Mountains, Genes and Time

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(*Plates 81, 82*)

Several years ago a friend and I, after climbing some peaks in the Gran Paradiso area, planned to finish our holiday with an ascent of Mont Blanc by the Old Brenva Route. We arrived at the Trident hut in clear weather, but cloud to the south suggested unstable conditions, and nocturnal flickering of lightning across the Val d'Aosta deterred us from setting out in the early hours. When dawn came, the expected bad weather did not materialize. Instead we watched a perfect sunrise, pink turning to gold on the highest slopes of Mont Blanc, and stealing down the features of the Brenva face and the Peuteret ridge. Swallowing our disappointment, we turned our backs on the Brenva and climbed the Little Gervasutti couloir on the Tour Ronde instead.

When my colour slides came back from processing they recalled vividly the hues of sunrise on the great Brenva face. They also interacted with my thoughts at work. I was writing a research paper about a piece of sub-microscopic machinery that plays a central role in living cells. So central, in fact, that large parts of its structure have hardly changed at all during 65 million years of mammalian evolution. I looked at the slides again. Where was Mont Blanc 65 million years ago?

The answer, of course, is that it was nowhere to be seen. Entire mountain ranges, including the Alps and Himalaya, were built within this time-scale. The fact that features in the design of some biological structures should be more stable than the Earth's great mountain ranges is not intuitively obvious. What is the explanation?

Mountain building

Mountains are thrust up by colliding plates of the Earth's crust. The plates are in a state of continuous, slow movement relative to each other, carrying the continents raft-like on a substructure of basalt that spreads out from the mid-ocean ridges. The primary driving force for the movement is convection of heat generated in the Earth's interior, largely by the decay of naturally occurring radioactive atoms.

The rates of sea-floor spreading have been estimated by magnetic measurements, and are in the region of two to five centimetres per year.[1] The movements are transmitted through the rigid crustal plates. At boundary zones where two plates are being pushed into each other, one plate goes under, the

other overrides, and folds and crumples. The detailed consequences depend upon additional factors including whether continental land is involved on either side of the collision zone. Collisions involving continental masses on one or both sides of the colliding zone generate land-based mountain ranges; colliding oceanic plate boundaries generate island arcs and ocean trenches. The general point is that two to five centimetres of relative movement per year add up to 20–50 *kilometres* per million years, enough for very extensive folding and crumpling. Add to this the attritional effects of weathering and glaciation, and it becomes obvious that great geographic changes occur at plate boundaries even in one million years.

The Southern Alps of New Zealand have been thrust up in the last few million years. India had not yet collided with Asia 65 million years ago, the interactions that have pushed up the Alps had not yet happened, and the Atlantic, with America moving away from Europe, was little more than half as wide as it is now. The face of the Earth was very different then.

And yet the design of the particular component of living machinery that I and my colleagues had been studying had remained virtually unchanged through all this time. Immortality does not reside in the component itself, however, but in the blueprint for its construction. The blueprint is a gene. The essential features of genes that determine their immortality can be illustrated very simply.

Gene replication

Imagine a long string with red, yellow, green and blue beads. The order in which the coloured beads are arranged carries coded information, eg:

red, blue, green; red, red, yellow; blue, green, red; etc.

Then imagine a second string paired with the first. On the second string the beads are arranged so that at each position the colour is complementary to that on the first string: red opposite to green, yellow opposite to blue. Now take the strings apart, and next to each string, make up a new string by following the same rules of complementary pairing, red opposite to green, yellow opposite to blue. You now have two pairs of strings. Each pair, comprising one old string and one new complementary string, is a perfect replica of the original pair. This is exactly how gene replication works, except that instead of beads of four colours there are chemical units of four shapes. The material that is made of these four units is called DNA, and genes are made of DNA. The order, or *sequence*, in which the chemical units occur is unique for each gene, and the chemical shapes dictate complementary pairing and very accurate replication.

Two examples can illustrate the kind of functions that genes specify. Both examples are of mountaineering interest: the first concerns oxygen transport.

