Jeremy Woodward
Illustrations by Charlie E. Manning

The Gastro-Archeologist

Revealing the Mysteries of the Intestine and its Diseases

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Preface

I have worked as a gastroenterologist—a doctor specialising in guts—over the last 25 years. During this time, I have witnessed dramatic advances in our understanding of diseases and our ability to treat them. At the same time, I have seen how there is a growing desire amongst non-specialists to understand how our bodies work. Thanks to the Internet and the 'popular science' press, not only have terms such as 'DNA' and 'protein' become familiar to those without a scientific background, but also the general concepts behind them. Over these years, the nature of my job has also changed. A doctor is appropriately no longer an authoritarian figure, expecting the patient to dutifully take their medicine with little in the way of explanation, but is now primarily an educator.

At the time of writing, the only treatment available for coeliac disease is the lifelong and absolute avoidance of eating gluten—there is no other 'medicine' for it. In order for patients to accept such a change in their lifestyle, my prescription therefore has to be the imparting of sufficient knowledge to understand not only *how* but *why* to follow such a diet. For 2 hours every month over the last 8 years, a dietitian and I have done exactly that in an informal group setting with patients newly diagnosed with coeliac disease. The benefits of this approach have been frankly extraordinary (and have saved substantial healthcare resources) simply by empowering patients to look after themselves. The overview of coeliac disease that I provide in these sessions is necessarily very superficial. However, I often get asked interesting and challenging questions that lead me to realise that quite a few people wish to understand the condition in more depth.

Working as I do in Cambridge I actually have quite a few molecular biologists as patients, but how does one begin to describe to those people without any prior knowledge of biology the complexities of intestinal immunology? It is a subject that popular science authors have assiduously avoided and is notoriously challenging to teach even to medical students. However, a few hilarious sessions at local Coeliac UK patient groups and one occasion with catering managers showed me that it is not altogether impossible—albeit with the use of oven gloves, scrunched up paper balls attached to a length of string and audience members participating in role play! This is where this book started—but as with all such projects it took on a life of its own and I found myself describing the history of the gut and the immune system in order to explain coeliac disease before embracing other conditions such as food allergies and Crohn's disease as well.

This book is not intended as a textbook, as I have avoided any jargon unless absolutely necessary. Neither is it really 'popular science'—it covers far too much ground for that. I hope that it will be accessible in most part to people with relatively little biological knowledge, but will equally entertain those who also have some or even a lot of science behind them as it may present well-known concepts in an unusual or interesting way. To the experts reading this book, I apologise in advance for the degree to which I have simplified complex processes. However, the view is often clearer when free of intricate details. Just as a long-distance path can be completed very enjoyably in stages and each part may differ in its appeal, so one should not feel bad about not completing the journey in this book to its conclusion. The history of the gut and the workings of the immune system make for perfectly interesting stories in their own right, but I have kept them together in order to provide the complete story (so far) behind the diseases. Many unknowns remain for us to uncover in these conditions as I point out along the way but I have made every effort to make sure that the stories I relate here are as accurate and up to date as possible.

Cambridge, UK Jeremy Woodward

Acknowledgements

There are so many people who have contributed to the telling of this story (often without knowing that they have) that I simply cannot acknowledge them all here, but my gratitude to them is none the less for that. I list those without whom I would probably never have started, or finished.

Jane, my extraordinary, amazing wife, has supported me, fed me and generally looked after me whilst I was helplessly 'in the zone' ignoring everything and everyone around me for hours on end whilst staring at this laptop screen. I cannot begin to express my gratitude for this indulgence. Or indeed for the life that we share with our five fabulous children, Josh, Toby, James, Jack and Tom.

My parents, the kindest and most generous folk that I know, undoubtedly shaped this book through me. My father, John, instilled in me my captivation and enthusiasm for life in all its forms and my mother, Anne's revulsion of snakes, moths and butterflies, might have had something to do with my fascination for those lifeforms in particular! My first publication at the age of 14 (in 'Camping and Caravanning World'—much to the hilarity of my academic colleagues) was written with my father on the reptiles of the UK, with photographs taken by him. Memories of developing and printing black and white photographs in the attic of our home in Sidcup remain as a magical experience.

Bob Allan was my gastroenterologist mentor in Birmingham, and I owe him a huge debt of gratitude for passing on his love of the subject, as well as to John Owen, Eric Jenkinson and Graham Anderson in the thymic biology laboratory, for opening up the amazing vistas of immunology research.

My long-suffering patients and my equally forgiving students are of course my teachers and I continuously learn from them. Extra special thanks to those of them who have sense-checked and proofread for me. Equally my colleagues who have acted as sounding boards for my ideas, and others who unwittingly started my writing in ways that that they will never know. Stephen Moss, Dunecan Massey and Andrew Butler in particular helped me to shape my ideas through stimulating discussion. Matt Mason, University of Cambridge Physiologist, rigorously corrected my spelling, grammar and schoolboy howlers for which I am forever indebted to him (despite the need for substantial rewriting!).

All at Springer Verlag have been enormously patient with me and I am very grateful to them for taking on this project—with special thanks to Phillipp Berg, Ulrike Daechert, Tanja Weyandt, Parthiban Kannan and Birke Dalia for getting it into production.

Introduction

The primal importance of our guts has long been reflected in our beliefs, our language and our culture. From antiquity, gastrointestinal organs have been considered to originate emotions and temperament. Today, we talk of 'gut feelings' and use the word 'visceral' to mean something derived from deep feelings rather than rational thought.[1] The words for 'bowels' and 'mercy' even share the same Semitic word root for 'something deep within'[2] signifying the origin of the sense of compassion (and incidentally leading to some rather humorous interpretations of Bible passages). Similarly, the use of 'guts' to represent courage dates back to at least the Middle Ages and persists in most modern cultures—in Finland the word 'Sisu' (which quite literally translates as 'guts') has become a popular word to define a stoic tendency in the national characteristic.[3] The symbolic disembowelling of criminals guilty of treason in

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[1] The Norwegian psychologist Gerda Boyesen (1922–2005) even developed a branch of alternative medicine—'Biodynamic psychotherapy'—on her ideas that linked the emotions to the gastrointestinal tract. She would use the sounds made by the intestines to interpret moods and emotions and called the process '*psychoperistalsis*'.

