Why Icebergs Float

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'What’s the point of viruses?' interjected Sally with an edge of exasperation in her voice. These five simple words captured what everyone in the group was thinking. They had just learned that all these pernicious microbes ever do in life is break into some innocent cell, grab hold of its reproductive machinery, commandeer it to replicate themselves and then push off, obliterating their host in the process. This insight into the reproductive cycle of viruses emerged in the midst of a discussion about the causes of disease.

It had all started after Malcolm and Lucy had been to a talk by two scientists, not on viruses, but on the related subject of bacteria and tuberculosis. There have recently been some worrying statistics showing that the disease is actually on the increase in some of the poorer parts of the UK. Growing resistance to antibiotics was becoming a major concern for TB and for bacterial diseases generally. The discovery of the antibiotic streptomycin towards the end of the Second World War had marked a huge step forward in the treatment of TB. It was the first effective drug treatment for the often lethal disease, which affects the airways of the lungs. Previous treatments had relied on exposing patients to as much fresh air as possible – hence the sanatoria in Switzerland for those who could afford it.

Shortly after the First World War, in 1921, the first TB vaccine (known as BCG) had been introduced, and had had a major impact on the incidence of the disease. Twenty-five years later treatment of TB patients with the antibiotic streptomycin had had a similarly powerful effect on the mortality rate. Since the 1980s, however, just as hopes of eliminating the disease completely were rising, it has become apparent that strains of the bacteria are evolving that are resistant to the antibiotics used to combat it.
Antibiotics

‘Before we go any further,’ interjected Jean, always keen to sort out the basics before getting deeper into a topic, ‘what exactly do we mean by antibiotic?’ The question proved popular. ‘Yes, surely the terms “anti” and “bio” just suggest these drugs are hostile to life in general,’ said Helen, looking carefully at the etymology of the word. In fact, the term had been originally introduced as an adjective in the late nineteenth century to describe threats to microbial life generally; its use as a noun for drugs that worked against microbes dates back only to the 1940s. Interestingly, dictionaries today seem a little unclear about the precise meaning. One describes them as ‘drugs that cure illnesses and infections caused by bacteria’; another, more broadly, as ‘substances capable of destroying or inhibiting the growth of microorganisms, esp. bacteria’. For practical purposes the word is used today to refer to substances that kill off bacteria in particular.

Meanwhile, back to the talk about TB. The key point impressed on Malcolm had been the new problem arising today: the growth of bacterial strains resistant to antibiotics. The effectiveness of streptomycin has been particularly compromised in this manner. To deal with this a range of new and different antibiotics have been developed in recent decades; some are effective in certain cases, others in different ones. So the common practice today is to treat patients with several drugs simultaneously, typically a cocktail of four drugs.

‘That’s odd,’ commented Sally. ‘I had rather thought that a bug could either be killed or it couldn’t. How can one antibiotic kill it off, but another one can’t? Is one drug entirely different from another or just a variant?’ In raising this question Sally had lifted the lid on the deeper issue of what antibiotics actually do to a bacterium.

Bacteria

Microscopic though bacteria may be, they are nonetheless relatively complex life forms. They are single cells with many component parts, each carrying out a different function as with all types of cell (Fig. 10.1). For example, the cells of bacteria have outer walls to insulate themselves from the environment, an interior place called the nucleoid where their genetic information (DNA) is stored and a place where the vital proteins are made (ribosomes). Most intriguingly, the cells of bacteria have
an external whip-like structure called a flagellum. This enables them to move around actively rather than drift aimlessly in the surrounding currents.

Without wishing to sound too militaristic, it’s not hard to see how this relatively sophisticated structure offers several possibilities for attack. Where a bacterium poses a threat to health, the job of an antibiotic is to prevent it from functioning and, above all, from
reproducing itself. As it turns out the various antibiotics developed over the decades do indeed interfere with bacteria in a range of different ways. Streptomycin, the first TB antibiotic, acts by inhibiting the production of proteins in the TB bacterium. The drug molecule attaches itself to the place where proteins are manufactured (ribosomes) and stops the creation of vital proteins the bacterium needs to survive (Fig. 10.3).

