Hope behind the smokescreen

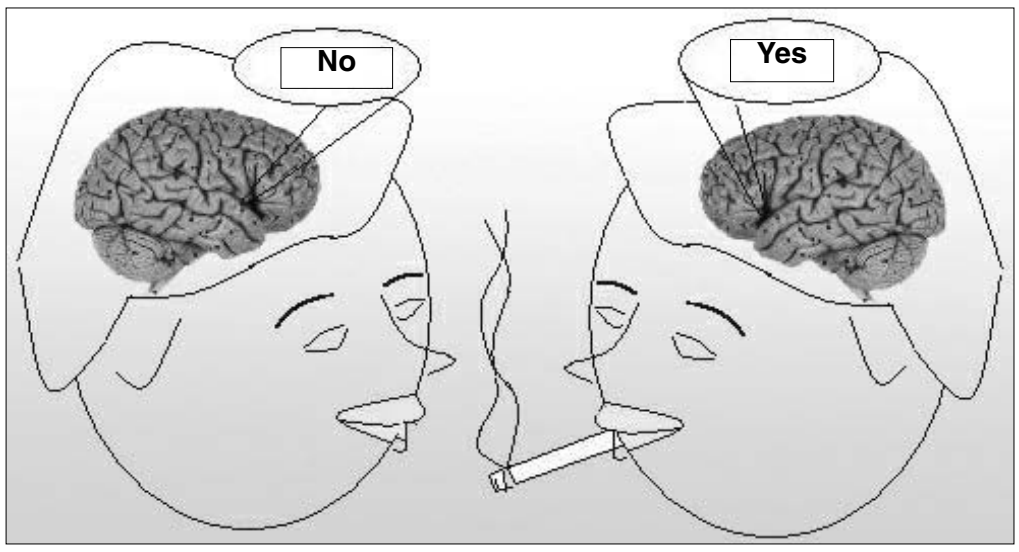
Gene-level manipulation may help smokers kick the habit, says s ananthanaryanan

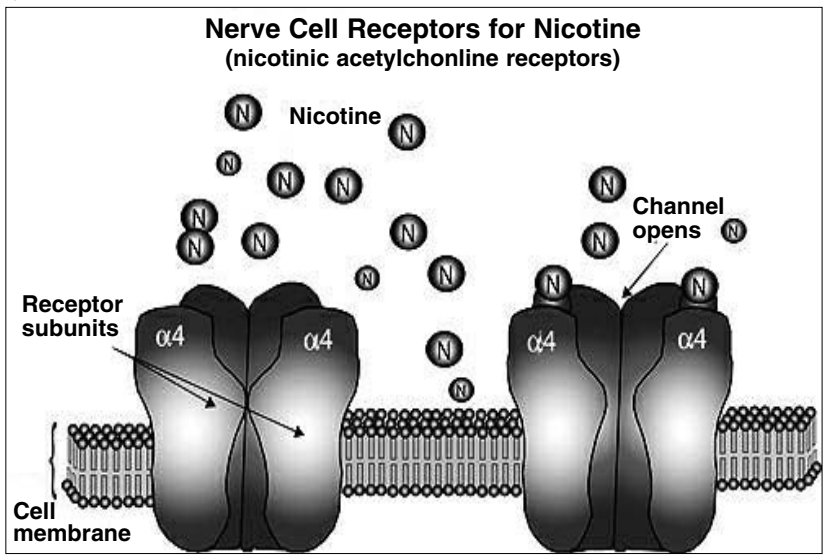
TOBACCO smoking kills more than five million people each year and is the cause of 90 per cent of the deaths from lung cancer. Practically every smoker knows this fact as well as anybody who does not smoke, but yet the bond between the smoker and the cigarette is difficult to break.

Christie D Fowler, Qun Lu and Paul M Johnson of the Laboratory for Behavioural and Molecular Neuroscience, Department of Molecular Therapeutics, The Scripps Research Institute, Florida, and Michael J Marks and Paul J Kenny of the Institute of Behavioural Genetics, University of Colorado, Boulder, report in the journal *Nature* that they have identified the genetic causes of the greater tendency that some people have to the lethal addiction.

