

Serendipitous Insights Involving Nonhuman Primates

William R. Morton and Kathryn Swindler

Abstract

Serendipity is discussed as a form of controlled chaos, a phenomenon in a class with synchronicity and other actions affecting research in terms of theory versus observation (e.g., “optional stopping”). Serendipity is a fundamental aspect of basic research, a profitable and normal outcome in the context of “informed observation.” The serendipitous finding fits into the following pattern: it is unanticipated, anomalous, and strategic. All observations that have meaning must fit into some context in the observer’s mind or suggest a revolutionary new context. It is critically important to maintain access to the resources provided by established primate centers and similar laboratories to capitalize in a timely way on serendipitous findings and to benefit from valuable discoveries made in more directly targeted development investments. Examples are given of serendipitous insights gained in experimentation and observation relative to nonhuman primate research, including both broad and narrow topics. Genomics, which uses comparison-based strategies and capitalizes on the DNA sequences of genetic information, presents what might seem the basis for endless serendipity because nonhuman primates are likely to share most genes present in the human genome. Other topics discussed include infant behavior, birth periodicity, leprosy, cystic fibrosis, environmental enrichment, endocrinology, drug development, and the rapidly expanding study of infectious diseases and pathogen-based bioterrorism.

Key Words: nonhuman primate; observation; research; serendipity; synchronicity

Serendipity or Informed Observation?

One does not need to look very far in the annals of science and scientific laboratory research to find examples of serendipity or the related concept of synchronicity. An early citation of both phenomena centers on the Augustinian monk Gregor Mendel, whose order encouraged him to learn. He set out to do so, as instructed, in

the monastery gardens, and from this work arose the foundations for modern genetics (Luria et al. 1981). This scenario has been cited as serendipity: Why not Brother Abbot? Why not the library or vivarium? Perhaps the monastery fathers had an inkling of what kind of mind they were dealing with. Perhaps the pairing of Mendel and the garden may indeed have resulted purely from chance and the results from serendipity. Mendel himself might consider the eventual development of a prenatal test for Tay-Sachs disease (Direen 2000) a serendipitous result of his studies, although it also may be the predictive result of a cumulative store of vast amounts of research and knowledge and a defined line of inquiry.

That no one recognized Mendel’s achievement in the mid-1850s certainly is not serendipitous. However, the simultaneous rediscovery in 1900 of Mendel’s rules of heredity by three scientists, Erich Tschesnak von Seysenegg, Karl Correns, and Hugo De Vries (Luria et al. 1981), may be cited as an example of synchronicity, certainly as accurately as the synchronicity of the theories of Darwin and Wallace. Serendipity and synchronicity are quite different occurrences but, as pointed out by Dr. Campbell in the Introduction to this issue (Campbell 2005), both occurrences rely on the breadth of knowledge and the quality of discipline in the researcher, and both may occur as a result of investigations that have yet more to discover.

Steven Shapin (2004), in his review of Robert K. Merton’s book *The Travels and Adventures of Serendipity: A Study in Sociological Semantics and the Sociology of Science*, regards the ideal scientific position for encouraging discovery as somewhere between the extremes of inductive and deductive reasoning. Shapin proposes that one have a reasonable expectation of what is being sought so that both expected and surprise results will be recognized, yet at the same time be ignorant enough of what one may find (or open enough) to consider alternative outcomes (Shapin 2004). The term “serendipity” is frequently used to identify advantageous discoveries revealed in the search for something else. Yet whether or not an event is serendipitous may be in the eye of the beholder. Gary Fine and James Deegan assert that theory itself does not develop out of thin air, but instead comes from an amalgam of trends of thinking in favor at the time in the context of the researcher’s own experience (Fine and Deegan 1996). Furthermore, it is also possible that observations may be discounted because they fit into one of the following categories: they are not in sufficient agreement with the theory advanced, hence pre-

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senting the observer with an opportunity missed; or they are somehow flawed and rightly dismissed. Lewontin (2004) has noted that “the problem of how to cull observations honestly is a constant preoccupation.” There is also the possibility that some experiments end as a result of “optional stopping,” in which a researcher believes the theory to have been proven at an arbitrary point and so stops (Lewontin 2004). Author Lewontin notes that Mendel’s results were possibly too close to the 3:1 ratio he expected and may represent a case of optional stopping, despite the validity of the results, which are now recognized.

