Chance findings that changed the course of cardiology forever

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Abstract

In scientific research, the general norm is that a scientist formulates a research question to fill gaps in scientific knowledge, and may then make a contribution to the existing knowledge. However, the history of medicine is peppered with chance discoveries which have occurred due to 'happy accidents' in the laboratory. This article is about three such chance discoveries that have greatly advanced our understanding of cardiology.

Sydney Ringer failed to perform an experiment that his technician Fielder routinely performed on the amphibian heart. The realization that the technician used 'hard tap water' which contained calcium, led Sydney to conclude that ionic calcium was necessary for the contraction of the amphibian heart muscle.

German physiologist, Otto Loewi, had a dream on Easter Sunday about an experiment. The dream was about a hypothesis on chemical neurotransmission that he had postulated seventeen years ago. His subsequent experiment led to the foundation of the modern chemical theory of neurotransmission. The first neurotransmitter Acetylcholine was discovered.

An accidental observation led Robert Furchgott discover that the endothelium was not inert and it released an agent which he called Endothelium Derived Relaxing Factor (EDRF). Later discoveries revealed EDRF to be Nitric Oxide. This led to the subsequent discovery of Viagra and a famous Nobel Prize for the scientists who discovered Nitric Oxide. Indeed, Furchgott said, "Nobel means Nitric Oxide is beautiful."

Key Word: Chance Finding, Cardiology, Nitric Oxide

Scientific investigations and experimental ideas may be born as a result of fortuitous and involuntary chance observations which present themselves either spontaneously or in an experiment designed with quite a different purpose. -Claude Bernard

Introduction

Discovery can be done in various ways. The established norm is that a scientist frames a research question to fill gaps in scientific knowledge based on research already published in a field. With his ingenuity he designs an appropriate experiment and if he is resilient enough, he perseveres with this research and may land with adiscovery after several arduous years. Occasionally,scientists have experiences in their laboratories which may be likened to 'happy accidents'. They encounter a finding which may seem irrational, nonscientific and unpredictable. This then leads to a discovery which forces a paradigm shift in the current knowledge. The history of medicine is fortuitously peppered with such *chance discoveries.* This article describes three such chance discoveries which have greatly advanced the understanding of the cardiovascular system.

The technician used hard tap water

The 'dreamgirl' of yesteryears, HemaMalini, appears these days on commercial television in India, making a cause for a household water purifier.

Theepisode here is of the times (1883 to be precise) when no one would have imagined that there would ever be a sophisticated mechanism to pure water! During such times, Sydney Ringer,though an astute clinician, conducted experiments on amphibians, such as frogs. In this case, the onusof conducting such experiments fell on Sydney's technician Fielder. As directed by his boss, the technician recorded themechanism of contraction of the frog heart muscle by bathing it in a solution made up of sodium and potassium. One day, Sydney decided to conduct the experiment by himself. He bathed the heart in pure saline. The frog's heart did not contract!! On inquiry, he learned that his technician used 'hard' tap water as a solution. This water contained an additional component - calcium. The obvious conclusion: *calcium was necessary for the contraction of the amphibian heart muscle*[1] *!!*

Sydney Ringer's discovery paved the way for a number of advances in cardiovascular physiology.

First, it offered the first experimental evidence that ionic calcium was necessary for the contraction of the cardiac muscle.

Subsequently, it was found that the cardiac muscle requires influx of ionic calcium from the extracellular fluid (unlike skeletal muscle, wherein membrane depolarization acts as a trigger for calcium release).

Second, a technique to study ion channels, called the patch-clamp technique was invented by two German scientists Neher and Sackmann, which paved the way for understanding the structure of the potassium channel (by Roderick Mackinnon) and discovery of water channels called as Aquaporins (by Peter Agre).

Third, the mechanism of action of an ionotropic agent, Digitalis, could be established.

A scientist's dream on Easter Sunday led to the discovery of acetylcholine

A German physiologist named Otto Loewi had a dream about an experiment on the night before Easter Sunday in 1920. He jotted down notes; when he woke up at 6:00 am, he could not decipher the notes. The next night, at 3:00 am, the dream re-occurred. It was about the design of an experiment to determine whether or not the hypothesis of chemical neurotransmission that he had uttered 17 years ago, was correct.Loewi woke up immediately and performed the experiment. He used two hearts, one with an intact vagus nerve, and the other in which the vagus nerve was denervated. He set up a connection between the two hearts. When the heart with the intact vagus nerve was stimulated, the rate of beating of the heart (heart rate) decreased. This was already known. But the heart rate of the second heart also decreased.Otto Loewi thereby concluded that a substance was released from the vagus nerve which innervated the first heart, which led to the decrease in the heart rateof the second heart also! He aptly named the putative chemical as Vagustoffe. Later on, scientists discovered that the said chemical was Acetylcholine. Thus, Loewi's discovery led to the understanding that the primary language of neurotransmission is chemical,and not electrical.[2]