[2] Confusion apparently arose during translation of the Septuagint Bible into Greek with usage of splanchnois (**σπλαγχνοις**) for words originating from the Semitic root resh/chet/mim (**רחם**) meaning 'from deep within' and used for both compassion (emanating from a deep feeling) and bowels in Hebrew. This is the possible explanation for verses such as Genesis 43:30 'And Joseph made haste for his bowels did yearn upon his brother' and Song of Solomon 5:4 'my beloved put in his hand by the hole in the door and my bowels were moved for him'.

[3] Interestingly, the Finnish word Sisu also derives from a word meaning 'inside' or 'interior'—Sisus. Whilst a part of the culture for hundreds of years, its first appearance in the English language probably dates back to this excerpt from *Time* magazine in January 1940: *'The Finns have something they call Sisu. It is a compound of bravado and bravery, of ferocity and tenacity, of the ability to keep fighting after most people would have quit, and to fight with the will to win. The Finns translate Sisu as "the Finnish spirit" but it is a much more **gutful** word than that.'*

medieval England presumably shares its origin with this intrinsic notion of the viscera housing the strength of spirit.[4]

And yet, there are few sights more shocking to us than that of the human body, stripped of its cosmetically enhanced and muscularly defined outer layers, with its inner workings fully on display. The guts (Fig. 1), filling the abdominal cavity in a squirming mass of wormlike tubing, bring about the most intense feelings of revulsion, not just in the squeamish or faint-hearted.

Why intestines should engender this reaction—more than for instance the heart or the lungs—may be explicable on many levels. It is not due to unfamiliarity—at first inspection our intestines resemble those of many other mammals on display at the butcher's shop or roadkill neglected beside our highways. The intestines often appear to have a mind of their own—writhing and wriggling in coordinated peristalsis completely independently of conscious control. Indeed, we are so rarely aware of the scale of the activity inside our abdominal cavity that this surprising revelation may endow the intestines with alien qualities that makes it feel that they are not actually even a part of us.

Ultimately however, I suspect that the distaste with which we relate to our own viscera has more to do with how we see ourselves in the natural world, set apart from other forms of life by our superior intellectual development. Our bodies—and our guts in particular—serve as a great leveller to diminish our conceit. Remove all the external superficial trappings of human beings and we are seen to be much the same as other animals. Even apparently simple creatures contain a gut which is often very similar in appearance to ours. The reaction that we have to seeing how we work on the inside is perhaps therefore akin to the shock experienced in futuristic fantasies when the skin of the major character peels back to expose electronic circuitry and reveals them as a mere android machine.[5]

Underlying this realisation is the tacit understanding that we all must have—that just as the robot's wiring is essential to its functioning—so the intestine is the basic necessity of life. We are fundamentally beholden to our aesthetically distasteful innards. All that we are has come through the wall of

[4] The revolting torture of 'hanging, drawing and quartering' involved hanging the victim for several minutes until near the point of death and then cutting open the abdomen and eviscerating them whilst still alive prior to decapitation and cutting the body into four parts. The practice was a statutory penalty for treason in England from 1351 and only removed from the statute books by the Act of Forfeiture in 1870.

[5] I entirely accept that I might be overstating the case here and that the reason that we are revolted by our guts is that they are messy and smelly and if you can see them then it probably means that the person they belong to has died unpleasantly!

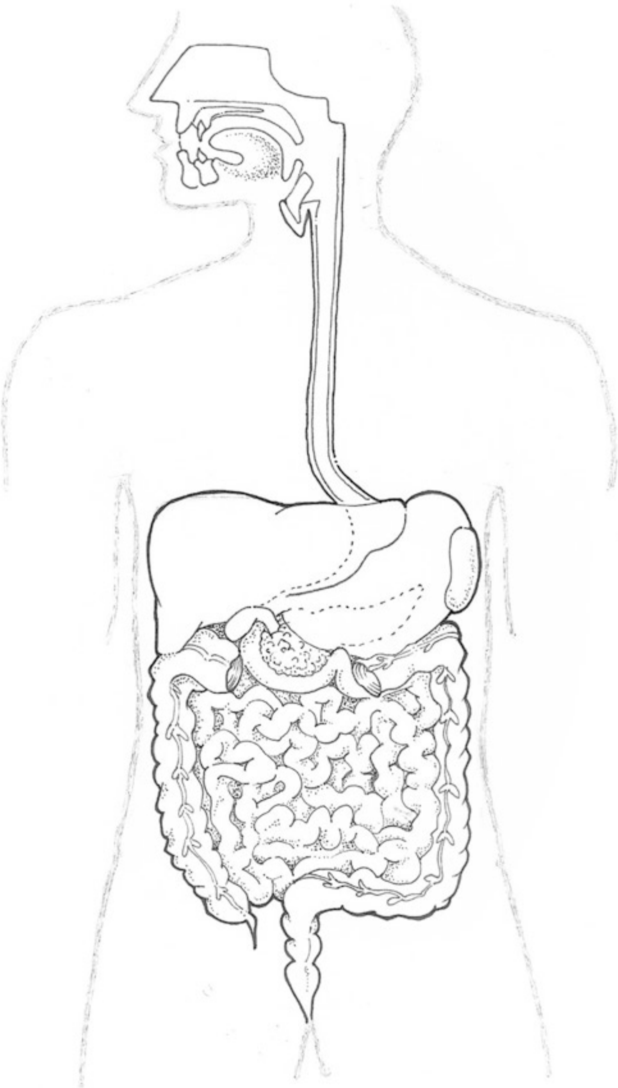


Fig. 1 The human gastrointestinal tract—from mouth to anus

the gut. The molecules that make us, the energy that drives us, even the fluid that hydrates us—all have been ingested, digested to basic constituents in the gut lumen, selectively absorbed through the lining of the intestine, repackaged and exported to the rest of the body.[6]

[6] Except some of the oxygen molecules which of course come through the lungs.

I number myself amongst the fortunate few privileged enough to spend their days working intimately with guts and the human beings that live around them. As a gastroenterologist, a physician specialising in internal medicine, I study the ways our intestines work, how they malfunction and how we interact with them—and them with us. In so far as we feed our guts and empty them on a regular basis (at least in part as a response to instructions from them, whether we are aware of it or not), we arguably interact more with our gastrointestinal tract than any other organ system. Over the last 25 years, my ongoing relationship with the gastrointestinal tract continues to awe and astonish me every day, on every level. I have come to appreciate the extraordinary beauty of the gut—I have to admit for instance, to lingering during endoscopic procedures that examine the small intestinal lining to admire the finger-like 'villi' wafting in the current like a bed of sea anemones in a rock pool. I still feel genuine excitement whilst watching 'peristalsis'—the periodic contractions of the tube that propel its contents along it—whether recorded on an oesophageal pressure tracing or observed directly in a newly transplanted intestine in the operating theatre.

