Podcast interview: Steven Benner

PNAS: I’m your host, Sandeep Ravindran, and welcome to Science Sessions. Humans have been consuming alcohol, and specifically ethanol, for a very long time, but exactly when alcohol first entered human diets is unclear. Steven Benner, a Distinguished Fellow at the Foundation for Applied Molecular Evolution, has been reconstructing ancient alcohol-digesting enzymes to gain a molecular perspective on the interaction between early humans and alcohol. Benner previously studied the molecular evolution of a different enzyme, DNA polymerase, in work that was published in PNAS. I met with Benner at the 2013 American Association for the Advancement of Science meeting in Boston, and he begins by describing how he decided to investigate the conventional explanation for the evolution of alcohol-use and alcoholism in humans.

Benner: People come up with evolutionary models for diseases and things all the time, so with alcohol the standard model that’s out there in the world is that civilization came along, you moved north, you needed to preserve fruit for the winter, and so the way you did that was by constructing pots that would hold malt liquor for beer, or at some point it’s going to become beer. So the conventional explanation for disease as it relates to alcohol consumption is that you have not adapted genetically fast enough to keep up with the changes that your civilization has. If your view is that alcoholism is a result of recent civilization producing alcohol, that the paleolithic diet that you had 6,000 years ago, 10,000 years ago, 20,000 years ago, did not have alcohol in it, that you’re poorly adapted to it, what you can say is, “Ok, if that’s my model for the history of alcohol interaction, and for the history and explanation of alcoholism as a disease, let’s try to do some tests.”

PNAS: How did you figure out when early humans may have first gained the ability to digest alcohol?

Benner: We can infer by experiments when ethanol first became available on Earth as about 80 million years ago. That’s the time of the dinosaurs. That’s a hypothesis, it’s associated with among other things the emergence of fleshy, fermentable fruit 80 million years ago. But it also is supported by chemistry, where you resurrect the ancient yeast enzymes in the modern laboratory. Then what you do is you discover as you go through these resurrections of ancient proteins in the primate lineages is that you’re not drinking alcohol 80 million years ago, at least your enzymes are not prepared to drink it. This is also true when the New World and Old World monkeys diverged, say 40 million years ago, give or take. And it’s also not true when you’re diverging from the Orangutans. But if I resurrect an enzyme from your ancestor who lived 10 million years ago, all of a sudden that enzyme has acquired the ability to eat alcohol. You’ve been exposed to ethanol for 10 million years, that means.
**PNAS:** Benner describes how he resurrected ancient alcohol-digesting enzymes

**Benner:** This is not Jurassic Park. You’re looking at the derived sequences of amino acids, and you write them on top of each other. So, you know, the alcohol dehydrogenase from you and chimpanzee are essentially the same. The more modern sequences you have, the more you can infer the sequences of ancient proteins, so that the sequences of modern proteins can be gotten with the smallest number of amino acid replacements. Students went out, they got all of these wonderful zoos to give us tissue, actually, from livers flash-frozen, because you want to preserve the RNA, because you want to reverse-transcribe the DNA and get the sequences out. And so what emerges from this is various alcohol dehydrogenases from 50 organisms, and then you build a tree which says their family relationships, and then you infer the sequences of the ancient proteins. And then, the magic of recombinant DNA technology steps in. These days I can order a gene that encodes a dehydrogenase that lived 80 million years ago. We then express these proteins in the laboratory, we purify them, and we’re basically looking at the same sequence that we would look at if we could build a time machine and go back.

**PNAS:** What led humans to evolve the ability to consume alcohol?

**Benner:** Alcohol in the vernacular means ethanol. So you have of course in your diet, all sorts of alcohols and aldehydes, and so before 10 million years ago you had an enzyme which was perfectly active against all sorts of long-chained big alcohols, but not against ethanol. It is the current interpretation of the fossil record, that at the same 10 million year time slot you’re starting to walk upright, you’re starting to have your hands free to collect and gather fallen fruit. Fallen fruit is likely to have its husk damaged. Fallen fruit is likely to have fermentation through yeast infection. Fallen fruit that’s carried of course gives the yeast time to make enough alcohol. You take it back to your mate, you give her the alcohol, she has got to be able to manage the ethanol at the level which yeast makes it.

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