‘What an amazing thing,’ observed Rosie. She added, in her characteristic probing way, ‘If the antibiotic can do this to a bacterium, why doesn’t it do the same in the human cells that are all around?’ It turns out that streptomycin is able to do its wonderful work against bacteria without damaging our own cells because the protein-making parts of human cells are fortunately structurally different from those in bacteria, so the drug does not affect them.

Other TB antibiotics, however, work in completely different ways. One, for example, interferes with the production of material to build the cell’s membrane, while another inhibits production of the molecules that provide energy for the bacterium. It is remarkable how detailed our modern knowledge is about the ways in which these drugs work. However, it would be misleading to suggest that they have always been
designed specifically with one vulnerable spot or another in mind. The possibility of designing drugs in such a precise way has only arisen in recent decades, thanks to the rise of technologies that enable the precise structure and functioning of molecules to be pinpointed. Traditionally the development of antibiotics and other kinds of drug has been much more hit-and-miss. Laborious testing of countless alternative substances was the common method, carried out with the hope of a fortuitous encounter between the test molecule and some target in the bacteria – a process dubbed ‘molecular roulette’. The drug itself may have been understood and its effects on tissues observed, but rarely were the two linked by a clear understanding of the causal mechanism.

With this insight into just how specific the interaction of each particular drug is, we can see the advantage of multi-drug treatments. Just because a bacterium may be able to resist an attack on its walls, it’s unlikely also to be able to resist interference in its protein machinery – and even less likely to be able to defend its energy-producing function on top of both of these. In other words, the chances of a bacterium being resistant to all three independent assaults are very low. That’s what makes the multi-drug cocktail effective against TB.

It was Rosie, fired by her natural inquisitiveness, who put the question on everyone’s lips: ‘How do these bugs become resistant in the first place? They seem to be engaged in some kind of struggle with the antibiotics.’ This well-timed question brought to the fore one of the central challenges in understanding biological systems: the question of purpose or, in technical language, of teleology. It is almost impossible to describe a biological process without ascribing a sense of purpose to it, wittingly or not. By using everyday forms of language we inadvertently imply intentions behind biological actions. I have done so in the paragraphs above – antibiotics ‘interfere with’ bacteria and bacteria respond by ‘resisting attack’. Each of these verbs suggests conscious intention – yet antibiotics are just molecules doing what molecules do, while bacteria are simple cells with no capacity to think or plan. So apologies for the unfortunate impressions that this kind of language gives; but let’s also defend its use in cutting down on long, dull sentences that lose the reader in their pursuit of precision.

Certainly bacteria and antibiotics have no intentions – no brains with which to wish destruction on an adversary. They simply are. The antibiotic is a molecule, a type of chemical, not a living thing; it remains as it is throughout a biological process, as long as it isn’t broken down. A bacterium, on the other hand, is a living entity. It consumes, it creates, it reproduces – and in this latter capacity we’ve hit upon its long-term
means of survival. The bacterium produces offspring, so inevitably it evolves. It doesn’t intend to, it isn’t looking for a better life, seeking to defend itself against rogue antibiotics. Evolution just happens, as it does with all living things. As one generation gives way to the next, minute and infrequent changes occur in the genetic material, often at random. Each generation inherits some changes, most of which make no overall difference to the offspring. A few, however, may confer some advantage or disadvantage. If those individuals advantaged in this way prove better able to survive and reproduce themselves, then more of them will be present in the new generation. In this way, over many generations small beneficial changes become embedded in the population – for bacteria as for any other life form.

