

## Chapter 1

# Getting Started

*If politics is the art of the possible, research is surely the art of the soluble.  
Both are immensely practical-minded affairs.*

*The human mind treats a new idea the same way the body  
treats a strange protein; it rejects it.*

Peter B Medawar, *The Art of the Soluble* (1967)

Everybody wants a better life for themselves and following generations. It is not difficult to agree on the necessity to improve the quality and availability of health care; that many people do not have enough to eat; our environment is a mess; that production of high quality food is important. Can gene technology help with any of these problems, or will it make things worse? Peter Medawar was awarded the Nobel Prize for his work on the rejection of foreign proteins by the immune system. He points out that people treat new ideas in the same way. Thus, the responsibility to change public opinion rests with people who understand the technology. This is a daunting task but there is an urgent need for everybody to have a better understanding of this new technology. Genetics is telling us more about evolution, the migration of ancient people across the globe and providing a new level of accuracy in forensic applications. We now face the prospect of treating genetic diseases by gene therapy. What are the risks to the individual and future generations? Farmers, for centuries, have been very good at breeding to improve their crops and stock and have done this without a detailed knowledge of how genes work. The advent of genetically modified plants has put them in a dilemma. Do they grow them or not? If they do, will it threaten their environment? Will they be able to sell the product? I will not answer all these questions because there is not always a simple answer, but an

understanding of the basics of genes and genetic engineering will help in these decisions.

The two quotes from Peter Medawar give an indication of his writing, which has been very influential amongst my generation of scientists. His simple clear prose changed the way many of us think about science. Although the perceptions have remained the same, things have moved on since Medawar was writing and we start this book in the midst of a genomics revolution. This is a coordinated effort to unravel the details of all the genes in the genome of different microbes, plants and animals. A massive volume of information is accumulating and spawning new words with the suffix *-omics*. This information is being assembled in super computers with information about proteins (proteomics) and metabolic pathways (metabolomics) and many other aspects of life in what the boffins call *systems biology*. This aims to bring together all aspects of life into an integrated overview, which can be interrogated to provide a basis for modification by drugs, chemicals or management to improve the quality of life. The science is exciting and challenging, and is indeed an immensely practical minded affair. Medawar would have loved to be involved in this new technology and the public debate, which surrounds it.

Prince Charles, future King and head of the Anglican Church with a corresponding large influence on public opinion in the UK, and the owner of a large company producing organic food, said only God should modify genes. It is hardly credible that he would seek to stop research to understand how genes work, which requires the production of a very large number of modified genes. Would he argue against modified genes, which can improve the life of children with hereditary diseases? After all, his family in an attempt to keep a pure “royal” lineage have had too many consanguineous marriages resulting in a higher frequency of genetic diseases. What about genetic modifications that can help clean up industrial pollution? Genes are continually being changed or *mutated*, by random errors in the normal copying of genes from one generation to the next. Mind you, it is not a big deal, mutations are very rare and only mutations in germ cell DNA is passed on to the next generation. This provides a basis for natural selection in evolution, and for the breeding of new crops and domestic animals. This natural change was not fast

enough for plant and animal breeders and so, before genetic engineering, genes were modified by exposing organisms to chemicals or irradiation. This increased dramatically the rate of *mutation*, and new traits appeared more frequently. Any useful traits could be selected by traditional breeding, but of course, there would be many mutations and traditional breeding would not separate completely the desirable from the undesirable. Genetic engineering allows this to be carried out in a targeted and precise manner, which means organisms can be modified in a shorter period of time and with less likelihood of unwanted genetic changes.

We have to face the fact that, like Prince Charles, many politicians and activists have not had an education in science, and yet are involved in making or negating policy. The Prince visited the Institute where I worked in Perth. Instead of trying to learn from the group of medical experts around the table, he insisted on pushing the value of “alternative medicine”. It did not go over well with the group of clinical scientists who spend their lives assessing new treatments in controlled clinical trials. None of us have a problem with “traditional medicine” which has given the world a number of important chemicals such as the anti-malarial drug quinine and the insecticide pyrethrum, and there are undoubtedly many more to come. The problem is that very few have been submitted to proper clinical trial. I am astonished that there are many people who worry about the health effects of genetically modified plants, which are submitted to detailed safety analysis, but will include alternative medicines in their diets that have not undergone any testing.