I have come to learn that our guts do indeed sometimes behave as if they have a mind of their own—we now call it the 'gut-brain'—and harbour so many other microorganisms within themselves that they are truly in large part alien to us. However, it is the amazing complexity and our nascent understanding (that still frankly amounts to little more than staggering ignorance) of the workings of the gut that fascinates me the most.

Sometimes it is simply a matter of seeing things differently. Early in my career I stumbled upon a metaphorical viewpoint that allowed an unfolding of the landscape below me as if standing on a rocky outcrop or having climbed above the treeline on a mountainside. I cannot claim to be the first or the only person to have enjoyed this view—it has always been there and like so many ideas it is obvious to the point of trivial once pointed out. However, the landscape that it opens up is always changing as, despite remaining mostly in darkness, discoveries begin to illuminate more and more of the vista. This is my invitation to you to join with me on the rocky outcrop to share the splendid view it affords (Fig. 1).

This book is split into three parts of which the first two describe the route to our viewpoint. In Part 1, our path follows a journey from the most basic concepts of life that prophesy the evolution of guts. We will then follow the way in which guts have dictated the paths that life has taken. In Part 2, we retrace our steps to see how guts have hosted the development of 'immunity'—not merely a defence system but the rules dictating interactions within organisms and with others. Having arrived with an understanding of how the gut has in large part written the story *of life itself, we will be able to see how the story has been laid down in layers over time. Just as an archaeologist would make little sense of a jumble of artefacts muddled together from different ages and learns much more by painstakingly recording the separate strata in which they are found, so it is with the gut. Seen as a whole, the functions of our intestines are bewilderingly complex. But visualise the individual layers over time and place them in an evolutionary context and suddenly everything begins to make more sense. This is my metaphorical viewpoint—I call it '****Gastro-Archeology****'.*

Diverticula

As with all journeys we will find along our way points of potential distraction. These will be labelled in a box as 'diverticulum'—a word which derives from the Latin word meaning a 'bypath' (from *devertere*, to turn aside). Diverticula (*sing*. diverticulum) are a common finding in the gastrointestinal tract and are simple outpouchings on the side of the tube. Whilst they can occur anywhere from the gullet to the rectum, they are commonly found in the human colon where their numbers increase over time. The terminology often causes confusion—'Diverticulosis' is the condition of having (colonic) diverticula (as do most people in the UK over the age of about 40 years), but 'diverticulitis' is the presence of infection or inflammation in a diverticulum. I tend to illustrate this by considering the human appendix. We are all born with this particular diverticulum, but relatively few people develop an infection within it and experience 'appendicitis'.

Whilst substantial distractions will be located in the diverticula, it is not unusual to find other points of interest on any journey and additional facts and historical comments will be found as footnotes.

Contents

About the Author

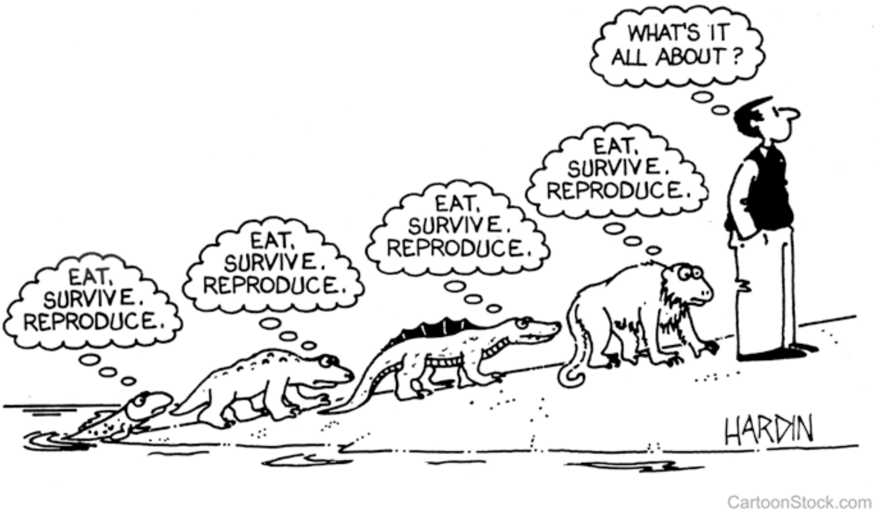
Jeremy Woodward is a consultant gastroenterologist working in Addenbrooke's Hospital in Cambridge. He specialises in diseases of the small intestine and clinical nutrition, which extends from tube-feeding techniques to intestinal transplantation. He lectures on gastroenterology and nutrition in the Medical School in Cambridge University where he is also a communications skills facilitator, and he teaches gastrointestinal physiology to undergraduates in Christ's College (where his own career started). An enthusiastic wildlife observer and photographer, he particularly enjoys studying moths in his back garden and hunting reptiles when on holiday in warmer climes.

Illustrator

Charlie E. Manning comes from a long line of creative folk. Educated in Saffron Walden, Essex, and in Cambridge, she has worked within the art industry in roles such as college technician, art and antiquities custodian and art materials advisor and retail for over 20 years. She chose to refresh some of her skills and studied illustration and visual communications with the Open College of the Arts. Whilst pursuing various creative avenues, she enjoys trying to incorporate recycling wherever possible, being a history nerd, folklore enthusiast, appreciator of traditional crafts and an avid plant collector. Working predominantly in pen and ink, gouache, coloured pencil, mixed media collage and Lino printing, she takes inspiration from the natural world and can be found recharging her batteries outdoors, preferably in the dappled shade of woodland amongst the flora and fauna, taking lots of photographs and possibly hugging a tree. Currently, she is dwelling near the Fenlands of East Anglia. She is a devoted auntie to her nieces and nephews and works part-time in floristry.