For us humans, changes of this kind have occurred extremely gradually, over hundreds of thousands of years. But the lapse of time between each generation of humans is particularly long. Imagine the difference with bacteria, capable of producing a new generation within 10 or 20 minutes, hundreds of thousands of times faster than humans. At this kind of pace bacteria simply evolve new capabilities over periods of time that are very short by human standards. Foremost among their new capabilities are bound to be mutations that help them survive, in particular ones that counter the actions of antibiotic molecules. It comes as little surprise, then, that current antibiotics are increasingly encountering new variants of bacteria, no longer susceptible to their actions. No wonder the hunt is on for new kinds of antibiotic molecule.

This insight into the action of antibiotics made a lot of sense for Helen. She had discovered early in life that her body was allergic to penicillin; she would come out in a rash and feel itchy all over. Despite this, however, she was not allergic to other antibiotics. She now saw that this is just what might be expected, given that each antibiotic operates in a distinct manner. Antibiotic molecules are quite different from one another, both in composition and shape, as the models of two molecules in the illustration show (Fig. 10.4). Here each ball represents an atom, with each colour indicating a particular element.

An allergic response occurs when a particular molecule is recognised by the body’s immune system and treated (whether justly or not) as foreign to the individual. The act of recognition occurs when the offending molecule fits into a crevice on a receptor molecule in the body. A crevice that neatly accommodates one of the molecules depicted above would scarcely suit the other. An allergic reaction is a response to a specific molecule; you’d hardly expect a body to react to all antibiotic molecules in a similar way, given their great diversity of forms.
Talk of antibiotics and allergies reminded Sally of her recent visit to her GP, during the height of the winter coughs and colds. She’d been suffering from an infection that had gone on for over two weeks, finally deciding to take time off work to see her doctor as it didn’t appear to be clearing up. The doctor’s verdict: it’s just a virus, wait and see if it goes away. ‘I asked if there was anything I could take, like an antibiotic to speed things up,’ she explained, ‘but was told that antibiotics don’t work for viruses.’ Sally had touched a nerve, as almost everyone in the group had experienced this. ‘Why don’t they work?’ was the common plea. Lurking beneath this question was a more fundamental one: what exactly is a virus? Helen had the first shot at answering this. ‘Is it just a thing that doesn’t respond to antibiotics?’ she suggested. ‘Maybe it’s not a type of organism at all, but is just defined by its behaviour rather than its structure.’
Helen’s guess turned out not to be true; viruses are in fact tightly defined entities. The word ‘entity’ is chosen deliberately here because, unlike bacteria, viruses can’t be described as organisms; in fact they cannot even be said to be alive. They don’t have the means to reproduce themselves autonomously. What they do have, the key to their potentially devastating impact on us, is the means to hijack the reproductive machinery of others. To be precise, they are able to enter living cells and commandeerr the cells’ capacity to reproduce. Viruses are structured in a particularly simple way; they consist of a long, thread-like molecule of genetic material covered with a coat of proteins – the absolute minimal structure. The genetic material is in some cases DNA, but more usually is the related molecule, RNA. This contains all the information needed for a virus to reproduce itself. A model of one type of virus is shown below (Fig. 10.5). Called tobacco mosaic virus, it infects tobacco plants. Its simple, rod-like structure shows how protein and nucleic acid (RNA) molecules can combine to form a larger virus structure.

Other types of virus have a different, often more complicated, architecture, but share the same basic combination of genetic material (DNA or RNA) and proteins.