Coming from a medical research background, my interest in genes was widened when I became the owner of a small farm near Albany on the south coast of WA. I joined a small group called the Rainbow Coast Commercial Horticulturists. While the name is reminiscent of something from a Gilbert and Sullivan operetta (‘rainbow coast’ refers to the beautiful climate of this region), the group is serious and reflects the way farmers across the world get together to share experiences. This group includes a cross section of farmers from organic (organicos) to high tech (technicos). My own farming efforts in viticulture, and visits to farms where families earn a living producing food, brought home to me that most consumers have little idea how food is produced, and how precarious is the production of this most important product. It also taught me a

little about the balance between the environment and food production and stimulated my interest in sustainable agriculture and the relevance of GM plants. I will argue that the sustainability credentials of certified organic farmers is somewhat exaggerated. It is a pity they have not encompassed GM plants, many of which will surpass their best intentions of achieving sustainable farming. Unfortunately, the organic movement provides much of the anti-GM activism and as such, I think it is important to scrutinise their claims and to counter their arguments, which, especially in relation to GMOs, are not based on balanced information.

The final decision to write this book came when I attended a high profile biotechnology conference in the USA. A large number of anti-biotech demonstrators were expected and an army of police were there with anti-riot gear and automatic weapons. They far out-numbered the demonstrators who were herded into a compound with a high fence, where they sat under a large black balloon with GENE painted on it and sang songs and shouted slogans. In the face of this intimidation, I felt sympathy towards them. They want what we all want: to make the world a better place for our kids. Unfortunately, for them, the balloon was a bit simplistic and their slogans made little impact. Sadly, many people have opinions, but little knowledge, on everything from genes to nuclear power.

I have been close to the coalface of genes and genetic engineering in medical research, and have seen the technology evolving at a rapidly increasing pace. It's hard to keep up with, even when directly involved in research. This technology is impinging on all aspects of our lives and is too important to be left to professional lobbyists and activists. We all need a basic understanding, and it is not difficult. I am an enthusiast for the potential of genetic engineering. I regard it as another step in the long history of human endeavour, but like many technical developments has the potential to be used both wisely and unwisely. Everybody who wants to have an input into the debate needs to be able to present an informed argument. Slogans are not enough. If at the end of the book you are against genetic engineering, but can admit to a better understanding of the issues, then I have achieved my aim.

## 1.1 Scientific Jargon

It is all too common to present science in a watered down version for the general public, but the language of science is part of science. I once had to give an interview about my work, which is about eosinophils and asthma. A colleague advised me not to mention eosinophils, as people would not understand. I disagreed: people want to know about asthma, and eosinophils are important in asthma, so they need to know what they are (it's explained below). Scientific jargon is usually based on a characteristic of the molecule or process. Some of it is quite clever and informative; some is difficult and hard to remember. Understanding DNA is no easier if the building blocks are called letters rather than *bases*, which is what scientists use.

Take interleukins (shorthand for hormones acting between blood cells), which was a name invented to rationalise an increasingly complicated field as new immunological molecules were discovered. When my group identified a new molecule, we called it "eosinophil differentiation factor", to describe its function, which is to stimulate the production or *differentiation* of eosinophils from bone marrow *stem cells*. At a time when new molecules were being discovered rapidly and many were found to have overlapping functions, it appeared sensible to have a common numerical system. That's how eosinophil differentiation factor became interleukin-5 (IL5), but the system has not been very successful as there are now large numbers of interleukins, and the name gives no indication of the function. Indeed, there are increasing calls from scientists for revision of the naming of genes. Many have been given irrelevant or skittish names by the researchers who discovered them and which are an impediment to an already immense and complex field. However difficult scientific jargon can be we have to live with it. Every occupation has its own jargon, and we all have to learn some of it. If we own a car or a computer, we will have learned some of the jargon necessary to use and maintain it. Don't be intimidated by scientific jargon, get used to enough of it so we all speak the same language.

So let's start with some basic definitions. **Organisms** are things that exist as a living entity. We are organisms. The paper you are looking at came from another organism, a tree. The basic units of organisms are

*cells* that are minute membranous bags containing the machinery of life. Organisms vary from single cells to large aggregates of cells in plants and animals. In all organisms cells are made up of four basic substances; ***nucleic acids, proteins, carbohydrates*** and ***lipids***, and we will go into the details of their structure later. Nucleic acids are found in the nucleus (the “acid” tells chemists something about their structure, and has little to do with what goes into a car battery). There are two forms of nucleic acid, deoxyribonucleic acid (***DNA***) and ribonucleic acid (***RNA***). The D and the R tells a chemist about the molecular structure, and are not important to understanding function. It is easier to remember them as “Durable” and “Recycling” which better describes their function. I will now summarise the roles of the four basic substances of life as a primer for later chapters.

