

A Life Writ on Water

Close to where I now sit is the cemetery at Testaccio in Rome where lay buried "the only mortal remains of a young poet" who asked that the following words be engraved on his tombstone, "Here lies one whose name is writ on water". These strangely evocative words are, of course, those of Keats. Close inspection of the tombstone shows that the medium in which the epitaph is inscribed, stone, will likely be a good deal less permanent than Keats' name; already, after less than 200 years, the inscription is being obliterated and may well be illegible in another 200 years.

Forty years ago in Cambridge the molecular structure of DNA was unraveled and we understood for the first time the process by which inheritance operated at the molecular level. In this thread like molecule is written the genetic code, defining all the physical characteristics an organism is born with. Here is a message that has endured, at least in essence, if not in every detail, not over centuries but over eons. If the stone mason's art cannot endure 400 years without degradation, how has Nature achieved the maintenance of the genetic code?

For indeed DNA is not a stable compound under physiological conditions. Where and when this important fact was first discovered is a little unclear. The discovery is usually attributed to Professor Tomas Lindahl in collaboration with another Swedish scientist, Nybourg in 1972, and indeed Lindahl is the author of a very recent paper in the journal *Nature* on the subject of DNA instability. However, it seems that the point may have been made a year earlier by the Russian scientist Mikhail Villenchick working at the Biological Centre of the Soviet Academy of Sciences in Pushchino near Moscow, and published in a report which did not receive wide circulation. Regrettably, Villenchick's career fell victim to the collapse of the Soviet Union in the late 1980s and he has received no recognition for this discovery outside the former Soviet Union.

That DNA is not stable should come as no surprise, but the implications of this instability are still far from fully realised and the remarkable stability of the code, seen against the impermanence of the medium in which it is written, should give us pause for thought.

In his *Nature* article Lindahl describes in detail the many processes which degrade DNA under physiological conditions. The most important is the molecule's own tendency to decay at body temperature but, in addition, several of the products released by the normal metabolic activity of the cell attack the DNA in much the same way as the pollutants released as a result of man's activities in Rome are eating away at Keats' epitaph. Broadly speaking, in the human cell, which contains approximately three thousand million of the base pair units of DNA, one hundred are damaged every minute of every hour of every day. Without what must be the most extraordinarily efficient and effective repair processes, we would be a catastrophic mess of errors within a very short time.

Forty years ago, the discovery of the structure of DNA showed how in effect the code was duplicated by means of a very specific pairing of bases in the two strands of the DNA duplex in much the same way as a photographic print contains essentially the same information as the negative from which it is produced. Thus, provided one of the pairs of bases is intact, the information is available with which to effect the repair. The probability of two paired bases being simultaneously damaged is infinitesimally small.

Lindahl suggests in his *Nature* article that mutagenesis, carcinogenesis and aging may be the result of DNA instability. Mutagenesis is an essential requirement for evolution to have taken place. If there were no instability, or all was repaired with perfect fidelity, then there would be no mutations to be exploited by natural selection and so allow the evolution of facilities such as sight, hearing, consciousness etc. However, this rate of evolutionary change (measured in events per thousand years) is so out of proportion with the rate of decay of DNA that it seems they cannot be causally connected.

Of course the instability of DNA must not necessarily be seen as evolutionarily beneficial; it may simply be a 'fact of life' that life has had to come to terms with. If this is so then it must be well worth trying to find out how it has done this so successfully.

Higher, that is multicellular, organisms such as man have evolved to have a fairly high rate of cellular turnover in parts. The cells of the blood and lymphatic system are a case in point but so are the male gonads, where part (half) the DNA code that will code for the next generation is stored. These functional cells are continually being generated and, in order to maintain a balance, they are of course also dying or being discarded. In some parts of the body cells are dividing every few days and the total DNA in each such cell is being replicated at each division. Since the degradation process cannot be halted even for a few seconds it is seemingly impossible that an entirely error free replication of the DNA could ever take place. There must always be some residual damage at the time of replication. That is not, however, the whole story. The capability of repairing DNA damage has to be written into the code in each cell, i.e., it too is written in DNA and thus is also subject to degradation and must also be prone to be replicated when carrying damage. It could be argued that there must be, in addition to the capability to repair damage at the 'base' level in the DNA, also some very efficient mechanism to 'proof read' the code after replication, but this raises the questions of against what is it read, and how this mechanism is maintained in an error- free state if it also has to be coded in DNA?.

The fact of the instability of DNA does not seem compatible with the fact of the stability of the genetic code, yet both are inescapable. Paradoxes such as this ought to make us question the very basis on which we think about the phenomenon of life.

Perhaps Keats saw something that has eluded us at the scientific level when he foresaw permanence going hand in hand with impermanence. In Nature we do see extraordinary stability in what are essentially dynamic systems; whirlpools or vortices in flowing water are but one example. In one sense they are stable, yet in another they are transient; they exist in essence but not in substance, or at least only very fleetingly in substance. Perhaps life has that quality even at the molecular level, and if so, the present methodology of science is not well suited to investigate it. But to be clear, this is not to say that there is anything mystical about life - any more, that is, than there is about whirlpools and vortices.

The discovery of the structure of DNA and the molecular basis of the genetic code led to the birth of molecular biology. From this technology much has been learned about the genetic origin of diseases, the nature of mutations and how they can affect health, of how genes can be switched on and off and much more. Forty years on, the subject is rightly flourishing, and is seen to be the key to major advances in medicine over the next decade. In the future is the prospect of modifying the code of individuals to mitigate illness or to endow the individual with desirable characteristics. Some would argue that before tampering in this way with the genetic mechanism we ought really to understand a bit better how it works. A central, even dominant, thrust of activity in molecular biology today is the sequencing of the of the three thousand million base units of the code. A truly gigantic, if somewhat pedestrian, technological undertaking, which will ultimately produce a directory of the human genome. I fear though we can expect to learn from this great labour as much about how life 'works', or in the case of disease, does not work, as we can learn about how a telephone exchange works, from a telephone directory.

In Testaccio the only mortal remains of Keats lie at equilibrium with the earth in which they are buried. The poetic output of this young man ceased the day that equilibrium was reached in 1821. If Keats' DNA could be sequenced I very much doubt that we could discern any trace of what gave rise, in those twenty six years of DNA replication and protein synthesis, to that output of magical imagery with words that has so captured the world's imagination since. Of course molecular biologists would not claim to be able to do so. But I for one would feel a great deal more comfortable about the future, in a world where manipulation of the human genetic code, through technology, was a reality, if someone could explain convincingly how the extraordinary stability of the genetic code is maintained on such a transient medium as DNA.

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