To reproduce, the virus has to attach itself to a cell in the body of its host, then pass its genetic material, a long, thin molecule of RNA or DNA, into the cell. From there, the RNA/DNA can cross into the nucleus of the cell, where it enters the normal replication machinery of the cell. The cell makes no distinction between material from the external virus and its own internal DNA. Unwittingly it reproduces the virus’s genetic code. As this alien genetic material passes back into the cell it once again enters the cell’s machinery, this time to produce the proteins needed to
make a new virus. Protein and RNA, freshly minted thanks to the apparatus of the host cell, then assemble themselves in an orderly fashion to form an entirely new virus – an exact replica of its ‘parent’. With its own capacity plundered by the invading virus, the cell is destroyed; its outer membrane breaks up, and a new generation of viruses breaks out into the surrounding medium. It only takes another cell to pass by – for a freshly minted virus to attach to – and the whole process is repeated. In this way viruses are able to multiply at great speed, expanding their own population while simultaneously destroying the population of cells upon which they had relied. The description of this apparently wanton and purposeless life cycle drew gasps of dismay from the group. ‘Why doesn’t the cell defend itself against attack by viruses?’ asked Rosie, expressing a kind of microbial solidarity. ‘Doesn’t the immune system help?’ added Sally. ‘Can’t it mount an attack on the virus or could it help the cell instead?’ ‘Why doesn’t the cell recognise the DNA of the virus as different from its own?’ asked Jean, keen to support the anti-viral sentiment.

It was Rosie who chose to follow on from the story of the virus’s reproductive cycle by wondering about the next stage. ‘So the virus kills the host, then what?’ she asked. Jean’s response came swiftly by reflecting on an everyday point: ‘They spread, you know: sneezing, coughing and so on… a contagion.’ This idea about the spreading of disease reminded Malcolm of something he had read. ‘Apparently you get different types of disease in parts of Africa where the populations are very scattered compared to Europe. In thinly populated places, you tend to get water-borne or insect-borne diseases because viruses need the close living of urban areas to get around through sneezes and physical contact. I think that’s a reason why TB didn’t get a hold in the early USA,’ he recalled.

‘So viruses just get inside cells, replicate themselves at their hosts’ expense, burst out, get sneezed on to another cell and do the same again, and again, and again. What’s the point of them?’ Sally expressed her reactions with distinct exasperation. She expressed once again the difficulty we tend to have in fully understanding meaning and purpose in biological processes. It’s not that viruses really ‘attack’ or ‘invade’; they don’t seek to destroy cells. It’s just that those versions that do so are more likely to replicate successfully – and as a result are going to be found in greater numbers in successive generations. In this statistical way, they come to be the most commonly occurring, for better or worse. In reaction to this rather bleak portrayal of viruses, Helen tried
looking for a more positive angle. ‘Is there such a thing as a “good virus” equivalent to the so-called “good bacteria” we hear about?’ she asked. By chance Jean knew something about this. She had been listening to a radio programme about new developments in which viruses are being engineered to deliver medical treatments of one sort or another.

Viruses are indeed proving useful in several ways, thanks to their special ability to make their way into the interior of normal animal or plant cells. An example of this type of treatment is gene therapy. Sometimes a gene is faulty, and this fault can be passed on from one generation to the next. The main job of a gene is to act as code for the production of the proteins upon which every living thing relies. Proteins both provide structure for living tissues and drive chemical processes. If a gene doesn’t carry precisely the right code, it may not be able to produce proteins normally. Gene therapy works by inserting a normal copy of the human gene in place of the faulty one. To achieve this, researchers have had to find ways to get the new healthy gene to the target cell without arousing the body’s defences and, once there, to penetrate its outer membrane to replace the defective gene.

Viruses are particularly good at both of these tasks. After all, that is why they cause disease: they are able to both elude defence mechanisms and burrow into cells. That’s the way they have evolved. To take advantage of this ability, recent research has focused on modifying viruses to eliminate their usual detrimental effects. Where this has proved successful the modified virus has been able to pass through the body and enter the target cells without destroying them. A copy of the normal human gene is inserted into the DNA of the virus, which goes on to introduce it into the target cells. These cells are then able to use the new healthy gene to produce the proteins the body requires. Exciting though this new form of therapy is, many challenges lie ahead in making it safe, effective and readily available.