## 1.2 Nucleic Acids, Proteins, Carbohydrates & Lipids

### 1.2.1 DNA: The template

Genes are the genetic code written in the sequence of the four DNA base subunits. The genetic code provides both the regulatory elements, so the gene can be switched on and off, and the template for the production of proteins. Collectively all the DNA and hence all the genes is called the ***genome***. DNA can be thought of as the durable material in the nucleus. Durable because as each cell divides it produces identical copies of the DNA for the daughter cells, and these in turn will make copies of themselves when they divide. Thus, every cell in an individual contains the identical set of genes. This applies to all living organisms, so when you eat a tomato (even a cooked one) you eat trillions of tomato genes. There is no need to worry they get broken up by digestion, and the building blocks are used to make your own genes as tissues are replaced.

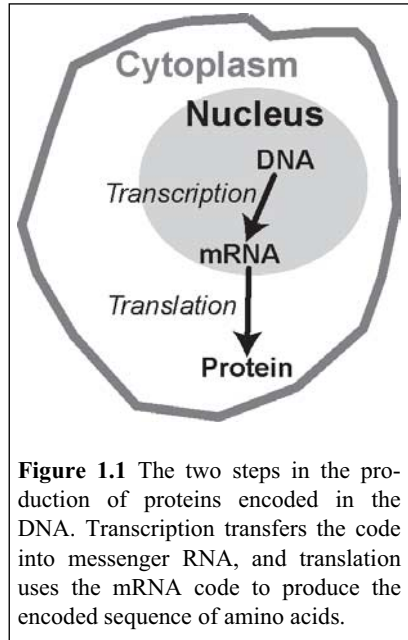
From the fertilised egg, cell division and differentiation produces the ***somatic cells*** forming the body of the new individual. Similarly, the genes in the ***germ line*** cells forming the eggs and the sperm remain stable from generation to generation (apart from a very low frequency of mutation). DNA is degraded when exposed to special enzymes. This can happen in the digestive tract or when tissues are damaged. Thus DNA is durable because it is protected and repaired in the cell. It is also protected

if the enzymes are destroyed or inhibited in the environment by freezing, dehydration or high salt concentrations. Thus, DNA can be extracted from ancient organisms especially those preserved in permafrost, and very large amounts accumulate in the salty water in the depths of the ocean.

### 1.2.2 RNA: The functional go-between

Like DNA, RNA is made up of four base subunits, but the structure is more fragile. Thus, RNA can be thought of as recycling: it is a fragile molecule that is degraded in the cell, and more is produced when required. The process from DNA to protein has two steps (Figure 1.1). The first step takes place in the nucleus; the genetic code in the DNA is copied into messenger RNA (mRNA) by a process called *transcription*. Think of the transcription of music from one instrument to another: the same tune (code) is maintained. The RNA then moves to the cytoplasm where it provides the code for the synthesis of proteins by a process called *translation*. The genetic code is now translated into a new language; a sequence of RNA bases to a sequence of amino acids that is a protein. These steps make up the basic dogma of life: DNA → RNA → Protein

Thus, RNA is the functional genetic material, but RNA also forms complex structures with biological activity. RNA can cut and splice itself and special *transfer RNA (tRNA)* molecules are involved in protein synthesis that takes place on large ribosomes that contain RNA. For these reasons, the first steps towards living organisms are thought to have been the production of RNA molecules. In addition, as we will see later, some viruses have RNA, rather than DNA as their basic genetic material.



**Figure 1.1** The two steps in the production of proteins encoded in the DNA. Transcription transfers the code into messenger RNA, and translation uses the mRNA code to produce the encoded sequence of amino acids.

### 1.2.3 Proteins: The structural and functional units

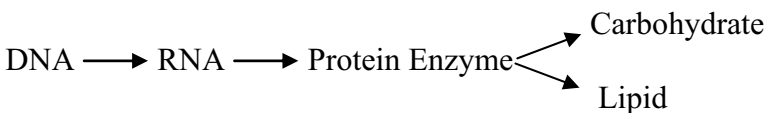
Proteins are the basis of the skin and muscles of the body, the antibodies and the albumin of the blood. They are the enzymes and the hormones that control and regulate the life of the organism. The building blocks of proteins are amino acids joined together in a chain. Unlike DNA and RNA that are made up of only four building blocks, there are 20 amino acids in the natural world. This allows for enormous structural complexity. Proteins come in all sizes and shapes. The order or sequence of amino acids making up each protein is determined by the genetic code in the gene (DNA), which is copied into RNA, and this in turn determines the structure and hence the function of the protein.