Haemoglobin

Oxygen is carried from the lungs to the rest of the body via haemoglobin in the

blood. In haemoglobin the oxygen binds reversibly to iron. The iron is held in a substance called haem, which in turn is held in a much larger substance called globin. In haemoglobin there are actually two types of globin, called alpha and beta, and there are two of each of these per complete haemoglobin molecule. This seemingly complicated structure determines the precise affinity of haemoglobin for oxygen, enabling efficient uptake in the lungs and release in the tissues.

Genes come into this scheme of things as follows. Each of the two types of globin is made from smaller units called amino acids, about 140 per complete globin. There are 20 chemically different amino acids, but it is the sequence in which they are assembled that is critical, just as with letters of the alphabet. The alpha and beta globin sequences are different from each other. Each of the two sequences, alpha and beta, is encoded in a separate gene.

There are also other globin genes. One of them encodes a globin called gamma, which is used instead of beta in the foetus. The resulting foetal haemoglobin has higher oxygen affinity than the mother's haemoglobin, enabling transfer of oxygen from maternal to foetal blood. Yet another globin gene specifies myoglobin, a transient oxygen store in muscle, relatively abundant in red muscle and especially in the diving mammals, whales and seals.

Rhodopsin

The second example of a gene concerns night vision. The eye has an exquisitely sensitive detection mechanism which makes it possible to see in very low levels of illumination, such as starlight on a glacier. The detector is called rhodopsin. In rhodopsin a molecule called retinal, a derivative of vitamin A, is surrounded by a larger structure called opsin. Retinal strongly absorbs light. Capture of an incoming photon of light causes retinal to flip shape, with consequent change of shape in the surrounding opsin molecule. This response triggers a cascade of further processes that result in a nerve impulse travelling from the retina of the eye to the brain. The summation of all such events gives us our picture of the (night) world.

Opsin and globin are both members of a large class of substances called proteins, all of which are made from the same set of 20 amino acids, but in a unique order for each protein. In opsin there are about 350 amino acids, and their order is totally unrelated to globin. Opsin is encoded by its own gene. There are also three other opsin-related genes. Their proteins are present in the retina in smaller amounts than rhodopsin, and they generate signals only in daylight. Each of these three additional detectors responds maximally to light of different colour, and together they mediate colour vision.

Many thousands of proteins go to make up a human being. Each protein has its own unique function, for example in digesting food, in extracting energy from the products of digestion, in muscular movement, in conducting nerve impulses, in fighting infections and so on. Each protein is encoded by its own gene.[2]

Gene ancestries

All human genes have long ancestries. For example, haemoglobin is present in all vertebrates, and a primitive form of globin is present in invertebrates. Thus an ancestral globin gene must have considerably preceded the origin of vertebrates, and globin genes must have been around for about 1000 million years. Most or all human genes can be traced back to ancestries from the beginnings of vertebrate evolution, many of them to the evolution of nucleated cells and some of them to the origins of life. The subcellular component that I and my colleagues had been studying is called a ribosome, a piece of machinery that is at the centre of the assembly line for all proteins. Its role is so fundamental that the origins of ribosomes must have been closely linked to the origins of life some 3500 million years ago.

Occasionally errors do occur in gene replication. Some errors are lethal and do not survive. Others are tolerated and some may be advantageous. Aberrations are of several kinds, ranging from incorporation of a wrong chemical unit at a particular site in the gene (called a point mutation) to duplication of an entire gene. The multiple human globin genes arose from successive duplications from an ancestral gene, followed by independent mutations. Thus the alpha, beta and gamma genes are related by descent.[3]

The rates at which mutations accumulate in genes are generally extremely slow. The rates can be measured by determining the sequences of the chemical units in the genes that encode the same protein in different animals, such as man, chimpanzee, mouse and frog. (Small samples of blood can supply sufficient DNA for the analysis.) Many such comparisons from a large number of genes show that to achieve divergence at one per cent of positions (or to change the colours of one per cent of the beads, using the earlier analogy) takes anything from one million years to 50 million years for different genes. Often the changes that do occur are such as to cause minimum effect on the function of the protein. These numbers explain how features in the design of some biological structures are stable over vast periods of time.