Basic research necessarily incorporates serendipity. In the Scripps “Case For Giving” article on the Scripps website, 2001 Nobel Laureate K. Barry Sharpless references the following phrase, which is often attributed to Pasteur: “It is axiomatic of basic science research: chance favors the prepared mind.” In another characterization of the concept, Fine and Deegan (1996) refer to “serendipity as controlled chaos.” In addition, one might consider the concept in an even more broad way, as John Lennon has written: “Life is just what happens to you while you’re busy making other plans” (Lennon 1981).

Serendipity Among Primates

Within the sphere of research involving laboratory animals, the nonhuman primate affords researchers a unique and valuable opportunity because humans, monkeys, and apes share many physiological, biochemical, and behavioral traits. These similarities reflect close genetic relationships and make the nonhuman primate an ideal animal model for many human diseases (Rand 2003). This special relationship also presents fertile ground for the serendipitous discovery. Most of the serendipitous occasions described below present such events in the course of nonhuman primate animal studies. Some are apocryphal. In particular cases, the nonhuman primate is involved in a chance find only in the testing phase after a serendipitous occurrence with human subjects (e.g., the case of minoxidil, a drug developed to control high blood pressure).

The examples of serendipity that appear below demonstrate the classic serendipitous condition—the coupling of insight with unplanned events (Fine and Deegan 1996). The following examples are briefly described and range from gross observations to fine endocrine detail: infant behavior, birth periodicity, leprosy, cystic fibrosis, environmental enrichment, founding of a primate center, endocrinology, and drug development.

Infant Behavior

Janice Beyer (2000), when an undergraduate student at the University of Wisconsin (Madison, WI), recounted in an article in *Organizational Behavior News* an example of serendipity in a well-known experimental study. Beyer was

performing computations in the Harlow laboratory when tests revealed that a recent shipment of pregnant rhesus monkeys was infected with tuberculosis. To avoid infecting the rest of the nonhuman primate colony, the mothers were euthanized postpartum, and the infants were put into individual cages to be fed and cared for by graduate students in an area of the laboratory easily observed by occupants of the laboratory going about their daily routine. Harry Harlow, knowledgeable and well accustomed to the behaviors of infant rhesus, saw something in the behavior of this particular group that differed from his prior observational experience of nonhuman primate infants. When another shipment of pregnant rhesus was received, he again separated the newborns, even though the mothers were healthy, and so began his famous experiments on mothering. Beyer comments that research students are taught to make predictions from extant theories, and that by testing their predictions, they test the theories. Testing theory-based hypotheses is not the best way to generate new insights or help us understand phenomena but can instead block understanding (Beyer 2000). The method of understanding that Beyer supports includes observing the setting and phenomenon to be studied so that something not anticipated by extant theory, if it occurs, can be understood in context and utilized.

Harlow’s studies of attachment and mother love arose serendipitously from his efforts to breed rhesus monkeys for his work on brains and intelligence. Infants, particularly in the early weeks or months, are generally sheltered by permissive adults. This period is crucial for the development of social skills. Laboratory experiments by Harlow and his associates during the 1950s and -60s demonstrated that when certain such experiences are not part of the animal’s early life, the damage to the animal may be irreparable or very difficult to correct later in its life. The Harlow deprivation studies and work on social development in rhesus monkeys have been of major importance to theories of early child development and socialization and to psychiatry.

Birth Periodicity

Serendipity was active at the University of Stirling, Wales, in discovering an additional periodicity in the births of nonhuman primates as perceived by the husbandry staff. Although circadian periodicity is the rule, species active by day giving birth at night, and vice versa (Jolly 1973), may also be characterized by the following other recurrent periods: annual periodicity, especially in habitats that undergo marked seasonal changes over the yearly cycle (Lancaster and Lee 1965); and lunar cyclicity, at least for prosimians. Additionally, Lancaster and Lee discovered “circum-weekly periodicity, i.e., differences over days of the seven-day week.” The authors postulate that the additional periodicity is induced by laboratory conditions that combine to create a statistically significant clustering of prosimian births in the laboratory on weekends rather than weekdays.