***Important concept: each protein is encoded by a gene, and the basic dogma of life is the order: DNA → RNA → Protein.***

### 1.2.4 Carbohydrates and lipids

Carbohydrates are chains (polymers) of sugars that have a carbon chain backbone. Unlike amino acids, there is an almost limitless list of sugars. Lipids are chains of fatty acids that have a hydrophilic head and one or more carbon chains that form hydrophobic tails. In water, they form micelles in which the tails point inwards and the heads interact with the water. They form the outer membrane of cells, as well as membranes of internal cell structures. Carbohydrates and lipids are not directly encoded by the genes. The genes encode protein enzymes that synthesize the basic units and link them together. We will come back to all these structures in more detail in Chapter 3.

***Important concept: whereas the structure of proteins is encoded in the genes, the structures of carbohydrates and lipids are not.***



### 1.3 Biotechnology

Biotechnology is the application of biological processes to technical production and can be said to have begun when people first found they could improve and preserve foods by fermentation. In European traditions, this includes cheese, bread and alcoholic beverages. A well-known Irish company that specialises in the production of Irish whisky uses the catch phrase “nearly 400 years of biotechnology”. An enviable claim indeed, but all human cultures have made use of fermentation, many over much longer periods of time. People have been making leavened bread or using fermentation to improve and preserve their cassava and other foods for centuries. It was not until the work of Louis Pasteur in the 18th century, that it became clear that they were manipulating microbes (such as bacteria and yeasts) from the environment to make these foodstuffs. Pasteur also showed that microbes caused infectious diseases, refuting the belief that they were caused by vapours or evil thoughts. Pasteur's remarkable work is commemorated in the institutes across France that bear his name. It is a moving experience to walk through the doors of the highly regarded, Institut Pasteur in Paris and see the display of items from the great man's laboratory. Beyond doubt, Pasteur was the first great biotechnologist.

There is no doubt that man has been very successful at using and adapting microbes to vary their diets; these days we use pure, stable cultures for fermentation, as everybody who makes bread or beer will know. Mind you, many families in the Anglo-Saxon tradition depend on yeast in the atmosphere to start their ginger beer fermentation. We acidify a sugar solution with lemon juice and leave it open to the air. The lemon juice inhibits many of the bacteria that would give it a foul taste. In all cultures, there are thousands of fermentation processes, developed over centuries to improve and preserve food, which depend on microbes blowing in on the wind. An important challenge is to identify and isolate the organisms involved in these fermentation processes. This will allow the production of stable starter cultures that will be more reliable and allow shorter fermentation times as well as giving control over the vitamins added to the food by the fermentation process. As microbes are relatively easy to genetically modify, we can look forward to a large

increase in the variety and quality of foods available, which one can only hope can be done to the benefit of all mankind, and not just the rich countries.

**Genetic engineering** (GE) is the buzz name for modifying DNA. GE is part of biotechnology. Modern crops and domestic animals have undergone major **genetic modification** (GM) by breeding over centuries. However, for clarity we will restrict the term GM to modifications of organisms made by genetic engineering. Thus, **genetically modified organisms (GMOs)** are living organisms that have been modified, in a permanent stable manner, by genetic engineering. It began so we could understand how genes work, but biotechnologists quickly realised that they could use the technology for medical and agricultural purposes. This is the basis for a large commercial, biotechnology industry. Some people prefer to call modified organisms genetically engineered organisms (GEOs) but I will use GMOs simply because I think it is more widely used. In some cases, and in some languages, GMO's are called **trans-genics**. There is a technical distinction that will become clear later, but the terminology is not as important as the message it carries. GM foods would be translated as "*comidas transgenicas*" in Spanish, but carry exactly the same message to the consumer, as GM food does in English.

## 1.4 Experimental Organisms

A very large number of different organisms have been used as models in scientific research. Scientists choose model organisms for experiments partly because they are cheap and easy to maintain in the laboratory, or they have some special property. The best animal for testing medicines designed for people are people themselves, but to minimise risk, medicines undergo detailed testing in other animals such as mice, rats or dogs and occasionally other primates. However, most genetic information has come from small relatively simple organisms. Here I give the scientific name in italics, and the name I will use in the rest of the book in bold. Firstly the microbes: the bacterium which we all have in our intestines, *Escherichia coli* (**E. coli**); bakers or brewing **yeast** (*Saccharomyces cerevisiae*; **saccharomyces** = sugar yeast, *cerevisia* = beer) which divides by

budding small offspring from the parent; **fission yeast** or African millet beer yeast (*Schizosaccharomyces pombe*; *pombe* = beer in Swahili) which divides by fission into two equal daughter cells.

Next the plant models: we will discuss Mendel's experiments in **sweet peas** (*Lathyrus odoratus*) which were the basis for modern genetics. As we will see, the success of these experiments was because sweet peas self-pollinate and so are totally inbred. In modern times, a small weedy plant, of little use to anybody, called *Arabidopsis thaliana* (Thale cress or **mustard weed**) has been the workhorse of plant genetics. Mustard weed has five pairs of chromosomes and very little junk DNA. It grows up to 30cm high, produces up to 10,000 seeds within 5-6 weeks of germination and is a powerful tool in plant research.