The *habenula* is an area deep within the brain, which stimulates generation of vital channels of communication among nerve cells, like *dopamine*, and plays an important role in stress response and learning, particularly response to reward and punishment. It has been found that the nerve cells in this area have surface features, called receptors, where nicotinic acetycholine, the active nicotine component in tobacco, can attach itself. These nicotine reception structures are called nicotinic acetylcholine receptors, or *nAChRs*'. There are different types of nAChRs components, some of which seem to be more closely related to tobacco addiction.

The nature of cells and the shape and details of the surface of cells is controlled by the genetic code in the chromosomes, which are present in the nuclei of cells. A major advance made with nAChRs has been that a particular genetic change in a known portion of the chromosome is found to increase susceptibility to tobacco addiction. It appears that variations in *CHRNA5*, the gene that affects the receptor subunit called the "?5 subunit" can reduce the function of the subunit and lead to tobacco addiction. Just how nAChRs that contain the ?5 subunit (denoted as ?5*nAChRs) influence smoking behaviour has not been clear, but it is significant that the CHRNA5 gene variability is also a major risk factor in lung cancer and chronic obstructive pulmonary disease in smokers. Which is a double disadvantage for persons who carry the genetic feature.





Study on mice

The researchers carried out studies on how ?5*nAChRs affect the reinforcing and, therefore, addicting properties of nicotine with the help of experimental mice. The mice were prepared with a surgical pathway that opened to the jugular vein for delivery of doses of nicotine. They were then trained to seek food rewards by activating a lever. Next, they were introduced to nicotine and trained to seek rewards of doses of nicotine. This preparation now made it possible to study both the quantity of nicotine taken up by the mice and the addiction to nicotine, related both to genetic variation as well as to the level of the dose of nicotine.

The study first showed that ordinary, wild strains of mice, which had no special tendency to express the CHRNA5 gene, developed the addiction to self-administer doses of nicotine, with an "inverted U" response pattern that is a pattern like this "?". This means the need to receive doses of nicotine first rapidly rises, then remains stable at a high level of dosage, till, at higher doses, it reduces, or changes to "aversion".

Mice where the ?5*nAChRs subunit was present, called knockout mice, however, responded more vigorously to nicotine infusions and, furthermore, they did not respond with falling desire for nicotine when they reached large doses. Another feature noticed was that while normal mice limited the quantity of nicotine they absorbed out of each dose made available, the knockout mice did not limit their response and consumed more and more as the dosage was increased. A case of "spiralling increase in drug motivation" without limits set by "drug satiation".

The study then looked at where in the brain the ?5*nAChRs subunits which responded to nicotine were to be found. Using methods of measuring the rate at which glucose was consumed, the team identified the part of the *habenula* where the response was triggered, separately for low and high doses of nicotine. It could then be shown that in the habenula, high doses of nicotine triggered an inhibitory motivational signal which was switched "off" by the ?5*nAChRs subunit.

The next step was to "rescue" the ?5*nAChRs subunits by injecting a virus-like agent that could make alterations in cells, which could be done at different parts of the mouse brain. These studies again showed that when the ?5*nAChRs had been "rescued", the mouse resumed the "inverted U" response to nicotine use. The result of the study is that a framework for understanding the motivation drives that control nicotine intake has been set up. This would be key to understanding genetic and brain structure related vulnerability to tobacco addiction. The study has identified ?5*nAChRs as an important target for developing therapies to help people stop smoking.

