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Discovery, Chance and the Scientific Method

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In the scientific world of controlled experiments, chance is seldom acknowledged as a contributing factor in important discoveries. There are, however, rare exceptions. In 1945 three men shared the Nobel Prize in physiology or medicine for the discovery and isolation of penicillin, an antibiotic medicine with great therapeutic potential. Those three men were Alexander Fleming, Ernst Chain and Howard Florey. Yet, despite the work of these three, and related research by other scientists, most textbooks credit a chance observation, made in 1928 by Fleming alone, for the discovery of penicillin. How rare was this serendipitous event and was the discovery of penicillin really the result of an unexpected chance observation by a single researcher?

The scientific method is typically noted for its orderliness and control; In fact, we are taught that without these characteristics, experimental research may yield invalid results. Therefore, chance should play little or no role in the process of the scientific method. But what is chance? When is chance truly an accident and when is it foreseeable? Historically, some chance discoveries have led to startling new ideas that eventually directed important further scientific investigation of natural phenomena.

The modern study of neurophysiology may have had its beginnings in a chance observation by the Italian anatomist, Luigi Galvani. Galvani observed, in 1791, that frog legs hung on a wire near a metal balustrade jerked violently when the wind brought the two metals into contact with each other. Galvani had, purely by chance, observed the physiological result of an electric current. It is interesting that although Galvani correctly postulated the link between movement of muscle tissue and electrical impulses, he incorrectly dismissed the role of the two metals in the scenario which he observed. Despite this, Galvani's chance observation helped to establish the medical study of neurophysiology and clinical neurology.

Was Galvani's discovery of the relationship between muscle activity and electrical impulse chance or was it predictable? Was the observation the result of happenstance or, conversely, was it an unexpected event in the midst of deliberate, controlled scientific research? If the role of science is to examine the world around us in a way which uncovers new and sometimes unexpected information, then science itself is intrinsically surprising. Even a deliberate scientific search for information may lead to an unexpected chance observation or discovery. But to have meaning, every observation or discovery must fit into a pre-existing pattern of ideas in the observer's mind. Just as a word means little out of context, a new observation or discovery needs a proper context in which to fit in order to be most meaningful. In other words, the mind must be prepared to receive the germ of a new idea. What is "chance" for the unprepared mind may be a fascinating springboard to new ideas for the prepared mind.

Louis Pasteur wrote, "In the field of observation, chance favors only the prepared mind." Discovery, like learning, is a phenomena that takes place in the human brain. The brain configures an event as a new pattern based on previous assumptions that were present at the onset of the event. Lewis Thomas, renowned science author and former president of Memorial Sloan-Kettering Cancer Center stated, "I'm not as fond of the notion of serendipity as I used to be. It seems to me now that as you get research going... things are bound to begin happening if you've got your wits about you. You create the lucky accidents." Many scientists agree with that position.

Let's return to a discussion of the discovery and isolation of penicillin - a process which involved a series of chance events spanning at least half a century and building on knowledge gained as early as 1500 BC. It was at this time that written records describe the use of molds and fermented materials as therapeutic agents. Similarly, the use of chemicals as medicines is described in ancient Greek writings of the fifth century BC. These early treatments - which probably either cured or killed the patients - were carried out without a firm understanding of either the active agents or the cellular processes involved. It was not until the late nineteenth century that progress was made on this front and a concerted effort was made to identify and isolate substances that would inhibit or destroy the causative agents of known human diseases. And still, "chance" played a role.

In the late 1800's bacteriologists and microbiologists set out to identify substances with therapeutic potential. One of the greatest problems faced by these scientists during their studies was the contamination of "pure" cultures by invading microorganisms (see graphic), especially fungi or bacteria - a problem which still plagues the modern day microbiologist. It is this problem of contamination which is most often identified as leading to the "chance" observation that eventually led to the discovery of penicillin.

These studies of contaminated cultures led to a series of observations by late 19th century bacteriologists and microbiologists describing the effect of mold on bacterial growth. These observations were as follows:

- In 1874, William Roberts (1830-99) observed that cultures of the mold Penicillin glaucum did not exhibit bacterial contamination.