In animal genetics, two invertebrates: the vinegar or **fruit fly** *Drosophila melanogaster* is the workhorse. It has a short life span, is about 3mm long and has four pairs of chromosomes. In some tissues, the DNA divides but stays within a single chromosome that becomes large and easy to work with. The female produces hundreds of fertilised eggs, making it ideal for genetic experiments. Next is the tiny soil nematode worm *Caenorhabditis elegans* (**C. elegans**), which feeds on *E. coli* and so is easy to grow in the laboratory. It is only 1mm long with a life span of 3 weeks and has six pairs of chromosomes. It was the first genome to be sequenced. *C. elegans* is transparent so the fate of every cell can be mapped during development to the 959 cells that form an adult.

Moving up the evolutionary scale to vertebrates, the small striped **zebra fish** *Danio rerio* grows to 6cm long and lives up to 5 years. It is a common aquarium fish and is available as a GMO that expresses a fluorescent protein, making it glow in the dark. We will discuss it in relation to the identification of the gene involved in skin colour in humans. Much closer to humans is the house **mouse** *Mus musculus* that is undoubtedly the most studied mammal. It has a smaller genome than humans have, because of deletions that occurred after divergence from the common ancestor. However, about 99% of mouse genes have an identifiable human homologue. The differences are largely genes that are involved in smelling and reproduction in the mouse. The mouse is an important laboratory animal and has been used extensively to study the function of

genes by introducing genes into the fertilised egg (transgenic mice), or by inactivating genes (knockout mice).

### 1.5 My Example of a Gene

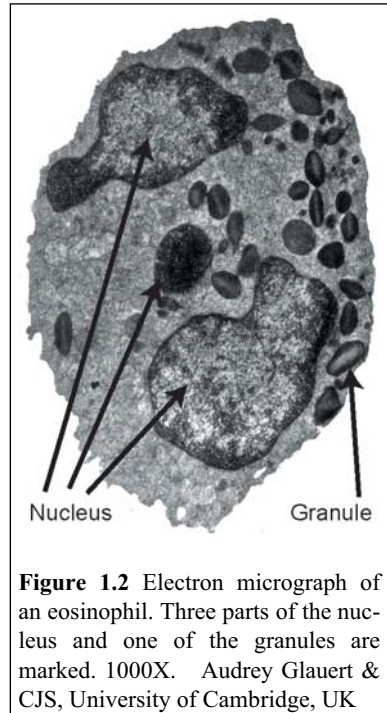
Throughout the book, I use as my main example a protein and its gene that I have worked on for about 20 years – interleukin-5 (**IL5**). Any gene would have done, but IL5 is one I know a little about. Genes are usually given the same name as the protein they encode. The protein IL5 is one of the cytokines (hormones) of the immune system that regulate the type of immune response directed at invading organisms. IL5 controls the production of eosinophils, which are one of the white blood cells. Before we go any further I have to give you a crash course in immunology and summarise the different white blood cells or leukocytes (leuco = white).

Lymphocytes are the smallest and most complicated, although visually the least interesting. B-lymphocytes (usually referred to as **B-cells** because they come from the bone marrow) produce antibodies. **T-cells** come from the thymus and come in several varieties: helper cells that “help” B-cells make antibody. Other T-cells produce cytokines and interleukins. Killer cells come in two varieties, cytotoxic T-cells have specific receptors allowing them to kill foreign and cancerous cells; **K-cells** are killer cells that can kill antibody-coated cells by means of receptors for the tail end of the antibody molecule that enables them to make contact with the “target” cell.

So that summary of immunology wasn't too hard was it? Next we have the phagocytic leukocytes (phago = to eat). The large **macrophages** that remove the debris of damaged tissues and phagocytise microorganisms. The **neutrophil** is especially adapted to phagocytise and kill antibody-coated microorganisms. **Basophils** have a receptor for a special class of antibody called IgE that is associated with allergy. Finally, to the **eosinophil**. To understand the relevance of the IL5 gene it helps to understand the role of eosinophils, and to explain this in some detail I will introduce you to some of my friends.