Genes and species

A difficult question remains: if most vertebrate animals contain most of the same (or functionally related) genes, why are there so many different vertebrate species? Notwithstanding Darwin's *Origin of Species* and much that has been written since, the processes leading to the origin of new species remain mysterious. The central problem lies in the extreme complexity of the interactions that are involved between large numbers of genes and proteins in the development of an organism.

Approaches to an answer are likely to come from three directions. First, duplication and divergence of genes as mentioned above provides a mechanism for some diversification of functions. Second, some genes produce proteins that are specifically involved in the activation of other genes during development. Some mutations in such genes (in fruit-flies, for example) exert major effects on

the developmental pathway. Possibly other changes accumulated during evolution might exert subtle developmental effects, and many such changes might contribute to species divergence.

A third source of biological variation may arise from the following relatively recently discovered properties of DNA and its behaviour. All genes are DNA, but not all DNA is genes. In man and in other animals the genes are linked to each other by long tracts of extragenic DNA. The extragenic DNA accumulates changes much more rapidly than the genes themselves, and its function is largely unknown. Increasingly, however, regions are being discovered within extragenic DNA that modulate the activities of genes, with regard to 'turning on' or to the quantity of a protein that is produced. This extragenic DNA affords potentially enormous territory for the evolutionary testing of changes in complex regulatory interactions among genes, such as those involved in developmental pathways. It is likely that biological variation leading to the appearance of new species is at least partly linked to changes in the rapidly evolving extragenic DNA.

Species exist for finite periods before being replaced by new species. Genes are passed on not only from individual to individual but, often with relatively little change, from species to newly evolved species. In contrast to the great evolutionary stability of most genes, species survival times are often of the order of a few million years before new species take over. Geographical factors play an important role in speciation, by isolating populations in which DNA variations may arise and become fixed. It may not be fortuitous that species lifetimes, as opposed to gene lifetimes, are often roughly comparable to the timescales for substantial geographic changes by the processes described above.

This discussion has traversed some distance from sunrise on Mont Blanc, but it is an interesting reflection that the analysis of life at the level of the precise structures of genes and DNA is leading to new and deep insights into life's origins and most ancient features, its long history, the emergence of new functions and new levels of complexity, and the mechanisms whereby we perceive and interact with the world around us.