Part I

Selection of the Fattest



The transition of the 'Enterocene' (Gut Age) to the 'Anthropocene' (or Brain Age) (Reprinted with permission from CartoonStock: www.cartoonstock.com)

> '*...one can perhaps even view an animal as nothing more than a group of cells clustered around a gastro-intestinal tract, differentiated for and dedicated to the task of keeping that gut full.*'
>
> Wayne Becker[1]

[1] Wayne Becker, Professor of Botany at University of Wisconsin. This quote comes from an unpublished set of course notes taken by a student that I found on the internet. The cartoon is by Patrick Hardin from Michigan. For our purposes the human's thought bubble should probably read 'I know I shouldn't, and I really don't need it, but that cream puff is just *too* tempting'. Or be replaced by Homer Simpson holding a doughnut…

Introduction

One of the greatest threats to human longevity is an evolutionary omission. Until now life has never existed in an environment where food was so plentiful that it was present in excess. As a result, we have not really required mechanisms to shed weight but only to conserve or gain. However, thanks to our developed brains, we can now manipulate our environment to be able to provide sufficient to feed us all. Dire warnings of global catastrophe will probably have to await the effects of climate change rather than population growth. Sadly, we have singularly failed to develop the societal mechanisms that allow us to share and to prevent the disintegration of kinship into conflict based on need or greed. We therefore live in a World where poverty and plenty co-exist—and those who have most suffer from the effects of excess.[2]

With the advent of human society, life on earth has now entered a period where our intelligence has allowed us to adapt our environment rather than to it. This 'Brain Age' has now even been credited with its own geological epoch—the 'Anthropocene'.[3] However, up until this point, it is the relative lack of food throughout time that has driven competition. The perpetual need to feed the gut, and the animal through it, has perhaps been the most potent selection process on the planet. Whether the 'Anthropocene' started around 12,000 years ago with the spread of settlements and farming or more recently in the nuclear age is debated. For our current purposes it is immaterial as our journey through the 'gut age' spans from the invention of guts around 600 million years ago up until now.

However, we will need to set off on our path considerably earlier than this. Life itself is born out of a set of temporary solutions to irresolvable conflicts and long before the first gut came into being, its future existence was prophesied by the necessary compromises. I promise that we will not linger over-long in the inhospitable environment at the dawn of life but we do have a lot of ground to cover—so we had better get going!

[2] The prevalence of obesity in the UK increased from 15% in 1993 to 26% in 2014. Even higher rates of obesity were reported in other developed countries such as the USA (35%) and New Zealand. Obesity accounts for approximately 44% of all cases of diabetes, and 23% of ischaemic heart disease. It is now (at the time of writing) the fifth largest cause of death worldwide, and one in five deaths in North America can be related to obesity. Tragically, it is not just the wealthy and the greedy corners of society that suffer from the complications of excess—cheap highly calorific but poorly nutritious foods are often consumed in poor societies leading to obesity co-existing alongside under-nutrition.

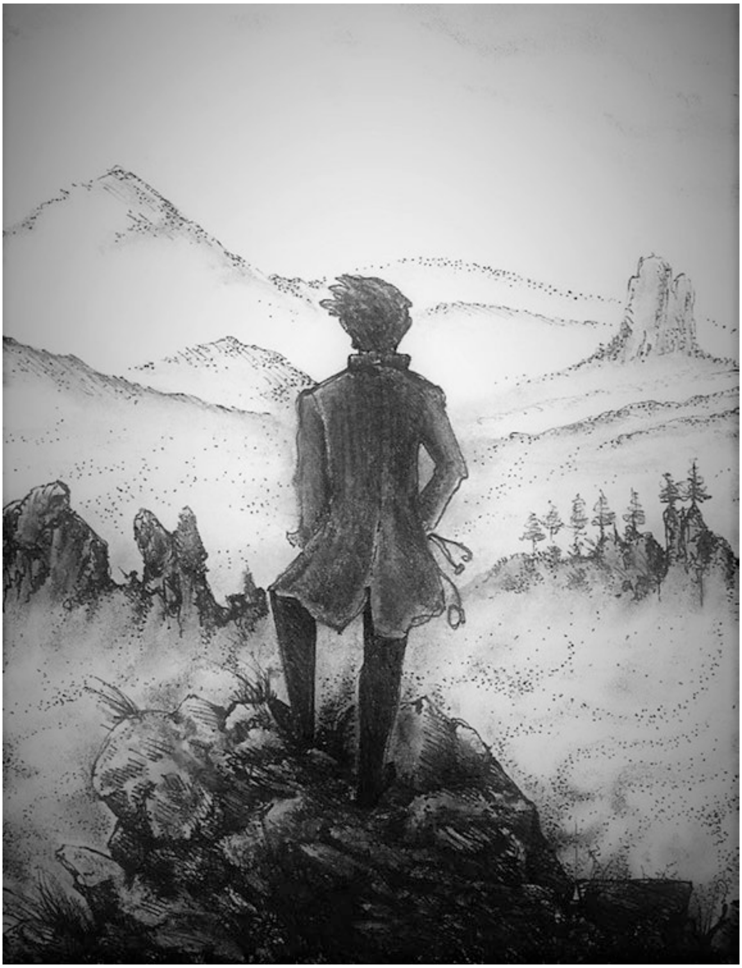
[3] The term Anthropocene is attributed to Paul J Crutzen. He is an atmospheric chemist who shared the Nobel prize for chemistry in 1995 for his work, particularly relating to the formation and depletion of ozone.

1

The Invention of Eating

Summary In which we see the cell membrane as the defining boundary of life but also as a confining barrier that must be overcome to allow substances in and out of the cell. This is the 'containment paradox'. Single-celled animals ultimately developed the ability to bring components from outside the membrane into their substance through mechanisms such as 'endocytosis' and 'phagocytosis'. This was the 'invention' of eating and significantly enhanced the organism's capacity to assimilate nutrients. The ability to ingest particles had enormous significance for the evolution of life. Whole bacteria that came to live as 'endosymbionts' within the cell took on the energy conversion processes from the surrounding surface membrane (where this previously occurred) and enabled it to take on additional roles. Importantly, phagocytosis led to the ingestion of whole living organisms. This was to alter the relationship between lifeforms with consequences that would lead ultimately to the requirement of both a gut and an immune system.

J. Woodward, *The Gastro-Archeologist*, https://doi.org/10.1007/978-3-030-62621-1_1



The sketch is inspired by a painting by Caspar David Friedrich 1774–1840 which is entitled 'The Wanderer (or 'hiker') in the Mists'. It was painted in 1818 and now hangs in the Kunsthalle in Hamburg. It has always enchanted me since I first saw it used as the cover illustration for the Penguin Classics edition of Friedrich Nietzsche's Ecce Homo and I have to admit I found it far more inspirational than the text. I love the portrayal of an emerging vista from a new viewpoint

The Containment Paradox

The first stage of our journey will take us from the beginnings of life to a momentous event in its history—we could call it the' invention' of eating. Although this will take over 2 billion years, we should not hurry to get started as we need first to establish one or two of the basic principles of life that ultimately made eating necessary.

