Pain-Free Biochemistry

An essential guide for the health sciences

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WILEY-BLACKWELL
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This edition first published 2009

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered Office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Other Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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ISBN: 978-0-470-06045-2 (HB) 978-0-470-06046-9 (PB)

A catalogue record for this book is available from the British Library.

Typeset in 10.5/12.5pt Times by Aptara Inc., New Delhi, India
Printed in Singapore by Markono Pte. Ltd.

First impression 2009

Contents

Colour code	Biochemistry – Blue
	Essential chemistry – Red
	Clinical topics – Green
	Other – Purple

Preface

This book is written in the hope of filling what I have felt as a teacher to be a glaring gap in the availability of books on biochemistry suitable for students of nursing and related healthcare subjects. Textbooks for medical students are relevant but far too detailed and offputting for students on a short course. Standard textbooks of biochemistry for science students, although there are many good ones, are not only too detailed but also misleadingly broad. The patient is unlikely to be an insect or a plant, and so the biochemistry of locust flight muscle or spinach chloroplasts is only of limited help to a hard-pressed nursing student. On the other hand, the various books on science for nursing are usually very sketchy when it comes to biochemistry.

At first encounter, biochemistry can be quite intimidating. I have therefore tried to strip away as much scary detail as possible, leaving out what I felt to be unnecessary structures, enzyme names and reaction steps, and keeping in only the bare minimum to allow some genuine understanding of what is going on in metabolism. I am sure students will find this quite scary enough! There are a large number of topics I have not touched upon, e.g. the intricacies of signalling, inflammation and molecular immunology. What I hope is that I will give a student a firm enough grasp of what biochemistry is all about to read up about anything else that they specifically need in their own speciality.

As my own experience comes from teaching nursing students in Ireland, where many arrive without a chemistry foundation, I have also interspersed some basic chemistry. This is in honour of the intrepid group of mature women students who pinned me against the blackboard some years back and said ‘Professor Engel, we can tell that you’re enthusiastic about these protein molecules you keep mentioning, but what you don’t seem to realise is that we don’t know what a molecule is!’

I need also to thank Margaret Deith who read it all with the combined eye of student, teacher and editor; my wife, Sue, who kept reminding me that not all students have the same learning style and pointing out where what I thought was obvious might not be obvious to a student; Carmel Nolan who read it from the point

of view of a lecturer in the School of Nursing, spotted obvious gaps and encouraged me to keep going; and Francesca Paradisi who checked the chemistry sections for any glaring errors. Finally, Nicky McGirr, my commissioning editor was ever helpful and enthusiastic, Fiona Woods, Izzy Canning and Robert Hambrook at Wiley in Chichester guided me patiently through the final stages and Lesley Montford handled the copy editing with efficiency and understanding!

Visit the book's companion website at www.wileyeurope.com/college/engel Here you will find explanations of the answers to the MCQs contained in the book plus an extended set of MCQs ranging more widely across the topics.

Paul Engel
July 2009

SECTION 1

Foundations

TOPIC 1

Why biochemistry?

Aims of biochemistry

'Why do we need to learn this stuff?' is a question that every biochemistry lecturer is likely to have met over and over again in teaching healthcare students. It is somehow easier and more obvious to see why you need to know what the heart and kidneys do, where the veins and nerves are, etc. than how and why we metabolise glucose. So do you as healthcare professionals really need to bother about biochemistry?

It is now possible to provide a reasonably good broad description of what is going on at a functional level in most of the processes of the body, e.g. fertilisation, growth and differentiation, inheritance, immunity, **hormone** action, nerve conduction, muscle contraction and so on without biochemistry, but all these accounts end up prompting a degree of disbelief and the vigorous question 'How on earth can that possibly work?' Each of these stories invokes shadowy objects and influences that seem to have amazing powers – substances that recognise an invading **bacterium** or **virus** and target it for destruction, substances that switch on a program to turn a girl into a woman or substances that allow something happening inside my head to move my fingers across my keyboard! Biochemistry recognises that none of the marvels of biology can be properly understood without getting right down to the chemical level. Over the past hundred years or so this discipline has emerged by developing and refining chemical and physical tools to study very complex molecules and systems and has achieved an in-depth understanding of many of life's processes that, even 30–40 years ago, were entirely mysterious.

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Health care and biochemistry

Even so, do *you* need to understand at that level? Leaving aside the thought that you might be genuinely interested and curious to find out, there are many other pressures on your crowded learning time. We should therefore recognise that the people you will look after will usually be under your care because something has gone wrong! Even healthy people coming in for a check-up need clinical staff who can recognise the early signs of a problem. These days the check-up is likely to involve a battery of 'tests', which typically involve sending blood and urine to 'the lab'. Some of these tests may involve microscopic examination, e.g. to recognise abnormal distributions of blood cells, but very many of the tests are biochemical, and 'the lab' is the hospital's biochemistry department (possibly under the label of chemical pathology). If indeed there is a problem, patients ideally want you and your medical colleagues to offer something more than sympathy. Accurate diagnosis and effective treatment are what they are after – in much the same way that, if there was something wrong with their car, they would also hope for accurate diagnosis and treatment!

All the same, could you not leave all that detailed biochemical knowledge to the physicians and surgeons? Here we need to think about where the analogy with getting a car fixed falls down: when a car is fixed the owner collects it at the end of the day and drives it home; when he or she takes his or her body to be fixed, the chances are that he or she will have an aftercare period in the hands of nurses, physiotherapists, etc. It will be the nurses who deliver the drugs, set up the drips, take the blood samples, change the dressing and supervise the feeding. The patient is going to have far more contact with the nursing staff than with the surgeon and therefore will hope that the nursing staff understand what they are doing!

In considering how far biochemistry is essential to that understanding, let us briefly touch on four disease conditions, two of them longstanding killers and the other two more recent, but all four in their separate ways a source of fear for the public, and see where biochemistry fits in. The first two are the main killers in Western society: cancer and heart disease.

Cancer

In 1972, US presidential candidate Richard Nixon announced that, if elected, he would devote \$100 million to curing cancer. The clear implication was that, in its pursuit of frivolous curiosities, the irresponsible, self-absorbed scientific community had overlooked this major source of public concern. It did not occur to Mr Nixon that the real problem was that we could not launch a full frontal attack on cancer until we understood what it was. Of course, at one level we knew that cancer involves our own cells growing out of control, and, knowing that, it was already possible to attack cancers by surgery, chemotherapy and radiotherapy. What we did not know, however, was what led a particular cell or set of cells to become cancerous, and scientists were hotly contesting various rival theories – cancer was caused by viruses, cancer was inherited in our **genes** or cancer was provoked by dangerous chemicals, **carcinogens**. These were all advanced as mutually exclusive alternatives. Today, we understand that all these factors play a part and that a cell has to take several steps, not just one, to become committed to cancerous development.

What had to happen to reach our current understanding was a whole series of discoveries from various unexpected directions, many of them helping us to better describe normality, before we could explain abnormality. The point is that the new understanding is entirely biochemical. No amount of staring down the microscope at stained histological sections of diseased tissues would have brought us to the destination. What was needed was a proper understanding of the various molecular switches involved in cell division, and also an understanding of what controls the development of new blood supply – because once a tumour acquires its own blood supply it becomes more dangerous, seeding new tumours round the body by a process called **metastasis**. Today, with a much fuller understanding of what is going on and of the differences between different tumours, it is possible both to refine diagnosis and to devise better targeted and more effective treatments, so that at least some cancers that were fatal 30 years ago, such as testicular cancer, are successfully treatable today.

Heart disease

What about heart disease? Again it has been known for a long time, at a plumbing level, that the pipes get furred up. A build-up of plaque on the walls of the coronary arteries eventually leads to serious constriction and angina, and, if a blood clot builds up, possibly also to a fatal heart attack. As with cancer, this level of knowledge has provided a basis for surgical intervention of various kinds for a long time, but what about prevention, what about prompt and secure diagnosis, what about long-term medication? And once again, if there are genetic factors, how does this work? Are we all equally at risk? And does it matter what we eat? A proper biochemical understanding is really rather helpful. Today, one of the most widely prescribed classes of drugs is the **statins**, given prophylactically (i.e. for prevention rather than cure) to middle-aged patients, especially men. These are designer drugs specially targeting the production of **cholesterol** by our own body chemistry (see Topic 21), excessive levels of cholesterol now being well understood as a risk factor. Recognising the role of cholesterol and then targeting the drugs to decrease cholesterol levels is based on detailed biochemical research.

AIDS

The other two examples relate to more recent scares. In the 1980s, there was near-panic among various communities over the emergence of a new and deadly sexually transmitted disease, AIDS (acquired immune deficiency syndrome). The first step towards effective action was a recognition that AIDS is caused by the human immunodeficiency virus, HIV. The panic, however, reflected the fact that the condition was so poorly understood that there was no basis for effective therapy. What followed over a very few years was a truly remarkable response by the international biochemical community, which established exactly what HIV was, how it worked and where its weak points might be, allowing us to attack it instead of letting it attack us. This work led on to several strategies for drug design and to the current combined therapies, which allow HIV-positive individuals many years of healthy life rather than a very high chance of debilitating and terminal illness. AIDS, of course, is still devastating many parts of the developing world, but this is now an economic and political problem. The scientific and clinical problem is largely solved.

BSE

Finally, even more recently, in the 1990s, we have had another panic in Europe, this time over bovine spongiform encephalopathy (BSE – ‘mad cow disease’) and beefburgers. In this case, the successful containment of the problem, which seems to be steadily abating now, has been down to successful public health and agricultural measures rather than clinical intervention. Nevertheless, those measures in themselves have depended on gaining an understanding of an exceptionally baffling disease. It was baffling because it was an infectious disease that challenged all our previous notions of infection – no bacteria, no viruses, just the **prion** protein. In this situation, epidemiology (the study of the pattern of the spread of disease) clearly took us some distance in identifying a link with cattle, sheep, etc. even before we knew exactly what it was in the meat that was so dangerous. This left political dilemmas over the correct way to proceed, as possible methods of prevention struck at people’s livelihoods. Deep study at the molecular level since then has helped our understanding not only of BSE but also of various so-called **amyloid** diseases, such as Alzheimer’s. The original puzzle is solved when one understands that prions (and similar **proteins**) are molecular troublemakers! They not only misbehave themselves but they also lead their fellow molecules astray. It is inconceivable that BSE could have been properly explained by anything other than biochemical research.

Aims of this book

Biochemistry, then, is very clearly the engine driving major advances in clinical understanding, in diagnosis and in intelligent therapy. It is also a fascinating subject, but it is undeniably complex. Life is complex, and we cannot escape some complexity if we want to understand it. If you want to read *War and Peace* in the original, you have to make an investment in learning the Russian alphabet and language. The effort, one assumes, is finally rewarding. Similarly, biochemistry has its own alphabet and language, which can seem intimidating. My contract with the reader is to try to explain things as simply as possible, to explain the language of biochemistry clearly, and not to introduce complexity for its own sake. I would like to produce a few converts, students with a real sense of intellectual satisfaction in understanding the scientific basis of procedures in everyday clinical medicine and nursing. However, even if I do not succeed to that extent, I hope I will persuade you that biochemistry is not an unnecessary imposition but an essential tool, and that, with a little effort, the main principles can be understood.

This book

Finally, a word then about the organisation of the book. The numbered chapters listed in the Contents are essentially of three kinds and are colour coded as such by title. The majority (blue titles), of course, are mainstream biochemistry, and the individual biochemical topics are presented in short chapters, each making one main point and of a size to be taken in at a sitting. Interspersed, however, especially in the first half of the book, are chapters (red titles) providing some basic chemistry. This is gently presented on the assumption that you may have done very little chemistry, may have found it hard or perhaps did it so long ago that you have forgotten it. On the other hand, if you have a confident foundation of school chemistry, you can probably skip these red chapters. Finally, a third category of chapter, especially in the later stages of the book, presents clinical topics from a biochemical perspective (green titles).

Throughout the book there will also be reference to a series of appendices. Biochemistry is a vast subject, and for most healthcare purposes you probably need only the broad outlines plus certain relevant details. On the other hand, here and there puzzling facts may seem to emerge like rabbits out of a hat. If you are happy to take these facts on trust, you can safely ignore the book's appendices without your patients suffering in years to come. If, on the other hand, curiosity or frustration draws you in further, the appendices are there to help out.

Like all subjects, biochemistry has its own secret language that is very useful once you know it, but a bit offputting till then. Therefore, there is also a glossary at the back for quick reference, to remind you of the meaning of individual terms.

Lastly, students always worry – Have I really understood it? Will I pass the examination? To help check on that there are about 150 MCQs, a few on nearly every topic and immediately following that section, with answers given at the end of the book. The best way to use these is probably not to look at them until a few days after reading the topic. The topics are so short that, if you look at the questions immediately, you are almost bound to get most of them right. If you revisit a few days later, the questions will be more effective in helping you decide what has or has not sunk in.

The book as a whole is intended to help and fill a need. In that spirit, feedback, no matter how critical, will be very much appreciated (to paul.engel@ucd.ie). Comments and suggestions from nursing or other healthcare students would be especially welcome.

TOPIC 2

Remarkableness of life

What's so special about life?

Can we put our finger on what it is, in a general sense, that is so special about life and living structures? As already mentioned, there are a large number of remarkable processes to describe and explain, but I propose to summarise what all of them have in common by contrasting two very different sorts of object: a sleek new sports car and a living cell (Fig. 2.1). The modern sports car is a triumph of precision engineering and has a large number of gadgets and components to give us a smooth, safe, controlled ride. It is also eye-catching and commands our attention and is physically strong and durable. The cell, by contrast, is tiny and fragile, too small on its own to be noticed except under a microscope.

Self-direction

Let us, however, look at the unequal comparison a little harder. The car may have 0–60 mph acceleration in under 10 s, power-assisted steering, satnav and all the rest, but without someone at the wheel it is going nowhere. The cell on the other hand can rove around on its own initiative, exploring surfaces, changing shape, perhaps engulfing the odd particle. It does not need a driver.

Energy source

What about the fuel requirements? They both need fuel in order to power their activities, but if the car has a petrol engine you will be in trouble if you fill up with diesel (or vice versa). The cell will not thank you for either petrol or diesel, but, on

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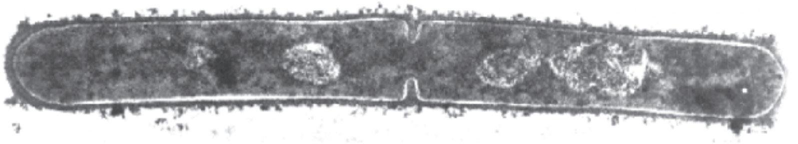
Figure 2.1 The dimensions in the image of the sports car are about 100 times smaller than reality. The mammalian cell, on the other hand, is shown with a diameter 700 times *larger* than reality, as seen under the microscope. (Porsche car image reproduced courtesy of Shutterstock.com)

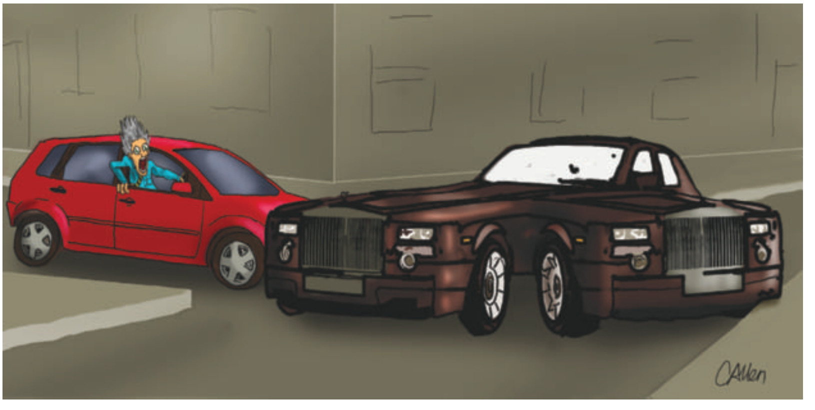
the other hand, depending a bit on just what sort of cell it is, it is likely that it will do pretty well on any one of a variety of different **sugars**. It might be reasonably happy to keep going with amino acids – fats might be another option; the cell in fact is likely to be remarkably versatile in its ability to use different energy sources. What is more, the cell goes out to find or soak up its fuel and does not depend on someone else to put a nozzle in its tank.