First, I had collaborated with Audrey Glauert, an electron microscopist working in the Strangeways Institute (Cambridge, UK), in a study

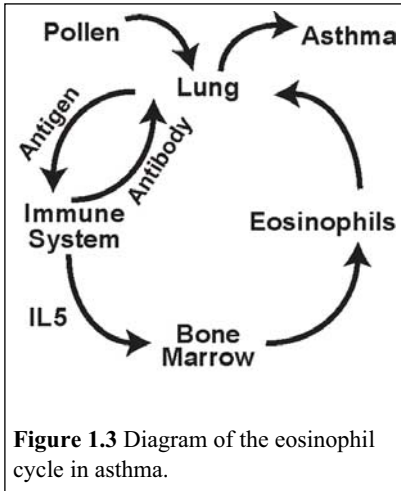
of the killing of tumour cells by lymphocytes, so it was natural that when I became interested in eosinophils I asked her to take some pictures for me. Figure 1.2 shows a picture taken of a very thin slice through the middle of an eosinophil and magnified 1000 times with an electron microscope. The electron microscope produces a grey scale image, at much higher magnification than the light microscope. The first thing to note is the multilobed nucleus, so a slice cuts through different parts of it. A key feature is the granules with their distinctive central crystalline wedge of toxic protein. Some granules are cut through the middle and others are cut near the edge and appear smaller missing the crystalline wedge.



**Figure 1.2** Electron micrograph of an eosinophil. Three parts of the nucleus and one of the granules are marked. 1000X. Audrey Glauert & CJS, University of Cambridge, UK

Eosinophil granules contain an array of toxic substances, which when released kill cells. Like other leucocytes, eosinophils have the ability to move, and can crawl out of the blood vessels into tissues.

Second, is Gerald (Jerry) Gleich then working at the Mayo Clinic (Madison, Minnesota, USA). For many years, the role of the eosinophil was not understood, but Jerry's research demonstrated they were an important agent involved in the damage to the lung and airways in asthma and tissue damage in other allergic diseases. Follow the steps in Figure 1.3: an allergen such as pollen enters the lung and stimulates the immune system to produce antibodies and IL5. The IL5 stimulates the bone marrow to produce eosinophils, which migrate back to the lung where they cause damage to the airways resulting in asthma. IL5 functions, like all hormones by binding to its specific receptor called the IL5 receptor. This has the normal receptor structure consisting of an outside lock, anchor region, and inner signalling region. It is found on the surface of stem cells in the bone marrow, and activation by IL5 stimulates



**Figure 1.3** Diagram of the eosinophil cycle in asthma.

the stem cells to divide and differentiate into eosinophils. Thus, IL5 has become a target for a new generation of anti-asthma drugs. Compounds that decrease either the production of IL5 or its interaction with its receptor are potential drugs.

It was difficult to understand why eosinophils had evolved simply to cause tissue damage in allergic reactions, as there is no selective advantage in that. The third friend in this story is Anthony Butterworth a former colleague at Cambridge University who has devoted his life to the diseases of Africa. Working in Nairobi, Kenya, Anthony provided a more plausible explanation for their evolution; they are adapted for the killing of parasitic worms (helminths).

When an eosinophil makes contact with a parasite, it releases its toxic granules to kill it. Living in a developed country makes it is hard to imagine the impact of worms on life in the natural world. Hookworms in the intestine suck blood and cause anaemia and malnourishment, some worms migrate into the tissues blocking blood vessels. People, especially children, living in unhygienic conditions without access to chemicals, suffer terribly from worms.

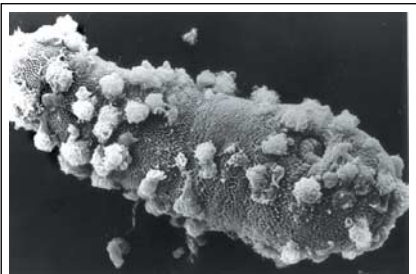
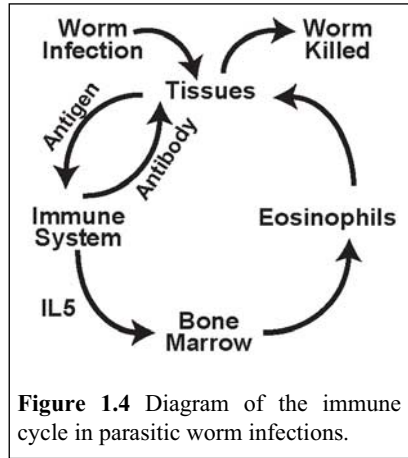
Apart from people, all animals are infested to some degree with worms. Domestic animals are treated with chemicals to control worms, but wild animals suffer like poor people. When doing a post-mortem on a kangaroo, killed after breaking his leg in one of my fences, I was horrified to find the gut was full of worms and the muscles showed evidence of parasite invasion. This is the natural world. Like other aspects of immunity, eosinophils are not totally effective in protecting us against parasitic worms, but it is easy to understand that they have been important survival factors throughout animal evolution.