The writer can be contacted at simplescience@gmail.com

Out of Africa

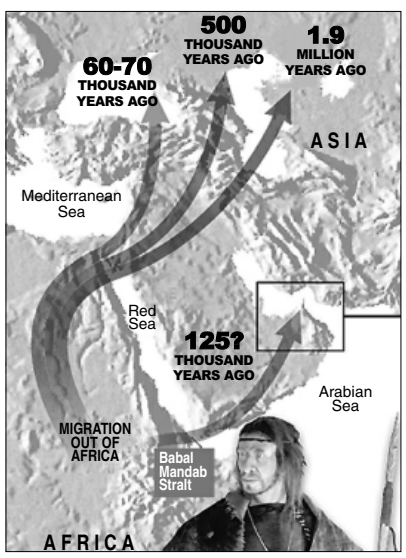
Stone tools rewrite history of man as a global species. steve connor **reports**

A view of the rock shelter at Jebel Faya shows the excavation trenches. Although extremely hot and arid today, the region was cooler and wetter 125,000 years ago, with more vegetation and wildlife.

A STONE age archaeological site in the Arabian peninsula has become the focus of a radical theory of how early humans made the long walk from their evolutionary homeland of Africa to become a globally-dispersed species. Scientists have found a set of stone tools buried beneath a collapsed rock shelter in the barren hills of the United Arab Emirates that they believe were made about 125,000 years ago by people who had migrated out of eastern African by crossing the Red Sea when sea levels were at a record low.

The age of the stone tools and the fact that they appear similar to those made by anatomically-modern humans living in eastern Africa suggests that our species, Homo sapiens, left Africa between 30,000 and 55,000 years earlier than previously believed. This casts new light on how modern humans eventually inhabited lands as far apart as Europe and Australia. Genetic evidence had suggested that modern humans made the main migration from Africa between 60,000 and 70,000 years ago, although there was always a possibility of earlier migrations that had not got much further than West Asia. However, all these movements were believed to have been made into West Asia by people walking along the Nile valley and over the Sinai Peninsula.

The stone tools unearthed at the Jebel Faya site about 50 km from the Persian Gulf suggests another possible migratory route across the Bab al-Mandab Strait, a tract of open water which separates the Red Sea from the Arabian Ocean and the Horn of Africa from the Arabian Peninsula. The scientists behind the study said that at the time of the migration, about 125,000 years ago, sea levels would have been low enough for people to make the crossing by foot or with simple rafts or boats. They also suggest that the waterless Nejd plateau of southern Arabia, which would have posed another barrier to migration, was in fact at that time covered in lakes and lush, game-filled vegetation.



"By 130,000 years ago, the sea level was still about 100 metres lower than at present while the Nejd plateau was already passable. There was a brief period where modern humans may have been able to use the direct route from East Africa to Jebel Faya," said Professor Adrian Parker of Oxford Brookes University, who was part of the research team.

Once humans had crossed into southern Arabia, they would have enjoyed the benefits of a land rich in gazelle and, with little competition, the migrant community could have quickly expanded to become an important secondary centre for population growth, which later migrated across the Persian Gulf to India and the rest of Asia, the scientists suggest.

Simon Armitage of Royal Holloway, University of London, the lead author of the study published in the journal *Science*, said that discovering the dates of the stone tools was the key piece of evidence suggesting there was a much earlier migration out of Africa than previously supposed. "Archaeology without ages is like a jigsaw with the interlocking edges removed – you have lots of individual pieces of information but you can't fit them together to produce the big picture."

Dr Armitage said. "At Jebel Faya, the ages reveal a fascinating picture in which modern humans migrated out of Africa much earlier than previously thought, helped by global fluctuations in sea level and the climate change in the Arabian Peninsula."

The stone "tool kit" found at Jebel Faya includes relatively primitive hand axes and a collection of stone scrapers and perforators. The scientists said the tools resembled artifacts found in eastern Africa and their primitive nature suggested that migration did not depend on the invention of more complex tools. "These anatomically modern humans, like you and me, had evolved in Africa about 200,000 years ago and subsequently populated the rest of the world. Our findings should stimulate a re-evaluation of the means by which we modern humans became a global species," Dr Armitage said.

However, not all scientist are convinced. Paul Mellars of Cambridge University told *Science*, "I'm totally unpersuaded. There's not a scrap of evidence here that these were made by modern humans, nor that they came from Africa."