All life exists inside a bubble. Its membrane is a highly organised two-dimensional fluid enclosing a three-dimensional space called the cell, the smallest independent unit of life.[1] This liquid skin just 4 millionths of a millimetre across,[2] is the sole interface between the vagaries of the outside World and the relatively constant and chemically different internal milieu required by life. Its essential structure is so basic that if you break it up into its constituent molecules it will spontaneously re-assemble itself, simply because oil and water do not mix.

Fat molecules—also known as 'lipids'—are chains of Carbon and Hydrogen atoms joined together. They repel water—hence when washing up after a roast dinner we see round globules of fat floating in the water in the sink. However, if we add a detergent such as washing up liquid, the globules vanish leaving a white emulsion of the fat in the water. The way in which detergents do this is that their molecules each have one end that dissolves in fat and the other in water. They are thence able to bridge—and mix—the two otherwise incompatible fluids. Likewise, the molecules that make up the cell membrane have a fat chain on one end and a water-soluble molecule (usually phosphate) at the other end—and are therefore called 'phospholipids'. When mixed with water, such chemicals spontaneously align themselves to have their lipid portions in proximity to each other and as far away from the water as possible. These molecules might for instance orientate themselves in a ball with the lipid ends all pointing inwards and the water-soluble ends pointing outwards.

Alternatively, if they enclosed a bubble of water they would be pointing the other way, but this would leave the fat soluble ends in contact with outside water and this would be unstable. However, if on top of this skin around the bubble there was *another* layer of phospholipids pointing the other way, then they have created a molecular sandwich—a lipid 'bilayer' with water on both sides separated by a fatty barrier.[3] Thus, we define the boundary of life—the double layered cell membrane (Fig. 1.1).

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[1] Cell (from Latin—cella—meaning 'small room'). The concept of the cell literally becomes the living room of life. Different types of cell are identified by the suffix '-cyte' from the Greek word 'Kytos' meaning 'container'.

[2] The thickness of the membrane can be estimated on the basis of an experiment performed by the American diplomat and polymath Benjamin Franklin on a pond in Clapham Common in the early 1770s! He poured a teaspoon of oil onto the pond and estimated that it covered about half an acre when it spread out—from this you can estimate the thickness of a single layer of molecules. The experiment was not designed for this purpose though but to see if there was any truth in the efficacy of pouring oil on water to calm choppy seas.

[3] The bubbles that are made by blowing through a film of washing up liquid between our fingers or in children's bubble toys are also a lipid bilayer, but the exact opposite of the cell membrane. Here the double layer is made up of the fat-loving ends pointing outwards from the membrane with a thin layer of water sandwiched in between the water-loving ends in the middle.

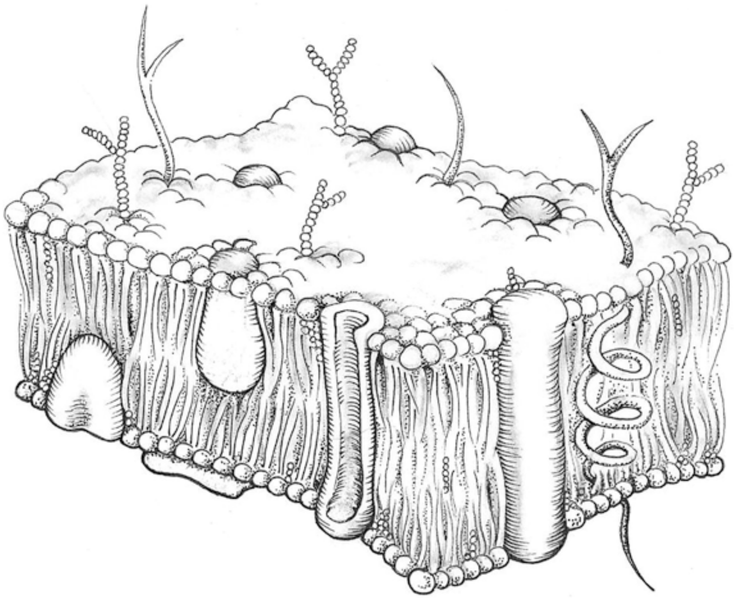

Fig. 1.1 The cell membrane—the boundary that defines life. A double layer of lipids pointing inwards with water soluble ends on each 'out'side, with proteins embedded or traversing it to provide passages and means of interaction with the outside world

The importance of the cell membrane cannot be overstated. Imagine it as the geographical borders of a country. It can control the flow in and out of the region it encloses. The environment on either side of the boundary can be very different, akin perhaps to crossing the border between two countries as different as North and South Korea. Trade can take place across the border and commodities can be exchanged by bartering. It can communicate by sending and receiving messages far outside its boundaries. The boundary permits the area inside to differ from that on the other side. The borders have created an 'entity' that can have its own individual 'id-entity'.

One can therefore understand the importance of the membrane in confining and defining the living space of the cell. It creates an enclosed environment which can be maintained stable regardless of the changes occurring outside. Toxins can be excluded or nutrients selectively accumulated across the boundary. Optimum conditions can be set within the cell for biochemical functions, such as the acidity and salinity. Enclosure by the membrane increases the local concentration of chemicals to encourage them to interact rather than simply diffusing away into the surrounding environment and this speeds up the reactions of life.

Containing life within the confines of the membrane and the creation of an 'entity' has further implications in the context of that essential pre-requisite of life—the means of reproducing itself. Self-replicating molecules exist within all living organisms as the basis of the 'genetic code' in the form of nucleic acids—DNA and RNA. The information encrypted in the four-letter alphabet of these vast molecules can be translated (by special cellular machinery) into the long chains of amino acids which form proteins. Proteins are the nano-machines that form the engines of life. They can be made of chains as short as 20 amino acids joined together (the hormone, insulin has just 51) to many thousands such as the appropriately named 'Titin' which is made of nearly 30,000.[4] Shorter chains of amino acids are called 'peptides' rather than 'proteins'. Unlike simple peptides, proteins are defined by their ability to form three dimensional structures which gives them their functional capabilities. For instance, they can catalyse chemical reactions (such proteins are called 'enzymes') by attracting molecules together into a cleft or 'active site' where they can react; they can act as messengers between cells (such as insulin) or they can build up structures (such as the proteins in hair, or titin, which effectively acts like a spring in muscles).