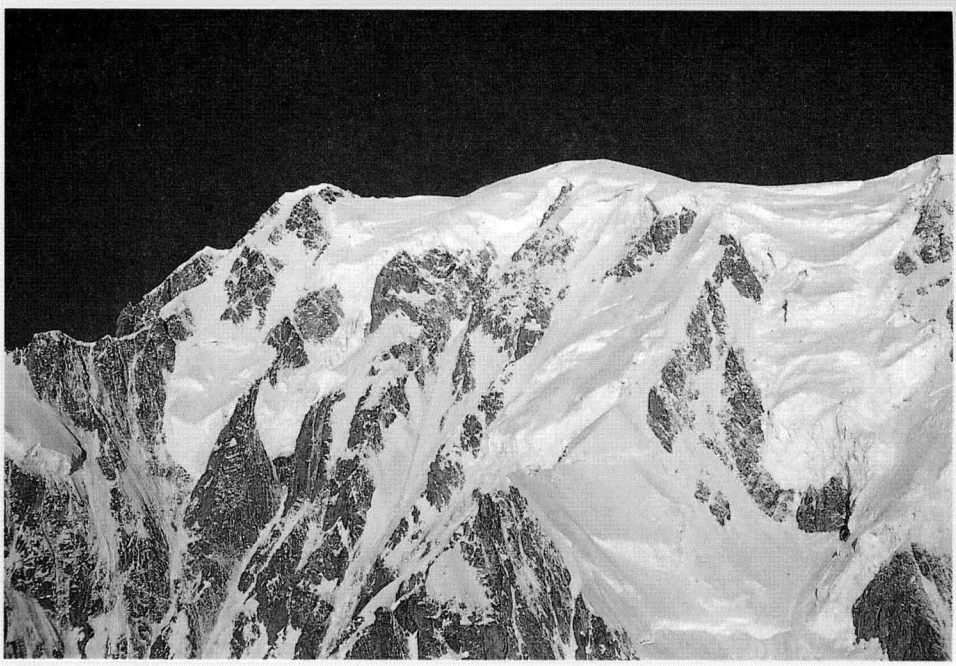
NOTES

1 The Earth's magnetic field has reversed in direction several times during geological history. Magnetism in the direction of the prevailing field becomes 'frozen' into basaltic rocks when they first form. The distribution of normal and reversed magnetized bands outwards from mid-ocean ridges, detected by measurements at the sea surface, together with the reversal times calibrated from land-based rocks of known ages, gives the rate of sea-floor spreading.

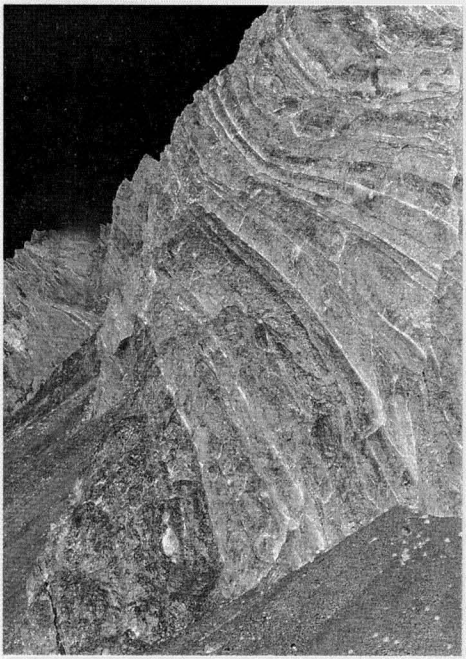
2 In a gene, a triplet of chemical units encodes each amino acid. This is indicated in the 'red, blue, green;' analogy above by a semicolon after every third colour. There are 64 such different triplets. Each of the 20 amino acids is encoded by one or more triplets, and the code linking

particular triplets to particular amino acids is (almost) invariant throughout nature.

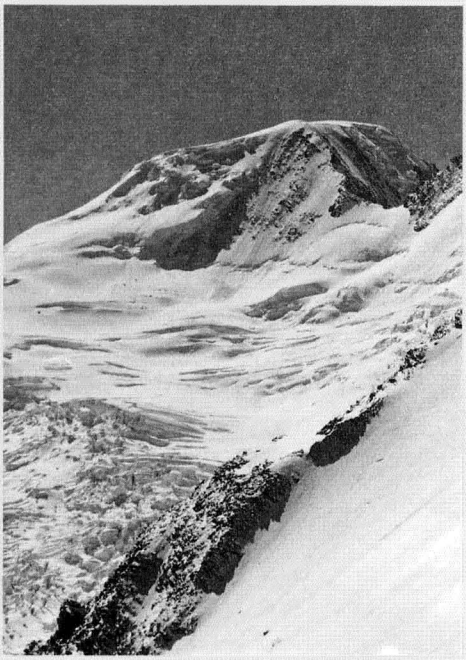
3 A group of genes can be recognized as being descended from a common ancestral gene not only because the genes specify related functions, but also from features of their internal structure called introns, which occur in precisely homologous locations in related genes. Introns are tracts of DNA that interrupt the continuity of the coding sequences. For example the coding regions of globin genes come in three blocks, with an intron separating the first and second blocks and another intron separating the second and third blocks. For a fuller account of introns in genes see P Chambon, 'Split Genes', *Scientific American* 244(5), 60–71, 1981.



81. Mont Blanc Brenva Face, July 1977. (Ted Maden) (p 182)



82. 'Folding and Crumpling': Zanskar Himalaya, July 1988. (Ted Maden) (p 182)



83. Alphubel NE face (L) and N ridge. (C A Russell) (p 215)