When an animal is infected with parasites, the immune response is stimulated by the parasite's antigens. Follow the steps in Figure 1.4: the immune system produces antibodies and IL5; the IL5 is taken via the

blood to the bone marrow, stimulating the production of eosinophils; the eosinophils migrate back via the blood to the site of the parasite infection; the antibodies attach to the parasite and allow the eosinophils to spread out over the parasite. The combining sites of the antibody make contact with the parasite and the other end makes contact with the eosinophil. We will see the structure of an antibody in Chapter 3.

I can illustrate Anthony Butterworth's important finding with an image from my own laboratory. The large object in Figure 1.5 is a schistosome (it's a worm) which causes Schistosomiasis (elephantitis) in people in Africa. It has been coated with antibody in the laboratory and then exposed to eosinophils, which are the fluffy looking objects crawling over the schistosome. The eosinophils empty the contents of their granules on to the worm. The enzymes and toxins in the granules puncture holes through the skin of the worm and eventually kill it.

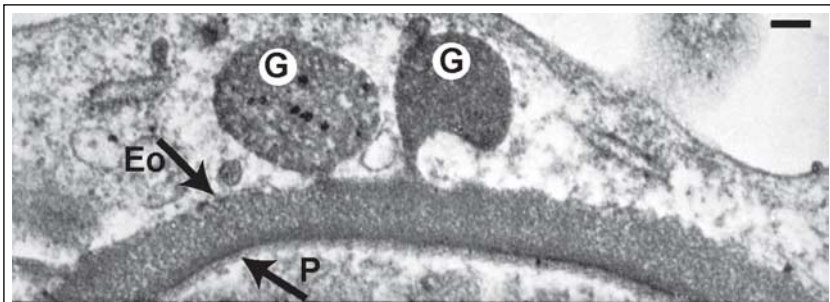
The next group of friends are South Americans. *Trypanosoma cruzi* is a protozoan parasite in South America that causes a chronic debilitating disease, mostly in poor people. While working at the Federal University of Rio de Janeiro in Brazil in 1976 I became interested in finding out which if any of the white blood cells could kill this parasite. Because of my previous work with killer T-cells and K-cells, I somewhat naively expected one or both of these cells to be involved. However, with Marlene Bunn Moreno and Angel



**Figure 1.5** Scanning electron micrograph of a schistosomula with eosinophils attached to the surface via antibodies directed against the parasite. Scanning electron microscope, 500X. David Warren & CJS, NIMR, London

Lopez we were surprised to find that the most effective killer was the eosinophil. While the medical importance of this finding is not clear, as protozoa do not normally induce the production of eosinophils, the finding provided some insight into the way eosinophils function. Firstly, as protozoa are very much smaller than eosinophils, they are surrounded by the cell. This phagocytosis is normally associated with macrophages and neutrophils, and not eosinophils. Secondly, when Wanderley de Silva produced pictures with his electron microscope, it provided details about the way the eosinophil granules release their contents. This can be seen in Figure 1.6 where two granules have formed channels to the outside of the eosinophil and granule material has been released into the space between the eosinophil and a parasite. This ensures that the concentration of the eosinophil granule contents remains high, and it is not surprising that it is very effective in killing even large parasites.

One interesting thing about IL5 is the way its production is controlled. Firstly, it is mainly produced by a group of specialised T cells. Secondly, it is largely produced in these specific types of diseases: worm infections and allergies. All genes are precisely regulated both in terms of the cell type in which they operate as well as the timing of their activation. While gene regulation is very complex, and the details of regulation differ very widely between different genes, the IL5 gene allows us to



**Figure 1.6** Electron micrograph of an eosinophil (Eo) in contact with a parasite (P). The outer membranes of the two are indicated by arrows. Two eosinophil granules (G) have formed a channel to the membrane and the granule contents are expelled into the space between them. The parasite will be killed. 30,000X.

CJS & Wanderley de Silva, Federal University of Rio de Janeiro, Brazil. Sanderson & de Silva (1979) *Journal Cell Science*. 37: 275

discuss the general points that are common to most genes. As we will see, the general properties of genes are common to all organisms – at least on earth.

## 1.6 What to Expect

My aim is to put genes and GMOs into a living context. Rather than a compendium of genetics, which would be a very large book, I present a series of snapshots to give an overview. I take you through the basic make up of organisms, and then discuss genes and how they work. We will discuss the structure of the major constituents of life and how genes encode them. With this in our heads, we can go through the magic of genetic engineering and how GMOs are made. We will discuss briefly how DNA is amplified, sequenced and mutated in the laboratory. There can be no doubt that genetic engineering is changing the face of health and medicine with new GM medicines and gene therapy, but also in the privacy and ethical issues raised by the new technology. Probably the most controversial aspect of genetic engineering is the impact on agriculture. This is partly because some people worry about GM foods, but also because of concerns that the large agribusinesses will dominate our lives.