Faults, or mutations, that occur in the genetic code or its translation into proteins might be catastrophic, but occasionally result in an improved version of the protein. This is a fundamental component of genetic adaptation and is critical to allow organisms to respond to change. Regardless of the outcome the membrane serves initially to limit the damage—or the benefit—of any such mutation to the single unit in which it occurred. The change relates only to the single cell and its progeny. If a harmful mutation leads to the death of a single celled organism and its progeny, it will not affect others of its kind. Whilst it could be argued (as Richard Dawkins does in 'The Selfish Gene'[5]) that natural selection can operate at the level of the replicating gene itself, it is enclosure by the cell membrane that turns the whole cell into the 'unit of evolution'.[6]

Evolution has tinkered with the cell membrane and found uses for it that extend beyond its boundary role. It has become a vibrant trading place and a

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[4] All proteins can be described by a given name, or by individually naming the amino acids that make them up—given that there are over 30,000 in titin this would therefore make an extremely long name indeed (over 189,000 letters) and some have suggested that this is the longest word in the English language, or indeed any. I think it is stretching it a little though to use a chemical formula as a word.

[5] At its simplest, life could be seen as the emergence of self-replicating molecules. Such a concept was promulgated by Richard Dawkins in 'The Selfish Gene' in 1976 in which he envisaged the genetic material as the being of life on which evolutionary selection worked, and the organism around it as the mere container or vehicle.

[6] A broader perception is that of David Hull who added the necessity for the 'interactor' to the 'replicator': 'A process is a selection process because of the interplay between replication and interaction. The structure of replicators is differentially perpetuated because of the relative success of the interactors of which the replicators are part. In order to perform the functions they do, both replicators and interactors must be discreet individuals which come into existence and cease to exist'.

chemical crossroad of reactions. A vast array of proteins embed themselves within the membrane and stretch out into the external medium or span across it. They function as passive channels or active pumps to alter the concentration of chemicals such as salts on either side, or to receive messages from outside or signal to other cells. The membrane acts as a two-dimensional fluid platform in which these proteins float such that they can aggregate together and work collaboratively to assemble larger structures, just like machines in a production line comprising different parts. The immense utility of lipid bilayers as both boundaries and scaffolds for useful proteins has led to the lipid bilayer configuration fulfilling a wide number of functions within the cell itself. It has been used to create sub-compartments within the cell, each with their own contained chemical environment. In some highly specialised cells, the boundary membrane only comprises around 2% of the total lipid bilayers of the cell.

There is a downside to all of this of course. By concentrating and controlling the matter of life within the boundary of a cell membrane there still remains the issue of how the cell is able to harness the nutrients from the environment that it requires in order to power it. Somehow it needs to get the raw ingredients into the cell in a form that it can use. It requires an ability to maintain strict border controls on immigration but allow trade for the essential commodities. This compromise between containment and consumption is the first great primal conflict of life that predicts the future development of the gut and will become one underlying theme of our story as it plays out over the history of time. I call this the 'paradox' of 'containment'.

With this in mind, let us commence our journey!

Diverticulum #1.1: The energy of life

Just being alive requires huge amounts of energy. Given our current sedentary lifestyles less than a quarter of our daily energy consumption is used in physical activity but even in those who exercise regularly it is still under half. The rest is needed just to maintain our bodies—not simply in breathing or the heart pumping blood, but in the internal workings of every cell.

Plants harness the energy from sunlight to make complex 'organic' molecules (the 'chemicals of life') largely from carbon dioxide and water which results in the generation of oxygen as a by-product. In beautiful natural symmetry, animals effectively reverse this process, using chemical reactions between oxygen and complex organic molecules (from food) to generate carbon dioxide and water. However, all living organisms ultimately use the resulting energy in the same way—by first converting it into electricity and then storing it in a chemical form, just like charging a battery.

The electrical generator in cells is found on the inside of specialised lipid bilayer membranes in compartments within the cell called 'Mitochondria'. The miniscule current it produces is quite literally the 'spark of life'—just as one can imagine passing between the outstretched fingers of God and Adam in Michelangelo's depiction on the ceiling of the Sistine chapel.[7] Or perhaps (more crudely) as the lightning bolt harnessed in a B-movie depiction of Dr Frankenstein's laboratory.[8]

The phenomenon that we recognise as 'electricity' is simply a flow of negatively charged particles called electrons. We are most familiar with them passing along a copper wire surrounded by insulating material such as PVC. Instead of a wire, life forms generate the current by passing an electron along a chain of proteins embedded on one side of a cell membrane—a bit like a rugby ball being passed down a line of players out of the scrum. Instead of copper, the conductor is made up of clusters of iron and sulphur within proteins and the insulator is the membrane itself.

The 'battery' to store the energy is a chemical phosphate bond in a molecule called ATP (adenosine triphosphate). Most energy-requiring chemical processes in the cell are powered by the effects of breaking the chemical phosphate bond—it has been called the 'energy currency' of life. We all apparently create and consume our own body weight in ATP every day! The battery is 'charged' (ATP formed) by pumping hydrogen ions (carrying a single positive charge equal and opposite to that of the electron) across the membrane using the electricity of the electron transport chain. This builds up a gradient of hydrogen ions across the insulating membrane—and the energy can then be harnessed by allowing these ions to move back in through specialised channels.[9] These channels contain a protein shaped like a turbine that even rotates as a result of the flow of hydrogen ions and creates three ATP phosphate bonds on each turn. In fact, it bears remarkable similarity to the three-cylinder radial engine used in Louis Bleriot's aircraft for the first flight across the English Channel in 1909![10] The entire mechanism is akin to that of hydroelectric power with water backed up behind a dam flowing down through channels to drive a turbine. The only difference is that life forms store the energy in the battery pack of ATP—engineers are looking at similar ways of storing generated electricity!

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[7] Michelangelo painted the ceiling of the Sistine chapel between 1508 and 1512. It depicts the Creation as told in the book of Genesis and the Creation of Adam is the centrepiece—famously as God and Adam nearly touch fingers in the giving of life. The image of God is surrounded by a red mantle—whilst many have pointed out the anatomical similarity of the shape of this ensemble to the human brain it also closely resembles the form of the uterus after giving birth. Which of these was intended is not known—is it possible that Michelangelo's genius was to combine both forms?

[8] 'Frankenstein; or the Modern Prometheus' was written by the young Mary Shelley who published it in 1818 at the age of 20. She referred to Victor Frankenstein's monster in different tellings of the tale as 'Adam' and the monster refers to himself in talking to Frankenstein as 'The Adam of your labours'. Interestingly, the actual animation of the monster is not described in her book, although she hints strongly that it was connected to Victor Frankenstein's interest in electricity.

