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Genetic Code

(Dr Isichei)

In 1869, Friedrich Miescher isolated a substance from the nucleus of a cell. He had no idea of its importance and did not pursue his discovery to its logical conclusion. It was only after half a century later that scientists began to suspect that Miescher's forgotten chemical, now called deoxyribonucleic acid (DNA) was the missing link between inanimate and animate matter. In 1903 a medical student by name Sutton proposed the chromosome theory of inheritance. He suggested that genes, the basic units of heredity capable of transmitting characteristics from one generation to the next, are carried on chromosome. In the 1940s Avery and his colleagues discovered that the chromosomes carry some acids and they quickly named them nucleic acids because they were associated with the nucleus. The basic unit of nucleic acids is the nucleotide. Nucleotides are found in the cell either as components of nucleic acids or as individual molecules, in which form they play several different functions. Each nucleotide is a complex molecule made up three distinct components: a sugar, a nitrogenous base, and phosphoric acid. The phosphate of one nucleotide is linked to the sugar of the nucleotide. The nucleic acids were later discovered that they were deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) respectively based on their sugar components. DNA is the store of genetic information while RNA is used in the expression of genetic information. There are four different bases in each class of nucleic acid. Three are common to both and one is unique to each. It was postulated that the genes were carried by the DNA; but the question is that "how can a DNA carry gene?" Research has proven that the biological information carried by a gene is contained in the nucleotide sequence. This information is in essence a set of instructions for the synthesis of an enzyme or other protein molecule. In 1953, Francis Crick and James Watson of Cambridge University deduced that DNA resembled a twisted ladder capable of zipping apart. They developed the double helix model of the DNA which suggested that the DNA was made up of a nucleotide base which could be purine or pyrimidine and

that each base is attached to a pentose sugar that is phosphorylated. They explained further that the nucleotides are arranged in a ladder-like structure. Each rung of the ladder is formed by a pair of nitrogenous bases. The frame of the ladder is made of deoxyribose sugars and phosphates arranged alternately and in a linear manner. The two chains of DNA are not held straight but are coiled double and twisted to form a spiral helix or a double helix. The gene contains the message that is responsible for inherited traits or characters. This message is stored in the form of a code. It has been shown by scientists that the code is responsible for a message that allows protein synthesis in the body. This code is known as the genetic code. It resides in the DNA molecules and is recorded in such a way that it can be replicated and passed on from one generation to generation. Very detailed experimental studies have shown that the genetic code resides in the sequence on the nitrogenous bases of the nucleotides down on the length of the DNA chain. The nitrogenous bases in nucleic acids are adenine guanine, cytosine, thymine and uracil. Adenine and guanine are purine bases while cytosine, thymine and uracil are pyrimidine bases.

Uric acid is generated in mammalian systems as an end product of purine metabolism. In most mammals, uric acid is further degraded to allantoin by the enzyme Uricase; however, this enzyme was mutated in hominoids five to fifteen million years ago (Wu *et al*., 1992). This loss of Uricase activity does not only result in higher plasma uric acid levels, but also limits our ability to regulate uric acid, such that widely varied levels may be observed in man. Uric acid possesses free radical –scavenging properties (Kuzkaya *et al*., 2005; Robinson *et al*., 2004) and is the most abundant antioxidant in human plasma (Ames *et al*., 1981; Kand'ar *et al*., 2006; Hediger, 2002). It may also act as a prooxidant under conditions of oxidative stress (Aruoma and Halliwell, 1989; Bagnati *et al*., 1999; Sanguinetti *et al*., 2004; Kittridge and Willson, 1984). Markedly increased levels are known to cause gout and nephrolithiasis, but more importantly have been

associated with increased risk of the development of cardiovascular disease, particularly hypertension, obesity/metabolic syndrome, and kidney disease (Iseki *et al*., 2001; Tomita *et al*., 2000; Johnson *et al*., 2005; Nakagawa *et al*., 2006; Masuo *et al*., 2003). Recent experimental and clinical studies have linked elevated uric acid with endothelial dysfunction and a reduction in nitric oxide levels (Khosla *et al*., 2005). Experimental studies have reported that uric acid can reduce nitric oxide levels in endothelial cells in culture (Khosla *et al*., 2005), block acetylcholine-induced vasodilatation of aortic rings (Khosla *et al*., 2005) and reduce circulating nitrites in experimental animals (Khosla *et al*., 2005). In human, a circadian rhythm has been identified in which uric acid and nitric oxide levels are inversely correlated (Kanabrocki *et al*., 2000). Chronic hyperuricemia is also associated with endothelial dysfunction (Khosla *et al*., 2005) and reducing uric acid levels with xanthine oxidase inhibitors have been found to markedly improve endothelial function. However, xanthine oxidase inhibitors also reduce oxidant generation, so the improvement in endothelial fuction could reflect a direct reduction of xanthine oxidase-associated oxidants as opposed to a reduction in uric acid per se.

While the importance of endothelial dysfunction in cardiovascular disease is well accepted, most evidence suggests that the primary mechanism by which this occurs is via oxidative stress in which superoxides either directly inactivates nitric oxide (by forming peroxynitrite), uncouples the endothelil nitric oxide synthase, or passively increase an inhibitory substrate (asymmetric dimethylarginine) by inhibiting the enzyme, dimthylarginine dimethylaminohydrolase (Forstermann, 2006). In this regard, uric acid has been shown to help preserve endothelial nitric oxide levels via its role as an antioxidant, either by blocking the uncoupling of endothelial nitric oxide synthase by reacting with peroxynitrite (Forstermann, 2006) or by preventing the oxidant-induced inactivation of extracellular superoxide dismutase (Goldstone *et al*., 2006). A paradox then develops, how can uric acid,

which is the most abundant (about six times as ascorbate) antioxidant in plasma (Hediger, 2002) induce endothelial dysfunction in vivo?