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# The Discovery of PCR: ProCuRement of Divine Power

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One of the great quests of humanity has been to understand and harness the forces that pervade the universe. A prime example was the ability to control nuclear chain reactions in the laboratory, which of course had immense ramifications for the generation of power and the production of useful isotopes, but also for the creation of weapons capable of massive destruction that to this day remain an existential threat to our planet. Just as Prometheus came too close to the divine fire, the revelation of these heretofore-unobtainable powers can be immensely beneficial or utterly destructive. Another kind of chain reaction, the polymerase chain reaction (PCR), invented several decades ago, is an additional example of humanity acquiring formerly unobtainable powers, in this case, the ability to exponentially amplify perfect copies of biologic material, which is an essential attribute of every known life form. In this case, the ramifications have been overwhelmingly positive, with an explosion of knowledge in a multitude of diverse fields, characteristic of a true paradigm shift. In the research laboratory, PCR has become indispensible for genetic cloning, sequencing and measurement of gene expression, among a myriad of other uses. In medicine, PCR is used to precisely identify microbes, whether an individual pathogen or a population of diverse organisms as constitutes the gut microbiota. PCR is also useful for the analysis of human DNA for mutations and polymorphisms, and for typing tissues and blood. PCR has also been of benefit to areas well outside of science and medicine as well: the use of PCR-based DNA “fingerprinting” represents the probable greatest advance in forensic analysis in the last 50 years. PCR has also revolutionized the field of molecular palaeontology, since DNA can be sequenced from dried or fossilized specimens that are thousands or even millions of years old.

The origins of PCR are somewhat murky, given the disputes over its provenance [1,2]. What is not disputed is that PCR would not have been possible without the pioneering work of others, in particular the discovery of the structure of DNA in 1953 by James D. Watson and Francis Crick (recipients of the Nobel Prize in 1962), and the discovery of DNA polymerase by Arthur Kornberg in 1956 [3] (recipient of the Nobel Prize in 1959). The initial description of the scientific concepts underlying PCR are attributed to Kjell Kleppe working in the laboratory of H. Gobind Korana (recipient of the Nobel Prize in 1968) who was reported to describe a process of in vitro DNA amplification involving oligonucleotide primers and DNA polymerase at a 1969 Gordon Conference [1]. The first published description of the technique can be traced back to a paper published in 1971 by Kleppe et al [3], where they state:

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> The principles for extensive synthesis of the duplexed tRNA genes which emerge from the present work are the following. The DNA duplex would be denatured to form single strands. This denaturation step would be carried out in the presence of a sufficiently large excess of the two appropriate primers. Upon cooling, one would hope to obtain two structures, each containing the full length of the template strand appropriately complexed with the primer. DNA polymerase will be added to complete the process of repair replication. Two molecules of the original duplex should result. The whole cycle could be repeated, there being added every time a fresh dose of the enzyme.

This method appears not to have been put into practice, due to the existing technical problems, including laborious hand synthesis of oligonucleotide primers and the need to purify large quantities of polymerase.

The origins of PCR are usually attributed to Kary Mullis, a technician at the Cetus Corporation, assigned to improve the synthesis of oligonucleotides. He relates that he envisioned the concept PCR while on a camping trip with his girlfriend as part of his 1969 Nobel Prize lecture: [4]:

> “Dear Thor!,” I exclaimed. I had solved the most annoying problems in DNA chemistry in a single lightening [sic] bolt. Abundance and distinction. With two oligonucleotides, DNA polymerase, and the four nucleoside triphosphates I could make as much of a DNA sequence as I wanted and I could make it on a fragment of a specific size that I could distinguish easily. Somehow, I thought, it had to be an illusion. Otherwise it would change DNA chemistry forever. Otherwise it would make me famous. It was too easy. Someone else would have done it and I would surely have heard of it. We would be doing it all the time. What was I failing to see? “Jennifer, wake up. I've thought of something incredible.”

After obtaining appropriate patents, the technique was first published in the journal *Science* in late 1985 [5] Due to the considerable progress that had occurred over the 15 years, such as the invention of automated oligonucleotide synthesizers, PCR could finally be translated into a practical laboratory method. As with all other paradigm shifts, the use of PCR, after a brief incubation, exploded into one of the most frequently used techniques in science and medicine, with over 300,000 publications in PubMed to date using the term, and manyfold more in the publications ranging from paleontology to forensics, and also the lay press.

In an accompanying article, Dr. Chung will detail how PCR has not only revolutionized the development of drugs used to treat hepatitis C, enabling the development of the current generation of direct antivirals that promise to severely curb the current hepatitis C epidemic, but has also revolutionized diagnostic testing of viral hepatitis. Indeed, the efficacy of this new generation of drugs threatens, for all intents and purposes, to virtually eliminate the scourge of hepatitis C, relegating it to the dustbin of vanquished infectious diseases such as polio, plague, and smallpox.

The invention of PCR again illustrates how insight, intuition, persistence, creativity, foresight, and hard work can pay off in major and unexpected ways, to the overall benefit of

humanity and our planet. It is up to the scientific community to continue to encourage our young scientists to keep thinking differently so that they can make the paradigm shifts of tomorrow.

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