[9] The coupling of the proton gradient to the synthesis of ATP is known as the 'Chemiosmotic hypothesis' and was first espoused by Peter D Mitchell in 1961—he was awarded the Nobel Prize in Chemistry for his work in 1978.

[10] In 1908 the Daily Mail newspaper offered £500 for anyone achieving a powered flight across the English Channel—Le Matin paper in Paris said that it could never be won. The prize was doubled to £1000 in 1909 when on 25th July, Louis Bleriot claimed it by flying his mark XI monoplane from near

The Journey Begins

Determining how long ago the first cells came into being on our planet presents a significant challenge. The history of life is written in the fossil record of the rocks of our planet, which helpfully assists in dating the era of death of the preserved form of the organism. The earliest fossils that are indubitably of bacterial forms are found in rocks that date back a 'mere' 3 billion years. However, specialised techniques are required to identify microscopic fossils and below a certain size it can be difficult to discern the structures of life forms from the crystals of the rock itself. Identification of organic molecules associated with life—such as the phospholipids of the cell membrane—may just date the availability of the chemical ingredients rather than their association into living entities.[11] Strong candidates for the earliest living things are unusual structures called 'Stromatolites' which are found in old rocks that have been made by the progressive layering of sediment. They resemble features made by modern day bacteria living in shallow waters. Such deposits found in Australia have been dated to around 3.5 billion years before the present and are thought to represent the oldest evidence of lifeforms similar to those in existence today. Nevertheless, there are hints of possibly more ancient life forms in even older rocks—up to 4.1 billion years ago. To put this into context, this is about as far back in time as any rocks can be reliably dated. The young planet, less than a billion years old—was up to this point inhospitably hot and the surface was constantly renewing itself through volcanic activity and being pulverised by meteorites. If life could form in such an environment so soon after the formation of the planet itself then perhaps it was not so difficult to create after all.

Calais to Dover in a time of 36 min. He crash-landed as he had not previously reconnoitred a landing site on the English side. Perhaps he never expected to make it across…. The radial engine, designed by Alessandro Anzani, became the prototype for all aircraft engines until long after the Second World War.

The rotating three step mechanism of the ATP synthase was first described by Paul Boyer at UCLA and confirmed by John Walker from Cambridge following elucidation of the structure of the molecule—they shared the 1997 Nobel prize in Chemistry for their achievement.

[11] These difficulties are faced by exo-biologists looking for traces of life on nearby planets and moons of the solar system, but compounded by the necessity of transporting a miniature laboratory across space, and constrained by knowledge of the molecules associated with life on earth. An example of such potential confusion is the presence—or not—of 'nanobacteria'. These are tiny structures which, by their complexity and ability to perpetuate themselves, have been considered by some to represent small organisms, about 100 times smaller than most bacteria. Nanobacteria have been implicated as the cause of certain diseases in humans—including calcifying conditions such as atherosclerosis and kidney stones. They have also been found on material emanating from other worlds (the 'Alan Hills 84001' meteorite from Mars that was found in Antarctica) and considered as possible evidence for the existence of extra-terrestrial life. Whilst the debate continues, it is most likely that these structures on Earth are simply mineral-protein complexes that are capable of self-propagation whilst the appearances on the Mars rock are now thought to be artefacts from the preparation for electron microscopy.

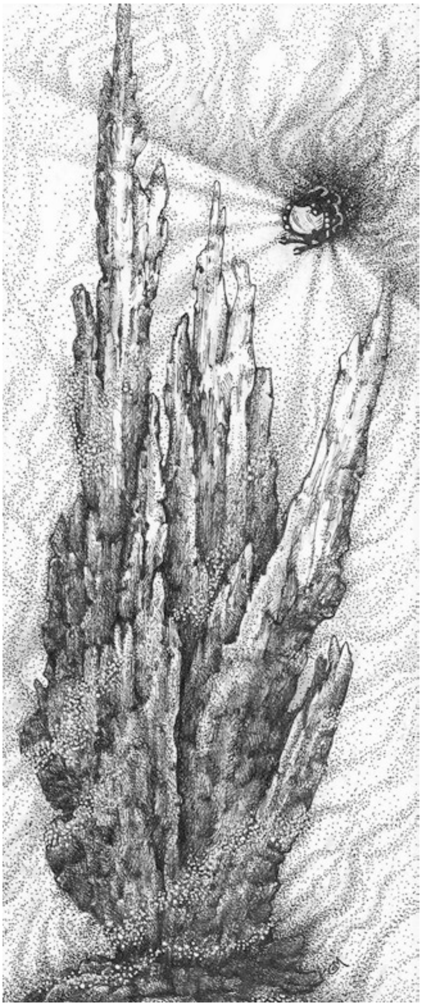

Fig. 1.2 The 'Lost city' under the sea: were structures such as these the original cradle of life?

Our journey begins at a remote point on our planet, some 2000 ft below the surface of the middle of the Atlantic Ocean. Here lies what has been dubbed the 'Lost City'—an eerie field of white chimney-like structures growing through the murky depths on the ocean floor (Fig. 1.2). Its discovery in December 2000 has radically changed our views on the potential origins of life. Unlike nearby volcanically generated 'black smokers' formed by the deposition of sediments from superheated water at up to 400 °C, the Lost City is produced at much lower temperatures (50–90 °C) by alkaline hydrothermal vents. Seawater percolating deep into the earth's upper mantle reacts with the particular type of rock found there (called 'Olivine') to generate heat and rise back up to the sea floor as an alkaline solution rich in minerals and hydrogen gas. (According to the NASA probe Cassini, a similar process appears to be happening currently in the oceans of Enceladus, one of the moons of Saturn).

On contacting the cold seawater, minerals such as magnesium carbonate settle out from the plume and form thin semi-porous inorganic membranes. In the tranquil stillness of the ocean depths these fragile structures can reach enormous sizes—up to 60 m tall in places. Such membranes would have been highly enriched in iron and sulphur in the oceans of the early planet—a combination that may well have been capable of generating electrical gradients through tiny pores in the structures.

The energy from such gradients generated inorganically could have powered the chemical reactions to create the organic molecules of life. In other words, unlike Frankenstein's monster, the electrical spark was not the finishing touch but the *start* of the creation of life. If life did originate at such sites as a result of inorganically generated electrical currents, then it is perhaps no coincidence that all of the proteins that make up the electron transfer chain (see Diverticulum #1.1) in all life forms use inorganic catalytic centres—made up of exactly the same iron and sulphur.