Viruses are used in other beneficial ways too. For example, by modifying them to carry a fluorescent dye they are able to show up precisely where cancer cells are located – a huge aid to radiography. In pharmacology, research is being carried out to see if modified viruses can be developed to deliver drugs directly to the target cells that need them, rather than distributing the drug everywhere in the body. In all these situations it is the specific ability of a virus to evade the body’s defence mechanisms that makes them so promising as agents for health-giving treatments. So yes, viruses can indeed be adapted for beneficial ends, whether or not we call them ‘good viruses’.
Anti-viral drugs

Frustrating as Sally might have found her doctor’s refusal to prescribe an antibiotic, the reason behind the decision is understandable. Destroying the living cell of a bacterium is an utterly different mission from preventing a virus from reproducing itself. A bacterium and a virus are quite different entities. Using an antibiotic to stop a virus would be as inappropriate as using scissors to build a brick wall. Helen saw this point as something of a challenge: ‘We’ve seen how antibiotics interfere with vital processes in bacteria, so couldn’t some other types of drug do the same for viruses?’ It was a good point. As already explained, antibiotics work in many ways. Some break up bacterial walls; others prevent them manufacturing the proteins or producing the energy they need. There must be some way in which a drug could intervene in a virus’s reproductive process to stop it multiplying.

It turns out that developing anti-viral drugs is intrinsically more difficult than developing anti-bacterial ones. This is because viruses don’t work autonomously, but exploit the body’s own cells instead; if we interfere with a virus’s means of reproduction, we risk damaging the host cell at the same time. In other words, our bodies would suffer as much as the virus – something we would experience as a ‘side effect’. Nevertheless, in the 1980s research on anti-viral drugs really took off as detailed knowledge of the precise structure of viruses grew, thanks to developments in basic molecular biology. Urgency was added to the task by the parallel emergence of the potentially deadly virus, HIV.

Various molecules have been developed to block the progress of the virus at different stages in its cycle. Some prevent a virus attaching to the host cell, others block its entry through the outer membrane of the host cell. A different type altogether gets into the replication machinery of the cell and jams the production of the virus’s DNA. The over-the-counter drug Acyclovir, used for cold sores caused by the herpes virus, is an example of this. Helen is right in that anti-virus drugs are indeed coming on-stream to complement the antibiotics used against bacteria. But, as anyone who’s suffered a cold knows only too well, not all viruses can yet be blocked; great advances have been made against some viruses, but there’s plenty of scope for further research and development. Progress in this most applied of scientific areas is intimately linked to developments in our fundamental understanding of molecular biology. It’s a prime example of how applied and basic sciences are both vital in their complementary ways – the former tackling real-life problems directly, the latter disinterestedly following the path of inquiry, wherever it may lead.
Conclusion

In this chapter we have seen how bacteria and viruses are in fact quite different kinds of thing, although their effects may be equally devastating. A bacterium is an organism, alive in every sense of the word; a virus, not alive in the conventional sense, relies on others to reproduce itself. Typically viruses are much smaller, on average a hundred times smaller than bacteria; they are not visible through an optical microscope, as most bacteria are. As the story of evolution shows, however, size is not all that matters; viruses are by far the most abundant biological entities on Earth. So next time you take time off work to visit your GP, only to be told to sit it out, you may be better prepared and able to take it philosophically. Knowing that antibiotics cannot possibly combat viruses, but your body’s defences eventually can doesn’t exactly solve your problem, but it may well make it more bearable.

As the past few chapters demonstrate, the human body is a rich source of questions about science in everyday life. Taken together, they show something of the huge range of topics inspired by our bodies: the organs we rely upon – eye, brain, muscles; the systems that connect them – nerves, blood, hormones; the threats we face – viruses, bacteria and disease. Discussion may begin with an everyday concern with health, diet or child-rearing for example, but it often moves on to an exploration of fundamental concepts in chemistry, physics and biology.

The human body is, of course, not the only starting point for inquiries; nor are biological issues the only area of interest and concern. The physical world – the environment, the Earth, the very cosmos itself – also inspires profound questions. Many discussions have begun with questions about these, and such topics also lead on to insights into deeper scientific concepts. One such discussion began with an innocent query about why icebergs float and ended with a philosophical debate about the meaning of nothingness. It forms the basis of the next chapter.