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FEATURE REVIEW

The three princes of Serendip
Notes on a mysterious phenomenon

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> "The seeds of great discoveries are constantly floating around us, but they only take root in minds well prepared to receive them."
>
> Joseph Henry, physicist and first director of The Smithsonian Institution

The word "serendipity" was entered into the lexicon by Horace Walpole in 1754. He had become intrigued with a Persian fairytale in which three princes of Serendip, (now Sri Lanka) traveled the world, "making discoveries, by accidents and sagacity, of things they were not in quest of..." Walpole proposed the new word, but then went on to give rather mundane examples of its meaning. It is only recently that serendipity has acquired its rather grand and mysterious significance.

The Oxford English Dictionary defines serendipity as "the faculty of making happy and unexpected discoveries by accident." Serendipity plays an important part in research of all kinds, but it operates only in a special environment; as Pasteur famously stated, "Chance favors the prepared mind." In research, what serendipity really means in practical terms is that scientists discover things in the course of their investigations that they were not looking for. And these new findings are often not the products of cold logic.

Sometimes, great discoveries are made because of a serendipitous situation or observation. One excellent example of a serendipitous observation which led to a great discovery occurred in 1922, when Alexander Fleming, suffering from a particularly juicy cold, happened to sneeze into a Petri dish full of bacteria. He absent-mindedly placed the dish on his cluttered desk. Some days later, as he was straightening his desk, he noticed to his great surprise that the bacteria in the dish had been destroyed. His curiosity was aroused, and following his nose (so to speak), he worked to isolate for the first time the "active principle" - lysozyme - the antibacterial protein found in tears and mucus. Convinced that more potent agents might exist, Fleming began searching for other environmental antibacterials, eventually coming up in 1928 with penicillin, for which he won the Nobel Prize in 1945. He shared the prize with Florey and Chain, who made the mass administration of the drug to humans practical. In his characteristic understated manner (he was after all the son of a Scottish farmer), Fleming commented,

> "Nature makes penicillin, I just found it; *one sometimes finds what one is not looking for*." (italics mine).

At the end of the 19th century and in another field, Wilhelm Roentgen, while working in his darkened lab with a Crooke's (cathode ray) tube, noticed out of the corner of his eye that several feet away, a piece of paper coated with barium cyanoplatinate was faintly glowing. He was puzzled, since the only conceivable source of energy in the room was the tube, which was not emitting visible light. When subsequently Roentgen found that sealed photographic plates in his desk had become fogged in the absence of a visible light source, he deduced that a novel form of radiation energy was being generated in the Crooke's tube. He termed the new radiation X-rays. Within a year after this discovery in 1895, X-rays were being applied in diagnostic medicine.

During World War I, a youngster named Cyril Astley Clarke was sent to the English countryside so as to be out of harm's way. It was there that he acquired what

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would be a lifelong fascination with butterflies. In fact, although he became a physician, he kept up his interest in inheritance of butterfly wing patterns, and made several original observations in this field. A friend of his suggested that he might also examine human blood groups from a genetic standpoint, and this serendipitous suggestion ultimately led Clarke to an understanding of blood group inheritance in humans, and to the development of an injectable antibody inhibitor (Rhogam) for Rh disease in newborns.

More recently, the multi-billion dollar biotechnology industry in great measure found its origins in a spontaneous, serendipitous detour:

> "It would sound reasonable if I were to say that the research work...began as a result of a grand design, with a vision of the goals in mind. Unfortunately, this would not be true. This work began the day I took a detour through Yellowstone National Park on my way to Seattle." (Thomas Brock)

On his first visit to Yellowstone, Brock became intrigued with the multi-coloured algae mats in the hot springs, and on a whim, took some samples back to analyze in his laboratory. In 1969, Brock and Freeze reported the discovery of *Thermus aquaticus*; this bacterium became one early source from which the heat-stable enzymes were purified - the key tools in recombinant DNA technologies.

And the pharmaceutical industry has benefited many times from serendipitous observations. Perhaps the best-known contemporary case is that of Viagra, which was originally tested as a treatment for angina. It was almost immediately found to be less effective than nitroglycerine for coronary artery dilatation, but then the patients in the first clinical trial reported an unusual, not at all undesirable and now well-known side effect. It is no wonder that the patients became depressed when the first clinical trials were brought to an end, and it was requested that the unused pills be returned to Pfizer. The company noted that never had so many unused clinical trial pills been reported as lost, misplaced, or accidentally flushed down the toilet...

