, London, colleague Maurice Wilkins failedto develop a rapport. Rosalind remained very isolated and she did not solve the DNA problem.

There is a caveat. If you make a major discovery that could easily be repeated by others, it's best to keep quiet about it until the initial research report is either published or 'in press' in a top journal.

Australia is different now, but Rolf Zinkernagel and I benefited back in the 1970s from the isolation of this 'distant shore'. Talking openly in the local immunology discussion group, the weekly 'Bible class' run by the department head, Gordon Ada, certainly helped to clarify our thinking. That would be much riskier today: Australia is definitely in the scientific loop, and national and global communication means people can hear about a discovery almost the instant it is made..

Tell the Truth

Telling the truth about data is an absolute requirement inscience. Apart from being the ultimate betrayal of scientificethics, a lie can set everyone on the wrong course-includingthe perpetrator. The public revelation of such deception islikely to destroy a career. Those who withhold credit mayget away with it for a time, but they run a risk if they wantto be recognized ultimately as luminaries in their field.

Be generous and culturally aware

Freely acknowledging the achievements of others is a sure sign of someone who is confident of their own worth and integrity. Give credit where it is due and acknowledge the work that came before yours and made your discovery possible. No senior scientist is ever hurt by giving precedence in authorship to junior colleagues who have done much of the hands-on work for a research paper.

Making virulent personal attacks on others in public, especially if the person concerned is young and inexperienced, can ultimately be counter-productive. Even if he or she is guilty of sloppy thinking or poorly presented data, it's easy enough to take someone aside later and talk through their conclusions. If they're obtuse and dogmatic, they will soon disappear from science anyway. Science is largely self-correcting, though this can take a while.

Though it is likely that a truly spectacular discovery or body of achievement will ultimately be recognized, nomatter what the personal characteristics of the recipient, there are situations where the decision could go either way.A record of vicious behavior, or a suggestion that the individual concerned claims undue priority, can seriouslydamage a case. With the Nobel Prizes, for example, thedecision can go to one field or another. There will always bealternative 'tickets'.

Be persistent and tenacious but be prepared to fail

The old 'Protestant work ethic' is true for science: nothingworthwhile is likely to be easy. If at first you don’t succeed, try, try, try again. Sayings like this pretty much describe the scientific life.

Every serious biomedical scientist will have had the experience of 'reverse alchemy', seeing what first looks like gold turn slowly into lead: an apparent breakthrough turns out to be a false trail that just can't be repeated in sub- sequent experiments. The process of moving systematically from high to low over an interval of weeks to months can be summarized by the Latin, *'sic transit gloria',* thus passes glory. When this happens to you-and it invariably will-see it as a good time to break the cycle, stop the studyand go to the pub or on vacation.

People who can't deal with failure, or can't acknowledge to themselves that they have been wrong, should probably avoid a life based in research. Nonetheless, it can be the case that those who are the most creative live on some sort of psychological edge. Such individuals have to develop strategies for dealing with the inevitable downs if they want to work in experimental biology. Sometimes theystart well, but just can't continue. Most scientists who'vebeen involved in leading a research effort over the long- term have had to deal with this type of tragedy.

Your time is precious

Winners and high-achievers will tell you that time is your greatest asset. It's accepted that novelists, painters and poets can be precious about protecting their creative time and space, but this territory isn't so clearly defined for those who do research for a living. Scientists work in large organizations and belong to global communities that organize meetings, and national and international societies. These things take up time! They are essential activities, and it is important that such roles should not be left only to those who are at the end of their careers. Even so, it is also necessary to be judicious and to set definite limits. 'Death by committees' is a particular trap for women scientists, who often have great negotiating skills but can be effectively drained by the demands of commitments, which may arise from the need for gender balance on this or that committee. That's fine for someone headed towards a career in academic administration, but such a commitment should be a conscious decision. When those committees come calling, just learn to say no.

Avoid prestigious administrative roles

Those bright people who accept a role as director, dean or president early in a career may well rule themselves out of the top league in the awards game. Leading a major institution is, of course, an energy-consuming activity. The same is true for running a major research program. My personal sense is that smart human beings commit themselves to what they like doing best. Some Nobel Prizes for experimental physics have gone to intellectually incisive, top administrators, but that isn't true for most areas of science. On the other hand, administrators earn the top dollars in the academic hierarchy, and those skills are increasingly in demand.

People who accept such posts sometimes win a Nobel Prize for work done earlier in their careers. Others who make the trip to Stockholm before they're too ancient often go on to be very effective university presidents or directors of prestigious research organizations. However, it's also the case that many who have the creativity and insight to succeed in research lack the types of skills and commitment that go into making an outstanding administrator. As Polonius in *Hamlet* would have it: 'This above all, to thine own self be true'.

Take care of yourself and live a long time

Given the nature of the Peace Prizes, a summons to Oslo is likely to come fairly soon after the achievement that is being recognized, but writers, scientists and economists may need to hang in there. It can take fifty years from the point of making a big discovery to the time that a Nobel committee comes to a decision that, at least from your point of view, is exactly the right one. Good habits start early: eat and drink moderately, take vacations, don't smoke or over-use recreational drugs (alcohol included), take regular exercise, avoid extreme sports, and seek professional help for suicidal thoughts. Scientists are a varied bunch and I know of very talented and effective individuals who have been taken out by each of the above factors. Given a way of life that is often more solitary, creative writers are likely to be even less armored against such dangers. Have fun, behave like a winner. See all the above.

On a more serious note, I want to emphasize that, while doing the type of work that leads to Nobel Prizes inevitably has its low points, on the whole it offers immense fulfillment. There can surely be no better feeling than the sense of having achieved an experimental result, or written a novel, poem or scientific paper that is personally satisfying, substantial and accessible, and is out there for the scrutiny of others. Nothing offers greater intellectual excitement than discovering something that no human being can ever have known before. Being able to live in a way that combines work with at least a measure of creativity is an immense privilege. My continued involvement in experimental science reflects this passion for discovery. Only a lunatic would expect to win a second Nobel Prize, so thatcertainly isn't the motive.

This is ultimately what science is about. Like most scientists I work in big institutions where, increasingly andinevitably, I don't know all the players, especially the younger ones, though they recognize me. If, for instance,I ride up alone in an elevator with some young postdoc whom I may never have seen before, I ask: 'How is it going,and what are you doing?' The invariable experience is thatthey are delighted to be asked and are just bursting to summarize their particular science story. For those with theright mix of curiosity and commitment, the sense of probing a difficult question, of uncovering some basic-though maybe small-truth gives the greatest possible satisfaction.It isn’t for everyone, but for those who get the message thisis a good and honest way to live.

ENDS