In order to leave the comfortable ancestral home of the alkaline vent, it is postulated that life-forms developed the necessary lipid bilayer membranes within the pores or pockets of the chimneys and the necessary protein pumps to create energy-generating gradients across them. Therefore 'life' would already have been quite advanced before it left home, and it is likely that if we had been able to sample the residents of the vents 3.5 billion years ago, we would have found a venerable distant relative still living there going by the name of 'LUCA', whom I shall now introduce to you.

The Tree of Life

When tracing our family origins, most of us are able to go back three generations with ease and if we are lucky to have access to the records we can then follow certain lines back a few more. Evolutionary biologists have taken this to the ultimate length in postulating that all current life can be traced back to single predecessors, or groups of genetically similar individuals. In other words, that there is a tree of life[12] that can be traced back to a single 'last common ancestor' at the base of the trunk.

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[12] Charles Darwin put this much more eloquently—"As buds give rise by growth to fresh buds, and these, if vigorous, branch out and overtop on all sides many a feebler branch, so by generation I believe it has been with the great Tree of Life, which fills with its dead and broken branches the crust of the earth, and

LUCA is the 'Last Common Universal Ancestor' for all currently existing life forms. Since the first complete bacterial DNA was decoded in 1995, the full genomes of over 100,000 different species have been published. It is possible to attempt to recreate the genetic make-up of LUCA by determining which genes have been preserved in 'primitive' life forms that are still in existence. Around 350 such different genes may be so old that they have been present since the time of this ancient ancestor. Significantly, these genes all encode proteins that would be required for life to exist at the alkaline hydrothermal vents—being able to utilise carbon dioxide and hydrogen, and appearing to associate with iron and sulphur.

Prior to 1977, all life forms were considered to fall into one of only two major categories depending on the complexity of the structures within the cell—either bacteria ('prokaryotes') or 'eukaryotes' which included all more advanced life forms including multicellular organisms, such as plants and animals. The two cell types are easily distinguishable by the presence or absence of internal membrane components—particularly a cell 'nucleus'. Prokaryotes have simple, often circular loops of DNA floating freely within the cell, whereas eukaryotes have their genetic material contained within a membrane-enclosed structure called the nucleus. They also contain a whole host of other such membrane-bound structures called 'organelles' by early microscopists.[13] These include the 'mitochondria' which generate the energy currency molecule, ATP within the cell (from the electron transport chain proteins embedded within its inner membrane) and 'chloroplasts' in plant cells where a similar process occurs, powered by light. All prokaryotic organisms comprise a single cell, whereas eukaryotes can be unicellular such as amoebae, or constructed of many cells (multicellular) such as ourselves—each of us is made up of about 30 trillion!

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covers the surface with its ever-branching and beautiful ramifications." Darwin, *The Origin of Species* (1872), 104f. Darwin was a student of theology at Christ's College in Cambridge between 1828 and 1831 (having failed to show any interest or aptitude in medical studies at Edinburgh) and embarked on the legendary voyage of the Beagle shortly after leaving Cambridge. His student rooms have been restored and are well worth a visit, as is the statue of him sitting on a bench made by Anthony Smith in gardens in the college recreated with species identified from his voyage.

[13] Robert Brown described the first eukaryotic organelle—the nucleus—in 1833. Like Darwin, he also dropped out of medical studies in Edinburgh, as he was more interested in botany. He also described 'Brownian motion'—the random motion of particles suspended in fluid due to collision with fast moving molecules. Although mitochondria were first spotted inside the cell in the 1850s, their definitive description fell to the German pathologist, Richard Altmann in 1890. He called them 'bioblasts' and thought that they were 'elementary organisms' living independently within the cell. He would have been gratified to know that this is concurrent with present thinking, even though his theory was initially ridiculed (as all the best are!). Mitochondria are now thought to have evolved from formerly free-living bacteria. The term 'mitochondrion' was coined in 1898 by Benda, from the Greek for 'thread' and 'granule' after the appearance of the mitochondria in the tail of the sperm.

However, we now know that the sapling of life had not two, but three main branches. A group of bacteria previously thought to be extremely primitive were found to have significant enough differences to classify them separately as an equal prokaryotic domain called the 'Archaea'. This branch of life is named after the Greek word meaning 'beginning' or 'origin' from which words such as 'archeology' are derived. Indeed, the similarities between the archaeans and eukaryotes appear greater than those between the archaeans and the bacteria.

Some investigators consider that the persistence of primitive traits within eukaryotes may lead us to discover that it is our domain that bears the most resemblance to LUCA.[14] The apparent simplicity of the other two branches may represent evolutionary fine tuning by cutting back redundant mechanisms—perhaps through separate common ancestors living in high temperature environments where RNA turns out to be unstable. Nevertheless, we have already travelled a great distance from our starting point—the first sign of 'eukaryotic' life appears only about 2 billion years ago. It has actually taken us longer to get there from our first stop at the hydrothermal vents than it took for LUCA to appear after the birth of the planet.

The Nourishment of Life

Cells require nutrients to provide energy and the necessary ingredients for the machinery of life. The 'Containment Paradox' is that the cell closes off the outside World but still has to find ways of getting what it needs and also disposing of waste products across the barrier of the membrane.

The membrane is not a hard wall but a fluid interface and some substances can pass across it quite easily. These include important gases such as hydrogen, carbon dioxide and oxygen. Being made of lipid, chemicals that dissolve in fat can also cross the membrane with relative ease. However, water-soluble chemicals and large molecules such as proteins are blocked. The cell has got around this problem by developing specialised proteins that are embedded within the membrane. Some of these proteins span the membrane and are capable of selectively pumping particular chemicals (including charged particles called

[14] Carl Woese (1928–2012), along with George Fox at the University of Illinois pioneered the use of 16s ribosomal RNA to understand the relationship of different bacterial and archaeal species over time. 16s ribosomal RNA is a structural nucleotide that makes up part of the 'ribosome' a subcellular structure responsible for the translation of the nucleic acid genetic code into proteins—effectively the 'protein factory' within cells. It mutates very slowly due to its critically important role and therefore changes in the 16s rRNA can be used to define different species. In common with many other original thinkers in science who challenge the established paradigm, Woese was considered to be something of a crank—but later recognised as a 'scarred revolutionary' as his theory became accepted by the end of the 1980s.