Here I speak as a small farmer, with a keen interest in the problems faced by the world's primary producers. I will argue that it is important to develop GM crops independently of the big agribusinesses, but just like medicines and motor cars it is likely that multinationals will play a large role as well. Last but not least, genetic engineering is affecting our environment in the risks and perceived risks of what is loosely called "gene contamination", but also because GMOs can play an important role in remediation. Most people recognise that 6 billion people (and 9 billion expected by 2050) cannot live on this planet without environmental impact. How can we minimise this impact for the benefit of present and future generations?

The subdivision into medical, environmental and agricultural is artificial. For example, is the ability to make vaccines in plants, medicine or agriculture? I include it in the chapter on agriculture only for conven-

ience. Is the ability to grow plants that absorb heavy metals for soil decontamination, environmental or agricultural? I discuss it under the environment (the natural world). The problem of putting GMOs into neat pigeonholes emphasises the fact that we are discussing overlapping facets of human existence on the planet. It is irrational to be exclusively for or against GMOs. Just as for drugs and pesticides, each entity has to be considered on its own merits. Furthermore, GMOs must be seen as part of a bigger picture. They are only part of the technology that we will need to ensure the survival of life on earth. For this reason, I include a chapter on sustainable agriculture, because GM food crops must be seen as part of a big picture of food production, and I fear that few consumers understand the food production chain.

It will now be very clear that I am a scientist presenting science, and it is important to remember that there are not two sides to an argument in science. There are often two points of view, but one is wrong. The methodology of science is to disprove hypotheses. Sometimes this can take a long time so two hypotheses co-exist until one is shown to be incorrect. This does not mean that the application of scientific results is not open to argument. We can visit the moon, generate electricity using nuclear power, make golden rice, or clone animals. Nobody can argue about the technology that makes these possible, but people have different views on how they should be used. Unfortunately, the basic science often gets lost in the rhetoric. People will worry about nuclear power causing another Chernobyl; cloning will be applied to despots, and we don't need any more of them; or they worry that poor people will become ill from eating too much golden rice.

I give little credence to opinions not based on science. Of course people can hold religious views, but these are a question of faith and do not deserve equal weight with solid scientific data. It seems that when people do not understand or there is no scientific evidence on a topic, they feel the need to default to some higher intelligence. We saw some religious leaders refute the fact that the earth is round and refuse to accept evolution by natural selection, only to retract and accept them later when they understood the science. A good example is the debate between intelligent design and evolution. As a young man, I encompassed Christianity and never thought too much about the conflict with science. As an older man,

I have given up on religion and any sort of intelligent agent overseeing what goes on in the universe, but I admit there is no evidence either way.

In contrast to the religious approach, I prefer a more humanitarian approach where we accept responsibility rather than transfer it to a hypothetical superior intelligence. I favour a philosophy where individuals are more important than dogma. In general, few scientists accept intelligent design, but there are a few who do. Sometimes these people feel very strongly about their religious views, and tend to get disproportionate publicity, that misleads the public into thinking that intelligent design is widely accepted amongst scientists. In fact, they are a very small minority and most scientists are too busy getting on with their work to spend time arguing about it.

When it comes to understanding genes and genetic engineering, the same principles apply to all types of organism. A plant DNA laboratory looks like my medical research laboratory. All the equipment and reagents are similar. Even more remarkable, for scientists, we use the same jargon. Genetic engineering is not complicated or mysterious, although like gardening, green fingers can help, and it is certainly a lot of fun. In this book I will take you through the most important steps, which is enough to know how DNA is manipulated, and GMOs produced. I take some artistic licence to make things clear, and I give enough information to understand the basics of gene technology without the detail that would make it tedious. For this reason, I give only one example of each technique. One way of mutating DNA to change protein structure is enough to understand how it can be done, although in practice there are many different methods. If you are hoping to set up your own laboratory to make your own GMO's, this is not the right book for you. Just in case you do have ambitions to make your own GMOs, it's important to remember that there are strict regulations and it can only be done in approved laboratories.

## 1.7 Take-Away Message

The basis of life is the sequence:

**DNA → mRNA → protein**

*mRNA* is produced off the DNA template by *transcription* and provides a copy of the genetic code for the production of proteins by *translation*.

Each *protein* is encoded by a gene.

*Carbohydrates and lipids* are not directly encoded by genes, but by a network of protein enzymes, which control their synthesis:

