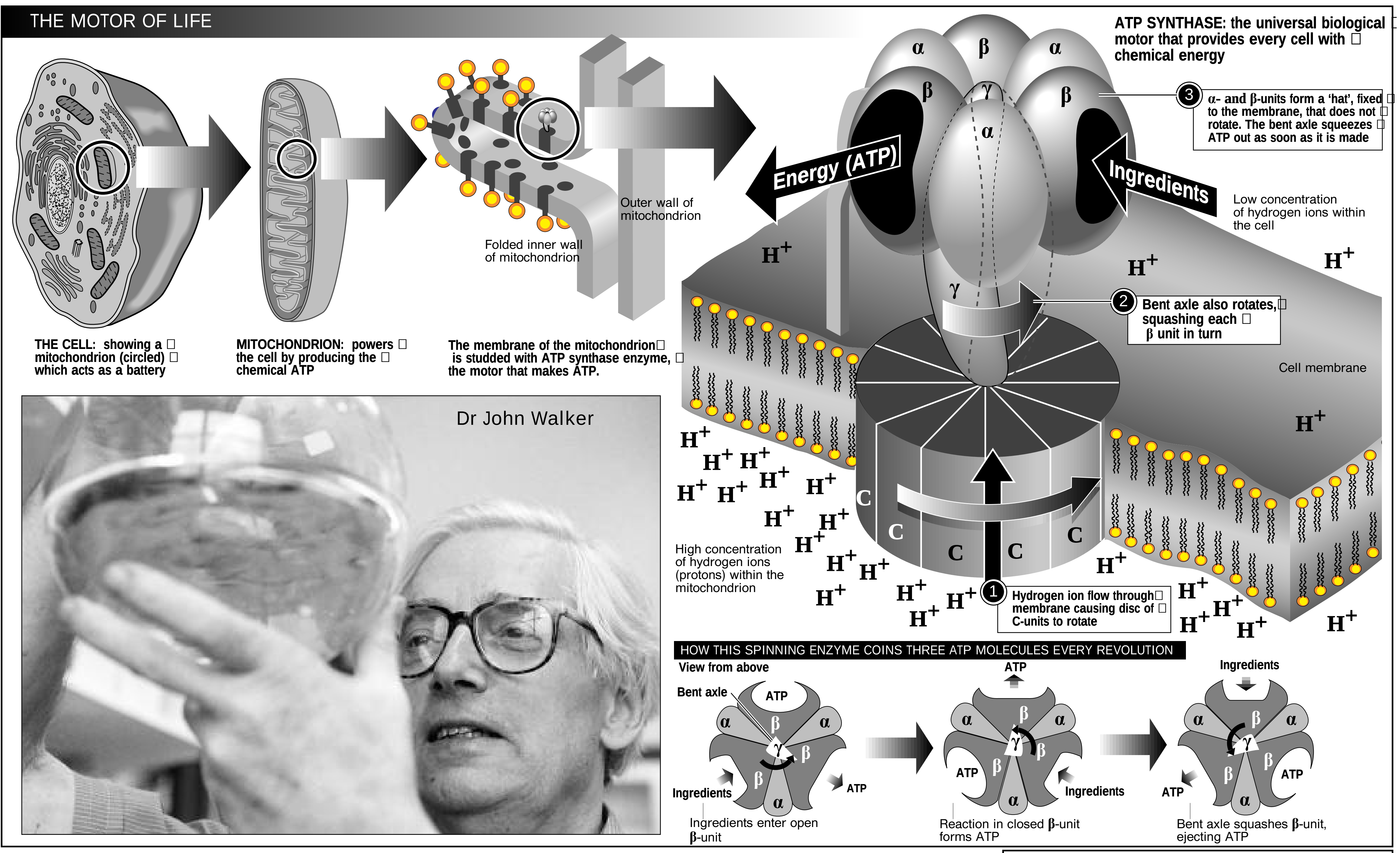
SCIENCE

The UK's latest Nobel prize-winner, Dr John Walker, revealed a wonder: a life-giving spinning enzyme. Roger Highfield reports

This is what drives you . . .



A brief history of ATP

1929: **German chemist Karl Lohmann discovered adenosine triphosphate, ATP.**

1939-41: **German-born Fritz Lipmann showed ATP is the universal carrier of chemical energy in the cell, winning Nobel prize in 1953.**

1948: **Englishman Lord Todd made ATP in the laboratory, earning the Nobel prize in 1957.**

1940s/50s: **Scientists establish that most ATP is made in mitochondria and chloroplasts the "batteries" found in the cells of animals and plants respectively.**

1961: **Englishman Peter Mitchell showed that a stream of protons — hydrogen ions — passing through the membrane of mitochondria drives the production of ATP. He won the Nobel prize in 1978.**

Late 1970s: **John Walker begins his studies of ATP synthase, the enzyme that makes ATP.**

1993: **Paul Boyer of the University of California, outlines the possible mechanisms by which ATP synthase worked.**

1994: **John Walker and colleagues produce an atomic snapshot of one key part of ATP synthase, revealing its spins like a tiny motor.**

1997: **Masaskuke Yoshida attaches a fluorescent filament so motor can be seen spinning under a microscope.**

1997: **Nobel prize for Boyer and Walker.**

THIS is the most important motor in history. As you think, walk, or digest your dinner, it is whirring away within your body to supply each and every cell with chemical energy.

Last week, Dr John Walker of the Laboratory of Molecular Biology in Cambridge shared a Nobel prize for his work to provide the first detailed picture of a wiggling "stalk" that forms the business end of this molecular energy machine, an enzyme called ATP synthase.

What is striking about this Nobel prize is that it reminds us that science is so much more than just an enterprise that generates patents and profits, as ministers try to tell us again and again.

Science is also about the beauty of the natural world, about mystery, curiosity and wonderment. Who can fail to be amazed by the thought that a spinning enzyme some 200,000 times smaller than a pinhead has enabled life to thrive on this planet for almost four billion years?

The prize marked the end of a 20 year struggle by Dr Walker to lay bare the mechanism of this microscopic whirling dervish.

The ATP synthase enzyme is huge compared with those that ceaselessly work throughout our bodies. Each one consists of 31 separate proteins. Working in harness they take proton power — a flow of hydrogen nuclei — to churn out a little molecule called ATP.

ATP, or adenosine triphosphate, has won a clutch of Nobel prizes for other researchers because of its profound importance: it provides the energy for the contraction of muscles, the beating of the heart and the functioning of the brain as you read this sentence.

This molecule is to our bodies what money is to economics. It is the energy currency of life. With ATP, you can run a cell — or a country for that matter.

Rather like energy can be stored away in a bent spring, so ATP locks it up within its energy-rich phosphate bonds. Snap one of these chemical bonds and energy is released to do work in a living cell. Without ATP, all living things — bacteria, fungi, plants, tigers — would die.

''We require our body weight in ATP every day,'' said Dr Walker. ''We are turning over that amount of ATP to keep ourselves thinking and walking around. It is incredible to think of these motors of life spinning around in our bodies.''

The spinning ATP synthase enzyme that coins ATP from its precursor, ADP, is found in rod-like structures called mitochondria that lurk in our cells. Every mitochondrion is studded with hundreds if not thousands of the enzymes.

Unlock the secrets of ATP manufacture and you have a clue to understanding human ageing, when our mitochondria flag, the fundamental mechanisms underlying Parkinson's disease, when our mitochondria die, and the way in which green plants convert sunlight into energy, the process that drives the living economy of the planet.

Plants also contain these cellular ''batteries'', though they are called chloroplasts. Even bacteria, the most ancient organisms, rely on the enzyme, revealing that this little motor has been spinning for almost four billion years, when the first primitive single cell creatures appeared on Earth.

DR WALKER embarked on his research two decades ago. He started with the idea that to understand ATP synthase, we have to know what it looks like — down to the last atom.

To take a molecular snapshot, he would have to purify large quantities of the enzyme, make a crystal, and then interrogate its structure with X-rays. When he confided with colleagues about his plans, a few thought that he was crazy.

The reason for their scepticism lay in the baroque complexity of ATP synthase. Genetic engineering can be used to make the 16 different protein components but it would take more than the patience of a Swiss watchmaker to assemble them into an actual working mechanism.

Old-fashioned, time-consuming methods had to be used instead. Every other week, Dr Walker or his colleague Dr Michael Runswick would go to a Northampton slaughterhouse to buy 25 fresh cows' hearts.

Mincing the hearts and extracting the enzyme was the easy bit. The hard part was producing a crystal of the enzyme, which was crucial if the team was to use X-rays to produce a picture of its atomic structure.

A substance crystallises when its component atoms or molecules arrange themselves in an orderly way, rather like a three dimensional version of soldiers forming ranks on parade.

This is trivial in the case of table salt: its component charged sodium and chlorine atoms can be stacked easily. But for a highly-complex molecule like ATP synthase, it is extremely difficult.

To make the job a little easier, Dr Walker took two steps. First he planned to use the X-ray source at Daresbury, Cheshire, one so bright that it would need only a tiny crystal of ATP synthase for an atomic snapshot. But the problem of how to grow that tiny crystal remained.

That is where the second simplification came in: Dr Walker decided to tackle only one part of the enzyme, the cluster of proteins where the ATP is made. Then followed years of trial and error to persuade these proteins to grow into a crystal of sufficient purity to yield good results. ''That was the crux of the whole project,'' he said.

The breakthrough took eight years and was due to the hard work of Dr Walker and Dutchman Dr René Lutter. The secret was to acknowledge that the working enzyme is, in effect, soaked in ATP and its energy-poor sister molecule, ADP. By introducing these molecules to the recipe, they could produce good crystals.

In fact, the feat was more subtle than this: they used molecules that were the same shape as ATP and ADP, to provide realistic ''padding'' for the enzyme, but which were chemically unreactive. ''That was quite tricky,'' said Dr Runswick. ''It was a slow tweaking process to get things right.''

Once a good quality crystal had been made, it was taken to the Daresbury laboratory where electrons are whirled around at speeds approaching that of light, producing bursts of X-rays rather like drops of water flying off a wet spinning bicycle wheel.

The way the crystal scattered the X-rays was measured by Dr Walker's colleagues, Dutchman Drs Jan Abrahams and fellow laboratory worker Dr Andrew Leslie. The resulting X-ray pattern was analysed by computer to determine the position of each and every atom in the enzyme.

The result, when displayed on computer, looks like technicolour tagliatelle. Each coloured strip corresponds to a chain of amino acids, the chemical building blocks of proteins. There are 3,000 amino acids in the business end of the ATP synthase molecule, making it one of the most complex biological molecules ever pictured.

After years of toil, Dr Walker was in a position to study this atomic structure and deduce how the enzyme works, revealing how it spins around to pump out ATP.

Each sausage-shaped mitochondrion in our cells is studded with the enzymes: one end, the motor, is embedded in the membrane of the mitochondrion and the other, where the ATP is made, dangles into the cell.

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The membrane end of the enzyme is a molecular wheel, made up of so-called ''c protein subunits''. As protons surge out of the mitochondrion, this wheel rotates at speeds of around 100 revolutions per second.

Attached to the wheel is a bent axle that also turns, the so called gamma protein subunit. It is supported at its other end by a ''hat'', a ring of six protein subunits — three alpha and three beta — that are anchored to the cell membrane and together form the part of the enzyme that fashions ATP.

Because the axle is bent, it deforms the hat as it sweeps around. This flexing action, it turns out, is crucial to the process of adding a phosphate unit to ADP so as to make ATP.

First, an ADP molecule nestles in one of the three beta subunits of the hat. A hollow in each subunit provides ideal conditions for ADP to mate with phosphate to make ATP.

The clever part comes from the way the bent axle pokes into the hat. As the axle rotates it wiggles, squashing each beta subunit in turn so it can no longer grip the small ATP molecule: ATP is ejected into the cell so that the hollow in each beta subunit can charge up with more ADP.

The work complements that of the scientist at the University of California who shared the prize with Dr Walker. Prof Paul Boyer began studying ATP formation in the early 1950s and, from indirect means, deduced this rotating mechanism, now called ''Boyer's binding mechanism''.