- French scientists Louis Pasteur (1822-95) and Jules Francois Joubert (1834-1910) observed that growth of the anthrax bacilli was inhibited when the cultures became contaminated with mold.

- The English surgeon Joseph Lister (1827-12) noted in 1871 that samples of urine contaminated with mold did not allow the growth of bacteria. Lister unsuccessfully attempted to identify the agent in the mold which inhibited bacterial growth. He later abandoned this research for the more successful work of introducing antiseptic procedures and sterile instruments into the operating theater.

Another event, although overlooked at the time, in the string of occurrences which led to the discovery of penicillin was a dissertation written in 1897 by the French medical student, Ernest Duchesne. In his dissertation, Duchesne reported the discovery, partial refinement, and successful testing on animals of a substance with antibiotic properties - that is a substance which inhibited bacterial growth. The source of Duchesne's substance was the mold penicillin. Duchesne died at an early age in 1912, never seeing the world's acceptance and use of his important discovery.

Thus the stage was set for the "chance" discovery of penicillin by Alexander Fleming in 1928. In most science textbooks, from middle school to college level, Fleming, alone, is credited with the discovery of penicillin. Yet, Fleming's discovery would have been nothing more than a fluke had the base of knowledge provided, at least in part, by the chance observations of Roberts, Pasteur, Lister, Joubert and others, not existed. Without a doubt, Fleming was searching for antibacterial agents. As early as 1922, he had discovered an enzyme present in biological substances as varied as egg whites, tears and mucus that causes bacteria to lyse, or burst. However, he was unable to successfully isolate the active ingredient in these materials.

In 1928, he was researching the properties of the group of bacteria known as staphylococci and became another in the long line of scientists to benefit from a seemingly chance observation. His problem during this research was the frequent contamination of culture plates with airborne molds. One day he observed a contaminated culture plate and noted that the Staphylococci bacteria had burst in the area immediately surrounding an invading mold growth. He realized that something in the mold was inhibiting growth of the surrounding bacteria. Subsequently Fleming isolated an extract from the mold and he named it penicillin. Despite this success, further attempts by Fleming to produce a concentrated extract of penicillin failed and he was unable to prove its therapeutic value.

It wasn't until ten years later, in 1939, that Ernst Chain, Howard Florey and Edward Abraham of Oxford University were able to purify and stabilize a form of penicillin that enabled demonstration of its therapeutic potential. Again, chance favored their work. Unknown to them, the species of animal that they chose for laboratory studies turned out to be one of few species that do not find penicillin toxic. Had they chosen to work with a species other than the one they chose, they might have deemed penicillin too toxic for use, and humankind would have been deprived of the phenomenal life-saving ability of this drug.

The first human trial of penicillin took place in 1941 and involved treating a man with osteomyelitis. Although the treatment produced improvement, the patient, a policeman, died when the limited supply of penicillin was exhausted. (Penicillin was so scarce that the patient's urine was collected and the excreted penicillin was recrystallized to be used again.) Despite the sad ending to this initial penicillin treatment, the therapeutic efficacy of penicillin was accepted. Interest in penicillin soared with the onset of World War II and bombings in England. These events gave great urgency to development of a process which would produce medicinal penicillin in sufficient quantities to treat ever increasing numbers of war wounds. But the British pharmaceutical industry was unable to cope with increasing wartime demands, not only for penicillin but for more traditional medicines, as well.

In an act of daring, Ernst Chain sailed across the sub-infected Atlantic to the United States to find the needed technology for mass production of the new drug. Chain turned to a beer-brewing technology to produce the huge amounts of the moldy liquor which was needed for penicillin production. The moldy liquor underwent a slow purification process to produce the large amounts of clinically usable penicillin that became available for military use in early 1940's. Penicillin's therapeutic applications in the later stages of World War II was credited with saving tens of thousands of wounded that would otherwise have succumbed to bacterial infections.

Though scientists pride themselves and the theories of science as being based on methodical research and the scientific method, one notes that key discoveries often occur by chance or serendipity. Luck or a scientific event whose time had come? With the current demands on scientific research to solve critical problems and provide modern amenities, the unexpected, chance event should not be discounted.

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- Glossary
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