Later, Henry Dale identified vagustoffe as Acetylcholine. He also discovered the muscarinic and nicotinic receptors. Acetylcholine was identified as a neurotransmitter in the parasympathetic nervous system. Subsequently, Henry Dale and Otto Loewi were awarded the Nobel Prize in Physiology or Medicine in 1936. Thus, chance had favored Loewi's prepared mind.

Acetylcholine causes vasodilation in the blood vessels by means of anagent released by the endothelium- the miracle molecule Nitric Oxide

Robert Furchgott, a physiologist by training, ventured into the new science of pharmacology in the early 1950s. From then on, he studied the effects of various drugs on the rabbit aorta. In the 1970s, Furchgott decided to conduct the experiments again, mainly to determine the receptor sub-types in the rabbit thoracic aorta. He gave a sequence of experiments to his technician. It may be noted that by this time it was known that theneurotransmitter agent Acetylcholine caused vasodilation in the blood vessels of human beings. The vasodilatory action of acetylcholine had not been demonstrated in vitro. During one recording by Furchgott's technician, such a reaction was demonstrated. Over the next few weeks, Furchgott zealously tried to determine the reason for such an observation by performing a sequence of experiments. He and his team realized that they normally rubbed off the endothelium before mounting the preparation, and that the vasodilatory effect was lacking in such a preparation. Furchgott and his team microscopically demonstrated that such mechanical rubbing *actually* removed the endothelium.

This was a *Eureka* moment for Furchgott!! He then devised an ingenious experiment. A blood vessel (in this case the rabbit thoracic aorta) lacking an endothelial surface was joined to a vessel with an intact endothelium - a 'sandwich' was created. On applying acetylcholine to the vessel with the intact endothelium, the 'other' vessel also dilated. Furchgott postulated that an agent was released from the endothelium which mediated the vasodilatory action of Acetylcholine. Robert Furchgott christened it Endothelium Derived Relaxing Factor (EDRF). A scientist Ferid Murad discovered that the agent from the drug Nitroglycerin which caused vasodilation in the coronary blood vessels, and hence, was used for the treatment of angina pectoris, was Nitric Oxide. Later, Robert Furchgott, and another scientist Louis Ignarro, discovered that EDRF was the gaseous neurotransmitter Nitric Oxide (NO). Nitric Oxide is considered as a miracle molecule because it has many widespread applications today including treating erectile impotence, and is considered to be one of the mechanisms by which aerobic exercise lowers systemic blood pressure.

Robert Furchgott, Ferid Murad and Louis Ignarro were jointly awarded the Nobel Prize in Physiology or Medicine for their discoveriesconcerning Nitric Oxide in 1998. Robert Furchgott joyously proclaimed in the Banquet Speech during the prize ceremony that "Nobel means – Nitric Oxide is beautiful!!![3]

To conclude, the course of cardiology was altered by these chance discoveries. Sydney Ringer discovered the ringer solution which Otto Loewi used in his experiment to discover Acetycholine. Robert Furchgott's discovery of Nitric Oxide established that the vasodilatory effect of Acetycholine is endothelium dependent and is mediated by Nitric Oxide.

The mechanism of action of digitalis (digoxin) was established.

Rapid advances occurred in the field of chemical neurotransmission with the discovery of receptor types of both the sympathetic (alpha and beta) and parasympathetic nervous system (muscarinic and nicotinic). Drugs acting on these receptors like Propanolol (beta blocker) and Prazosin (alpha blocker) advanced the treatment of hypertension. The discovery of the miracle molecule called Nitric Oxide led to a wonder drug called Sildenafil (Viagra) to treat erectile impotence, a condition which was previously difficult to treat.A putative hypothesis involving the release ofNitric Oxide (NO) evolved on the mechanism by which aerobic exercise lowers systemic blood pressure.

Thus, chance coupled with creativity changed cardiology forever, and made these scientists cult figures!

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Conflict of interest: None

Funding: None

Cite this Article as:
Paraliker S. Chance findings that changed the course of cardiology forever. Natl J Integr Res Med 2018; 9(5):1-3