This clustering is influenced, they believe, by the following factors:

- The greater the difference in routine of a captive colony between weekdays and weekends;
- The more “nervous, sensitive or difficult” the species (e.g, *Cacajao rubicundus* vs. *Macaca mulatta*);
- The more normal the rearing and housing conditions (McGrew and McLuckie 1984).

With the current emphasis on establishing successful breeding colonies, these findings add a practical focus to the field of nonhuman primate research.

Leprosy

Research into the incidence and treatment of leprosy gained momentum with the serendipitous discovery of a spontaneous case of leprosy in a single sooty mangabey (Rand 2003). Experimental leprosy was subsequently established by intravenous and intradermal inoculation of the *Mycobacterium leprae* in mangabeys, rhesus monkeys, and African green monkeys, producing disease that strongly resembles leprosy in humans. Since then, it has been reported that a second monkey contracted leprosy from the first monkey (Gormus et al. 1988). The animals had been housed in direct contact with each other. Clinical symptoms appeared in the second animal nearly 7 yr after lesions first appeared in the original monkey. This development suggested that the disease either passed from animal to animal or was acquired from an unknown common third source, and that where human leprosy is endemic, a potential zoonosis exists in wild monkeys. Although it has been proven that leprosy has zoonotic potential, this serendipitous finding is important for its demonstration of transmission and the identification of an animal model for the disease.

Cystic Fibrosis

Emory University (1978) reported that “a classic textbook case” of cystic fibrosis as found in humans had been identified in a nonhuman primate, an animal in which the disease had not been described previously. An assistant veterinary pathologist (whose name was withheld by Emory) unexpectedly discovered the disease during the routine autopsy of a 6-mo-old male rhesus monkey that died of unknown causes. The diagnosis was confirmed by Victor Nassar, an Emory pediatric pathologist at Atlanta’s Grady Memorial Hospital, and by John Easterly, a pathologist at the Chicago Lying-In Hospital and national authority on cystic fibrosis. The monkey, one of a group being studied for the space program, instead provided the first nonhuman primate model of cystic fibrosis. Yerkes Center Veterinary Pathologist Harold McClure said, “We are very fortunate that the rhesus monkey is the animal model that was found

by [the doctors] because more is known about this animal than about any other nonhuman primate. They are also available for research in fairly large quantities.”

Environmental Enrichment

One instance of serendipity in the 1940s ultimately led to programs that promote psychological well-being programs for nonhuman primates in the research laboratory (Cohen 2003). Psychologist Donald Hebb found that rats he raised in his home, a more challenging environment than the laboratory, displayed greater intelligence and problem-solving skills. His observations developed through a number of steps into the field of Environmental Enrichment. One of the significant steps involved a group led by Mark Rosenzweig, Professor Emeritus of Graduate Studies at the University of California-Berkeley. Rosenzweig’s group, in the early 1960s, reported that rats studied in environmentally enriched housing showed unexpected thickening of the cerebral cortex and increased numbers of neurons and synapses. Investigators increasingly have come to realize that animals raised without sufficient stimulation do not develop full growth of brain or full behavioral capabilities (Cohen 2004). Primate centers such as the Washington National Primate Research Center have developed sophisticated programs of environmental enrichment and psychological well-being as an outgrowth of these earlier studies.

Founding of a Primate Center

Carolyn Poirot (2002) described the following incident of serendipity in the Fort Worth Star Telegram, July 7, 2002:

“Founded 60 years ago by Texas oilman Tom Slick as an independent, nonprofit biomedical research institution, Southwest Foundation was established on a 5,000-acre ranch covered with mesquite. A serendipitous discovery in the spring of 1956 launched what would become the foundation’s best-known work. . . .

A scientist from the foundation was at Louisiana State University’s School of Medicine studying atherosclerosis with an LSU pathologist when a colleague sent them the aorta of a 16-year-old female baboon that had died of natural causes at New Orleans’ Audubon Park zoo.

They found that the baboon’s aorta closely resembled the human aorta—and, more important, the baboon had developed atherosclerotic lesions remarkably similar to those they had seen in autopsies on people who died of coronary artery disease. They knew immediately that baboons could teach them a lot about the development of human heart disease.