Self-assembly and replication

Just as the car needs a driver, at the assembly stage also it is manufactured according to an external blueprint on an assembly line, with people and other machines to put the parts together. The car itself cannot help the process along in any way, and if the assembly line shuts down, the car remains unfinished. The cell carries its own blueprint, and it interprets and carries out the instructions all on its own. A human cell might need a suggestion or a signal to get going, but once it gets the message it is autonomous. It makes or assembles all the parts it needs, and perhaps the most remarkable thing of all is that one cell will turn into two identical daughter cells as you watch it (Fig. 2.2a). If the Rolls stopped at the traffic lights turns into two Rolls, you should stick to the tomato juice! (Fig. 2.2b).



(a)



(b)

Figure 2.2 (a) The bacterial cell is shown undergoing its normal process of reproduction by binary fission, i.e. splitting into two identical daughter cells. Depending on the type of cell and the growth conditions bacteria can often accomplish this feat every half-hour or so! (b) An unlikely scene of a car undergoing binary fission.

Carrying the blueprint

Small and fragile maybe, but living cells have quite a bit to shout about in terms of their own precision engineering. If you consider what they can do, it is clear that, packed inside these tiny structures, there has to be an enormous amount of information content. The blueprint is somehow contained in the chemical substances that make up the cell, and, if we think about how the blueprint is put into action and about the fact that the whole structure assembles itself unaided, it is difficult to escape the idea that at least some of the biological molecules must be large and complex. Self-assembly implies a precise shape, to guide each piece in the molecular jigsaw puzzle into the right slot beside the right neighbours, and we shall see that shape is indeed critically important.

Thoughts about size

Superficially, there might seem to be a problem here. If cells are so small and their molecules are so large (and there are a lot of different kinds), how can we possibly fit all the molecules in? It sounds like the impossible pile of clothes on the bed beside the suitcase that is miles too small! The answer to this puzzle is that we are really talking about two different and unrelated scales of size: when we say the cells are small we are relating their size to what we humans can or cannot see with the naked eye. When we say that the molecules are large, we are not making any sort of statement about visibility. We are comparing them to much smaller chemical objects, far smaller than can be seen even under the most powerful microscope. Fortunately, this leaves enough space for biochemistry to do what it has to do! Even though in molecular terms these are big molecules, there is plenty of space for lots of them inside the average cell.

CHEMISTRY I

The basic structure of substances: atoms, molecules, elements and compounds

Do you need this section?

This is a reminder of (or introduction to) basic chemistry. If you have recently done and understood school or college chemistry, you can probably skip the whole of the next two chapters, which are here to make sure that everyone is happy with atoms, molecules, **valency** and other basic chemical concepts that we are going to need to use and take for granted as we move on through the biochemistry.

Does biology obey chemistry?

Until well into the nineteenth century, chemists thought that biology occupied a separate world with its own rules, different from those of ordinary chemistry, and involving mystical 'vital forces'. It gradually became obvious, however, that, special though they seem, living things obey exactly the same chemical rules as inanimate Nature does. The substances inside living organisms are made up of the same fundamental building blocks as are used in the world outside. The only difference is that, as we have already mentioned, some of these substances are remarkably complex. Coming together in the full architecture of the cell, they perform the intricate network of reactions that we call 'life'.

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The building blocks – atoms, elements and molecules

If you look at a shiny, gold ring it looks smooth and continuous, likewise a glass of water – both the glass and the water. But, even back in ancient Greece, philosophers wondered whether matter, the multitude of solid, liquid and gas substances that make up our world, was truly continuous or might perhaps be made up of tiny particles too small to see. Although they thought deep thoughts, they did not have ways to test their ideas. Humans had to wait patiently for a couple of thousand years for definite answers. At last, the experimental scientists of the seventeenth and eighteenth centuries produced the evidence. They concluded that:

1 Every pure substance (pure gold, pure water, pure oxygen, etc.) is made up of minute particles called **molecules**, all of them identical for a particular substance, so that every water molecule is like all the other water molecules. The water molecules are also different from all the molecules of oxygen or of any other substance.