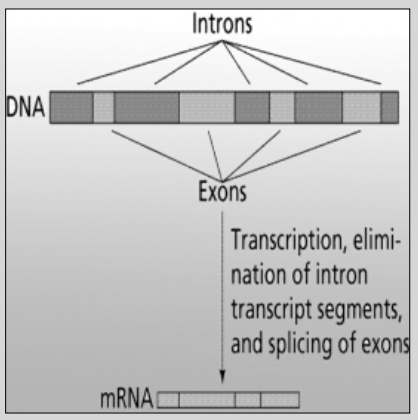
The Independent, London

The genetic puzzle

tapan kumar maitra reflects on current research and its impact

SINCE the discovery of introns, geneticists have been trying to figure out why they exist. Several views have arisen. Walter Gilbert suggested that introns separate exons (coding regions) into functional domains — that is, they separate different exons that presumably have specific tasks. In a given protein, one exon might code for a membrane-binding region, one might code for the active site of the enzyme, and one might code for ATPase activity. By recombinational mechanisms, or by excluding an exon during intron removal, exon shuffling would allow the rapid evolution of new proteins whose structures would be conglomerates of various functional domains. In a 1990 article in Science, Gilbert, with two colleagues, calculated that all proteins in eukaryotes can be accounted for by as few as one thousand to seven thousand exons; all proteins may be conglomerates of this primordial number. However, this view is controversial.

J Darnell and WE Doolittle have expanded Gilbert's idea of exon shuffling into the introns-early view These suggest that introns arose before the first cells evolved. After eukaryotes evolved from prokaryotes, the prokaryotes Lost



their introns. This is supported by the evidence that, pmerally, prokaryotes lack introns. This view is also consistent with the opinion that the original genetic material was RNA. In this "RNA world", introns arose as part of the genetic apparatus; they were the first enzymes (ribozymes).

An alternative view is that introns arose later in evolution, after the eukaryotes split from the prokaryotes.

At first, the justification for this introns-late view was that introns evolved late to give the organism the ability to evolve quickly to new environments by an exonshuffling type of mechanism. However, evolutionary biologists don't accept the rationale of evolution based on future needs. An alternative explanation is that introns are actually invading "selfish DNA," DNA that can move from place to place in the genome without necessarily providing any advantage to the host organism. We call these "jumping genes" transposons.

Thus, both time frames for the development of introns — late or early — have conceptual support.

Evidence exists to support both views. Gilbert's exonshuffling view is supported by the analysis of some genes that do indeed fit the pattern of exons coding for functional domains of a protein. (Analysis consists of DNA sequencing, RNA sequencing, and protein structural analysis.) For example, the second of three exons of the globin gene binds heme. Similarly, the human low-density lipoprotein receptor is a mosaic of exon-encoded modules shared with several other proteins. Autocatalytic properties of introns lend credence to the view that RNA was the original genetic material and that introns can move within a genome.

Additional evidence for the introns-early hypothesis includes the discovery of several introns in phage genes and introns in transfer RNA and ribosomal RNA genes in ancient bacteria (archaebacteria). Until recently, however, no introns were known in the true bacteria (eubacteria). That changed with recent work from the labs of D Shub and J Palmer, who independently discovered an intron in a transfer RNA gene in seven species of cyanobacteria (blue-green algae of the eubacteria). This intron was suspected to exist because it occurred in the equivalent chloroplast gene; the chloroplast evolved from an invading cyanobacterium. However, this discovery has been viewed as supporting both the intronsearly and introns-late view. The introns-early supporters say this evidence confirms that introns arose before the eukaryotes-prokaryotes split. Introns-late supporters say they expect to see some introns in prokaryotes because of the mobility these bits of genetic material have.

Both the introns-early and the introns-late views may be correct. It is possible that introns arose early, were lost by the prokaryotes, which prioritized small genomes and rapid, efficient DNA replication, and later evolved to produce exon shuffling in eukaryotes.

The writer is head of the department of botany at Anandamohon College, Kolkata