Two years later, the National Institutes of Health awarded the Southwest Foundation a grant to es-

establish a colony of baboons for medical research, and the Texas Heart Association awarded the institution \$10,000 a year, for five years, to construct large outdoor pens where the baboons could live in colonies. The primate center was born.”

Currently, the Southwest Foundation for Biomedical Research (SFBMR¹, San Antonio, TX) is one of the largest primate centers in the world. SFBMR maintains 3,700 baboons that are used in research on a wide array of human diseases, including atherosclerosis.

Endocrinology

In a study conducted with the rhesus monkey at Duquesne University (Pittsburgh, PA), investigators attempted to determine the role of the ovary in the prepubertal hiatus of gonadotropin secretion. They concluded that the open loop activity of the gonadotropin-releasing hormone pulse generator during juvenile development of the female monkey is only partially suppressed due to prepubertal suppression of gonadotropin by the ovary (Pohl et al. 1995). The authors also report the serendipitous finding that juveniles separated from their mothers and subsequently placed in individual cages demonstrated a temporary but significant reduction in circulating gonadotropin concentrations.

Drug Development

Nonhuman primate models utilized in drug testing, compared with rodent or other laboratory models, may indicate a more predictable outcome and benefit for the human subject and decrease the time needed to advance to clinical trials. Many drugs in current use are the result of purely serendipitous events (Williams 1993). Particularly in the case of antimalarial drugs now in use, most were not developed from preidentified targets but instead, from the serendipitous identification of the antimalarial activity of natural products such as quinine and artemisinin, compounds chemically related to natural products or compounds active against other infectious pathogens (e.g., antifolates and tetracyclines) (Fidock et al. 2004.) These examples include the class of antidepressant drugs for which the animal model is not a good predictor (Palfreyman et al. 2002). Recently, neuroimaging has been utilized in drug development to identify both the biochemical and functional characteristics of particular drugs. Positron emission tomography (e.g., magnetic resonance imaging) allows a researcher to address “whether a compound has a central effect, where that effect occurs, in what relationship to dose, with what

behavioral implications, and in what relationship to other compounds” (Brown 2004). The use of this technology increases the efficacy of preclinical development using non-human primates.

The drug minoxidil is an example of serendipity in drug development. The arterial vasodilator minoxidil was originally intended to treat hypertension but was unexpectedly found to cause the growth of thick hair from follicles that normally produced only fine hair (Chader and Wyngaarden 2003). The drug operates by opening potassium channels in vascular smooth muscle. Wisconsin National Primate Research Center Hideo Uno and colleagues demonstrated that by applying it externally to the bald front scalp of the stump-tailed monkey, minoxidil both grossly and microscopically enlarges vellus follicles to the size of mid-sized and terminal follicles (Uno et al. 1987). The macaque became the animal model for androgenetic alopecia for the testing of minoxidil and later proscar and RU58841 (Kamel 2004).

Capitalizing on Serendipity

Serendipity appears to be most prevalent and productive when an investigator who is well informed and experienced in a subject carefully observes the course of a project and looks for and considers all that the project suggests, rather than simply determining whether or not it proves the hoped-for result. The serendipitous finding then fits into the following pattern: it is unanticipated, anomalous, and strategic (Fine and Deegan 1996). Every observation, to have meaning, must fit into some context in the observer’s mind (Slowiczek and Peters 2000) or suggest a revolutionary new context. What the well-informed, insightful, and attentive mind discovers to be an exciting next logical step that is waiting to be discovered someone else may see as a chance, fortuitous discovery—or may miss altogether. In the former case, the result can be groundbreaking. In the latter case, the stage is set for synchronicity in the form of logical progression to the next step by multiple investigators. Serendipity, if one uses the term, favors the prepared mind, and an active field of inquiry opens the door for synchronicity.

Optimally, financing for research should provide a substantial proportion of funds to create a scenario that allows researchers to proceed in some agreed-upon general direction, yet to follow their noses wherever the trail may lead. Without a doubt, collaborative work with other departments and even other fields of interest increases the occasion for serendipity. The involvement of traditional laboratory researchers with nonacademic ventures may also increase this happenstance, as long as the focus of the combined research is not too narrow.