Some have likened the action to that of a water hammer used to mint coins. The wheel is the part of the enzyme rotating in the cell membrane.

The flow of protons is the waterfall, and the deforming beta subunit allows three ''coins'' of the ATP currency to be minted for each turn of the wheel.

This motor has now been seen in action, thanks to a beautiful experiment conducted by Prof Masasuke Yoshida and colleagues in Tokyo. They attached a fibre of muscle protein to the bent axle and ran the motor, upside down, under the gaze of a microscope. Videos showed how the fibre whirled around with increasing speed as concentrations of ATP increased.

THE work is of profound significance in biochemistry but could already find direct applications in treating heart disease. In sick heart tissue, ATP synthase ''runs backwards'', burning up the supply of ATP so the tissue perishes. Armed with the structure, we can begin to think of drugs to prevent this from occurring.

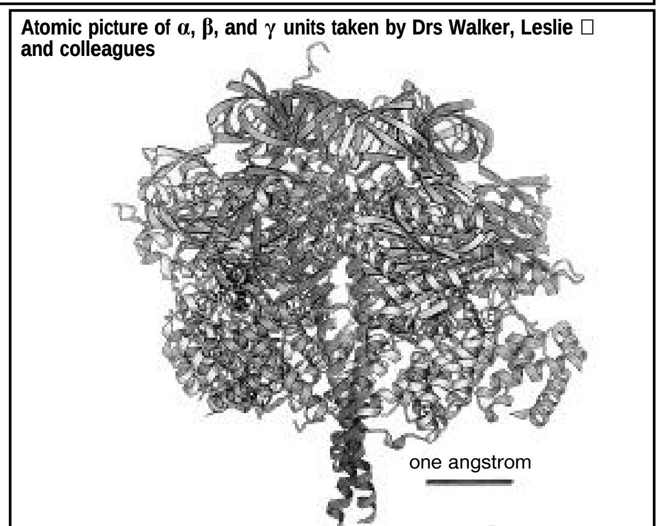
The epic timescale of Dr Walker's achievement underlines another feature of scientific endeavour. Given the increasing emphasis on short term projects and instant results, this kind of research is becoming a rarity.

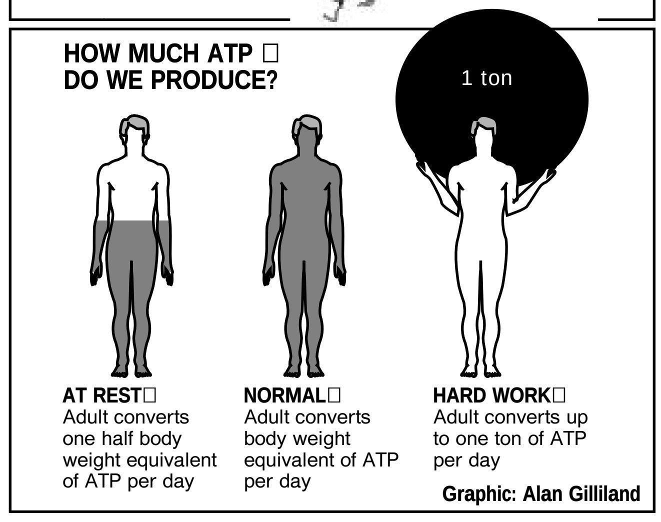
The Medical Research Council's Laboratory of Molecular Biology supported Dr Walker through the thin years, when there was little to show for his efforts. ''I am glad to say we backed him,'' said Sir Aaron Klug, former director and fellow laureate.

''I have been in an inspirational environment,'' said Dr Walker. ''Without this long term vision, I would not have been able to do the work.''

Nor has his mission ended. He and his colleagues have now turned their attention to the molecular structure of the enzyme's spinning disc, the motor that turns in the membrane of every mitochondrion. And how long will it take? ''A decade, perhaps even longer.''

Atomic picture of α, β, and γ units taken by Drs Walker, Leslie and colleagues





Graphic: Alan Gilliland