2 Many substances are mixtures. A lump of granite, a bucket of sea water, a breath of fresh air and a piece of cake are all made of many different substances and therefore contain different kinds of molecules. In the case of the granite you can see separate bits of different substances – in other words, it is not very thoroughly mixed, but there is nothing immediately visibly obvious to tell us that air or clean sea water are mixtures.

3 Although there are vast numbers of different chemical substances, and accordingly vast numbers of different kinds of molecule, they are all made up from a much more limited set of smaller units called **atoms**. In fact, there are only a hundred or so different kinds of atom, each different sort with its own name. In the same way, a few dozen fixed kinds of Lego block will allow you to build an unlimited number of different structures.

4 Substances made up of only one kind of atom, carbon, hydrogen, oxygen, iron and so on, are known as **elements**. Therefore, since there are a hundred or so kinds of atom, there are also a hundred or so elements.

5 Most atoms have to have partners – rather than travelling around as lonely individuals, they form stable couples or families. This is what molecules are – precise groupings of exact numbers of certain kinds of atom linked together. Thus, oxygen atoms generally prefer to exist in pairs. The oxygen atom is given the symbol O and so the oxygen molecule is written as O_2 to indicate the pairing (Fig. I.1). Occasionally, a threesome is formed, and the different **formula**, O_3, makes this a distinct chemical compound, ozone in fact.

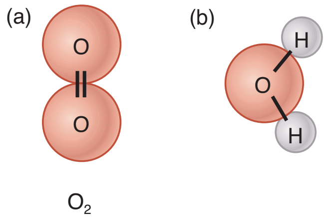

Figure I.1 (a) Pairing of atoms in an oxygen molecule. (b) Combination of different kinds of atom in a water molecule.

6 The pure substance water has a molecule made up of two different kinds of atom, oxygen and hydrogen, and in this case two hydrogen atoms (H) team up with a single oxygen atom (O) to make H_2O (Fig. I.1). The formula H_2O tells you what kind of atoms are in the molecule and how many of each. In the case of the gas, carbon dioxide, as the name implies (di = 2), one atom of carbon (C) combines with two oxygen atoms to give CO_2. Marriages of this sort between two or more different kinds of atom are called **compounds**.

Self-test MCQs on Chemistry I

1 Brass is made by melting together copper and zinc in variable proportions. Brass is therefore

(a) an atom? (b) an element? (c) a molecule? (d) a mixture?

2 CH_4 is the basic unit of the gas methane. Methane is therefore

(a) a compound? (b) a formula? (c) a mixture? (d) a molecule?

3 Hydrogen peroxide (found in hair rinses, washing machines, etc.) has the formula H_2O_2. Which is true?

(a) Hydrogen peroxide is a mixture of hydrogen and oxygen.

(b) Hydrogen peroxide is a mixture of water and oxygen.

(c) Hydrogen peroxide is a compound of hydrogen and oxygen.

(d) Hydrogen peroxide is a molecule of water and oxygen.

CHEMISTRY II

Atomic structure, valency and bonding

Fleas with little fleas: subatomic particles

As we have seen, chemists worked out over time that the world around us is made up of a huge range of different substances, usually mixed up together, but occasionally separate and pure. Each of these substances is made up of molecules, and the enormous number of different kinds of molecule is made up, in turn, of a limited set of possible atoms: carbon atoms, oxygen atoms, hydrogen atoms and so on. Molecules are therefore the smallest possible unit of any substance. However, in seeking to understand the difference between different sorts of atom and also what is actually happening when they combine in molecules, chemists and physicists eventually deduced that atoms themselves are made up of even smaller units called subatomic particles. Amazingly, the hundred plus different kinds of atoms are made up of different combinations of just three kinds of particles! These are

- **protons**, which carry a positive electrical charge;
- **electrons**, which carry an equal and opposite negative charge; and
- **neutrons**, which have no charge.

Every atom of every chemical element, carbon, oxygen, gold and all the others, is made up of combinations of different numbers of just these three kinds of particle.

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