An example of extreme narrowing of scope occurs in the current field of pharmacological research, which traditionally involves nonhuman primates in the testing phase. According to Joseph Schlessinger, the William H. Prusoff Professor of Pharmacology at Yale University (New Haven,

¹Abbreviations used in this article: SWFBR, Southwest Foundation for Biomedical Research; WNPRC, Washington National Primate Research Center.

CT), "It is becoming more and more difficult to develop drugs in an academic setting. . . . The technology requires such a huge investment that academic labs can't compete with the Pfizers and Mercks" (Wortman 2003). Indeed, endlessly sifting data in an effort to find scientific truth is counterproductive and expensive.

The current trend is to move away from serendipity and happenstance. Science and industry, in drug investigation and development, are looking toward evidence and statistics. Rather than hunches, an automated, industrial-scale analysis of compounds, or high-throughput screening, is the norm (Wortman 2003). In such a research environment, it is critically important to maintain and develop access to the resources provided by established primate centers and similar laboratories to capitalize in a timely way on serendipitous findings such as those described in this article and to profit from valuable discoveries made in more directly targeted development investments. Serendipity without access to the necessary fundamental research tools and environments that constitute a solid foundation may produce nothing.

Comparative Genomic Analysis/High Throughput

Genomics is among the most recent branches of biology to use comparison-based strategies. This technology capitalizes on the DNA sequences of genetic information, presenting what might seem the basis for endless serendipity because nonhuman primates are likely to share most genes present in the human genome (Nobrega and Pennacchio 2003). Comparative genomic tools include phylogenetic shadowing, combinatorial paradigms, and high-throughput screening, which allow analysis of a large number of experiments at the same time (Ng 2004). In the area of antibacterial research, early work relied on serendipitous discoveries of drug-like molecules that had certain properties without regard for their action mechanisms.

Recently, significant advances in the fields of genomics, high-throughput screening, and structural biochemistry have been made in the hunt for novel drug-target pairs that will be effective against drug-resistant bacterial infections (Lerner and Beutel 2002). A rational high-throughput screen versus a serendipitous one must be used. The approach is based on automation, validation, and integration of in vitro absorption-metabolism models and database management (Rodrigues 1997). According to one researcher, such screening is where "serendipity meets prediction" (Jessen 2000). Whereas early pharmaceutical discoveries were made by serendipity through clinical testing, these technological advances in molecular and cellular biology, together with genetics and genomics, may reveal more about the disease itself and drive such research toward a disease-based approach. High-throughput screening allows a wide chemical diversity to be applied to obtain tractable leads, which can then be optimized by the medicinal chemist (Ratti and Trist 2001).

Serendipity Close to Home

The selection of the Washington National Primate Research Center (WNPRC¹) for current studies into the origins and nature of the 1918 flu epidemic came about serendipitously. Beginning in the 1970s, in response to restrictions on importation of nonhuman primates (Rand 2003), breeding programs were established for many species that included the rhesus monkey and the chimpanzee. The pigtail macaque (*Macaca nemestrina*) was chosen as the research animal-of-choice at the WNPRC because of its perineal tumescence and detumescence, making it a good model for studies into reproductive timing. This early use of the pigtail macaque and establishment of a reproductive colony supported many studies indicating that the pigtail is susceptible to a number of infectious diseases, including AIDS, and provided a useful model for the important study of this and other infectious diseases. The serendipitous result is that in addition to building on decades-long contributions to varied and valuable studies, the WNPRC was the recipient of established resources for stepping into the important arena of studying infectious diseases and pathogen-based bioterrorism.

It would not be surprising to find that these studies will themselves lead to unexpected contributions in other areas. Serendipity is opportunistic and as invasive as water. If one is to examine the world in a way that is intended to uncover new and sometimes unexpected information, then science itself is intrinsically surprising (Slowiczek and Peters 2000). To quote Dr. Sharpless, "I do chemistry the way I used to fish. . . . My training consisted of busily poking and perturbing the Manasquam River, a curriculum both urgent and leisurely, on that permitted exploration without assumptions. . . . When I became a bench- and desk-bound explorer, my method stayed the same" (Lerner 2004).

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