But sometimes the serendipitous insight eludes the original experimenter, and alights instead on the reader of the experimental report, or (how embarrassing!) on a competitor. A well-reported published experiment may reveal to "prepared" readers a serendipitous discovery that might have been made at the time, but was missed by the original investigators. The fascinating experiments with sponge cells performed by H.V. Wilson in the early part of the 20th century fall in this category, and in a stunning way. Wilson set out to create chimeric sponges by dissociating cells of three sponge species, and placing them in the same dish to coalesce as combinatorial new species. To his extreme disappointment, the cells from each distinct species only sought each other out to aggregate with, and Wilson was unable to induce any chimeras to form. He wrote:

> "*I shall here briefly record some experiments which gave only negative results*... These experiments were based on the assumption that if the dissociated cells of a species will recombine to form a regenerative mass and eventually a new sponge, the dissociated cells of two different species may be made to combine and thus form a composite mass bearing potentially the two sets of species-characteristics..." (italics mine).

It was only later that other scientists, most notably Ernest Everett Just, an African-American who was one of the great biologists of the last century, recognized the extraordinary implication of Wilson's "failure." Just, in reading Wilson's report, correctly concluded that sponge cell surfaces must display precise determinants that only allow aggregation between cells derived from the identical species. Hence, the cell surface is not "lifeless," as textbooks of Wilson's time stated, but rather,

> "The cell membrane stands not simply as a barrier of the cell against the outside world; it is also the medium of exchange between the cytoplasm and the environment. It is the first cell region to receive impressions from the outside world; through its delicacy of adjustment and fineness of reaction, it constitutes the first link in the chain of cytoplasmic reactions and sets the path for the orderly succession of events comprising the course in the differentiation of development." (E.E. Just, *The Biology of the Cell Surface*)

Competitors may be annoying recipients of the serendipitous insight. In 1887, Santiago Ramon y Cajal visited Dr. Luis Simarro Lacabra, a psychiatrist friend of his who had a histological laboratory in his cellar (medical students harken - his hobby was histology!). Cajal had been formulating the principles of the neuron doctrine, an extension of the cell theory of Schleiden and Schwann, but had not as yet found a way to verify his hypothesis that each neuron was a self-contained entity. Simarro took Cajal to his cellar laboratory, and showed him some brain slices prepared by the "black reaction" method of Camillo Golgi, an eminent scientist of the time who was an ardent proponent of the opposing reticular theory - that neurons are connected to each other via protoplasmic continuities that essentially make the brain a large syncytium. Cajal recalled that he was "thunderstruck" on his first look

through the microscope at the Golgi preparations, and he recognized in an instant that those slides would show the error in the reticularist's position, and demonstrate the validity of the neuron doctrine:

> "[Individual nerve cells appeared] coloured brownish black even to their finest branchlets, standing out with unsurpassable clarity upon a transparent yellow background. All was sharp as a sketch with Chinese ink... ideas boiled up and jostled each other in my mind..." (Cajal, "*Recuerdos di ma Vida*")

Golgi had had the data right in front of him, but was unable to interpret it correctly. Later Cajal would write of Golgi that he was "hermetically sealed" against new ideas. Golgi would not accept Cajal's conclusions, even though Cajal had used Golgi's own techniques to clearly prove Golgi wrong. The two shared the Nobel Prize in 1906, were on the same stage in Stockholm, but never uttered a word to each other.

Serendipity still plays a major role in discovery and invention. It is the manifestation of inspiration, and of being in the right place at the right time. To some, it has a certain magic about it that suggests predetermination or intervention by the supernatural, or as Shakespeare wrote:

> "There is a tide in the affairs of men, which, taken at the flood, leads on to fortune..." (Brutus to Cassius, in *Julius Caesar*)

In the end, though, probably the best way to sum up the phenomenon was most thoughtfully stated by Julius Comroe:

> "Serendipity is jumping into a haystack to search for a needle, and coming up with the farmer's daughter."

Dr. David R. Colman is the Director of the Montreal Neurological Institute. A native of New York City, Dr. Colman received his B.S. in Biology from New York University, and his Ph.D. in Neurosciences from the State University of New York, Health Sciences Center, Brooklyn, NY. He became an Assistance Professor of Cell Biology at NYU School of Medicine and joined the faculty of The Columbia College of Physicians and Surgeons as an Associate Professor of Cell Biology in 1987, where he received several prestigious awards, including an Irma T. Hirschl Career Development Award, the Harold and Golden Lamport Award, the Basmajian Award for Teaching and Research, as well as a Jacob K. Javits Neuroscience Award from the National Institute of Neurological Diseases and Stroke. He was subsequent the Annenberg Professor of Molecular Biology and Neuroscience at the Mont Sinai School of Medicine in New York City and the Vice-Chairman for Research in the Department of Neurology and the Scientific Director of The Corinne Goldsmith Dickinson Center for Multiple Sclerosis of The Mount Sinai School of Medicine. He began his tenure as Director of the MNI in September 2002. He holds the Penfield Chair in Neuroscience and a Tier I Canada Research Chair. Dr. Colman's research focuses on problems related to myelination and on nerve cell development with particular emphasis on synaptogenesis.